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MINIREVIEWS

Uses of knockout, knockdown, and transgenic models in the studies of glucose transporter 4

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Abstract

Currently, glucose transporter 4 (GLUT4) has been considered as the key player for the insulin-stimulated glucose transport in the muscle and adipose tissues. The development of recombinant DNA techniques allows the creations of genetically knockout, knockdown and transgenic animals and cells for the study of GLUT4's physiological functions. Here, we have used key words to search the PubMed and summarized the methods used in *Slc2a4* gene knockout, GLUT4 knockdown and overexpression in the whole body and tissue specific manner. The whole body GLUT4-null mice have growth retardation, but normal glucose tolerance and basal glucose turnover rates. Compared with whole body *Slc2a4* knockout mice, adipose and muscle double knockout mice have impaired insulin tolerance and glucose intolerance. The results of GLUT4 knockdown in 3T3-L1 adipocytes have shown that its expression is needed for lipogenesis after, but not during, differentiation. Transgenic mice with the whole body GLUT4 overexpression have normal body weight and lowered blood glucose level. The adipose tissue specific overexpression of GLUT4 leads to increases in mouse body weight and adipose tissue weight. The insulin-stimulated GLUT4 translocation in the skeletal muscle contributes to the regulation of glucose homeostasis. Data from both transgenic overexpression and tissue specific *Slc2a4* knockout indicate that GLUT4 probably plays a role in the glucose uptake in the fasting state. More studies are warranted to use advanced molecular biology tools to decipher the roles of GLUT4 in the control of glucose homeostasis.

Key Words: Glucose transporter 4; Knockout; Knockdown; Transgene; Overexpression; Insulin

Core Tip: The whole body glucose transporter 4 (GLUT4)-null mice have growth retardation, but normal glucose tolerance and basal glucose turnover rates. The muscle-specific GLUT4 knockout mice have normal body weight and fat pad weight at least before 6 mo of age, whereas the adipose-GLUT4 knockout mice have glucose intolerance. The adipose and muscle GLUT4 double knockout mice develop hyperglycemia in the fasting state, suggesting the role of GLUT4 in fasting state. Compared to the control mice, wholebody GLUT4 transgenic mice have similar growth rate before 10 wk of age, lower blood glucose in the fasting, and lower insulin level in the fed state. The adipose tissue specific GLUT4 overexpression increases body weight, glucose transport rate and adipose tissue weight. Data from both transgenic overexpression and tissue specific knockout of GLUT4 indicate that GLUT4 probably plays a role in the glucose uptake in the fasting state.

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INTRODUCTION

Genes in an organism are codes responsible for genetic traits. In most cases, genes usually exist in the form of nucleotide sequences. In a cell, the DNA sequence of a gene is first transcribed into mRNA, which serves as the template for protein translation. The newly synthesized proteins contribute to biological processes in an organism. To understand the biochemical, biophysical, and genetic functions of a given gene and its protein, recombinant DNA technologies have been developed and used extensively. Since 1970s, the discovery of restriction enzymes has facilitate the development of molecular cloning methods and allowed the manipulation of DNA sequences selectively and specifically to create novel recombinant molecules[1]. DNA fragments are inserted into vectors to form recombinant genetic materials for their replication, studies of gene functions and productions of recombinant proteins. The recombinant DNA technology was first used to study gene functions when the genes responsible for metabolism of galactose in E. coli were fused into the SV40 vector in 1972[2]. For the past few decades, procedures of molecular cloning have been simplified and standardized to construct recombinant DNA with various sizes for different purposes[3]. All these have been applied to generate transgenic organisms and produce recombinant proteins for the use in variety of research and clinical settings.

Glucose enters cells *via* a family of proteins called glucose transporters (GLUTs), which have 14 known members. Glucose transporter 4 (GLUT4) encoded by *SLC2A4* gene in human genome and *Slc2a4* gene in others such as rodent genomes has 409 amino acid residues, and a Km value of 5 mmol/L for glucose[4]. GLUT4 was first identified in a screen for the insulin-stimulated glucose transporter in cell membrane preparations of rat adipocytes using monoclonal antibodies against these membrane proteins[5]. Subsequently, *Slc2a4* gene was cloned from rat adipose tissue, and is homologous with GLUT1, which is encoded by *Slc2a1* gene[6-8]. GLUT4 is expressed in not only adipose and muscle cells, but also other tissues such as the heart and brain[9]. The N- and C- termini of GLUT4 are located in the cytoplasm and responsible for the insulin-mediated translocation from the cytosol to the cell membrane [10]. The current model is that insulin stimulates GLUT4 translocation from the intracellular locations to the plasma membrane, where it facilitates the glucose entry into cells[11]. In addition, exercise also stimulates the expression of *SLC2A4* mRNA in the skeletal muscle and improves insulin sensitivity in human patients[12], which may be mediated by GLUT4[13]. Insulin-stimulated glucose transport is significantly impaired in the skeletal muscle of patients with type 2 diabetes[14]. Therefore, understanding the role of GLUT4 in the regulation of glucose homeostasis is critical for the prevention and treatment of type 2 diabetes.

Here, we summarize the recombinant DNA technologies used to study expression profiles and functions of GLUT4 in tissues and cells. Key words as indicated in the following sections were used to search PubMed. The title and abstracts of the retrieved articles were read by authors. Only the articles that contained descriptions of knockout, transgenic overexpression and knockdown molecular techniques, and confirmed gene or protein expression levels were chosen for further reading. The methods used to manipulate the expression levels of GLUT4 *in vivo* and *in vitro* and reported observations in retrieved studies were summarized here. This review may help researchers who are interested in the physiological functions of GLUT4 to have a clear understanding of the status.

THE COMMON MOLECULAR BIOLOGY TECHNIQUES TO STUDY GENE AND PROTEIN FUNCTIONS

The development of molecular cloning techniques allows isolation, generation, and production of DNA sequence independence of the species and organisms that carry the original sequences. DNA fragments isolated from genomes or created *via* polymerase chain reaction (PCR) are inserted into vectors that can replicate and express in the host cells, and in turn alter the genetic features of the host cells, tissues or organisms[15]. PCR technique quickly produces large numbers of copies of a specific DNA fragment for sequencing analysis and molecular cloning. Cloning of a specific DNA sequence helps to explore the gene's biological functions, and to create large amounts of protein, such as growth hormone, insulin and clotting factors for therapeutic purposes[16]. In addition, a comparison of DNA sequences from different organisms can determine the evolutionary relationship within and between species, and functional domains of a gene. Recombinant DNA technologies can be used in gene therapies to treat diseases such as immunodeficiency diseases and metabolic disorders[17] and diagnosis of genetic diseases[18]. Genetically modified organisms or genetically engineered organisms can be created *via* alterations of the genetic sequences of the chromosome or insertions of the foreign DNA fragments into the genome to alter the phenotypes of the offspring[19].

Genes in plants, animals and microorganisms have been deleted or their expression levels have been knocked down to investigate their functions or treat genetic diseases clinically[20]. Methods are developed to silence or remove the target gene, such as gene silencing, conditional knockout, homologous recombination, and gene editing[20]. Homologous recombination occurs when homologous recombinases (nucleases) recombine two linearized DNA fragments with the same terminal sequences to create a novel fragment for molecular manipulations[21]. This makes accurate gene editing possible and becomes emerging tools in genetics[22]. Zinc finger nucleases, transcription activator-like effector nucleases, and clustered regularly interspaced short palindromic repeat (CRISPR) are developed and shown differences in knockout efficiency, completion time, and off-target efficiency[20]. Each of these techniques uses a nuclease to introduce DNA double-strand breaks at the targeted locations with the guidance of homologous binding proteins or RNA[23]. Gene knockdown methods such as RNA-based RNA interference, small interfering RNA and short hairpin RNA (shRNA), and antisense oligonucleotides have been developed to inhibit protein expression[24]. RNA interference (RNAi) is triggered by double-stranded RNA and causes the sequence-specific mRNA degradation of the single-stranded target RNA[25]. Small non-coding RNA molecules can also act to inhibit RNA translation[26].

In addition to the change of gene expression, tagged proteins or fusion proteins with novel properties can be created using molecular biology tools[27]. Fusion or tagged proteins with two or more domains from different proteins can be easily obtained and purified for their uses in research and clinical treatments, detection of the expression levels, and visualization of the intracellular locations of the expressed proteins[27]. These have been used to create vaccines, multifunctional enzymes, targeted drugs, thrombolytics, antimicrobial peptides, *etc*[28].

MOLECULAR BIOLOGY TECHNIQUES USED IN THE STUDIES OF GLUT4

The identification of GLUT4 and cloning its gene[29] have facilitated the studies of its tissue distribution, functions, the mechanisms responsible for its translocation, and the regulations of its protein and mRNA expressions in different cells. The tagged or fluorescent GLUT4 fusion proteins are used to study its intracellular trafficking. GLUT4 overexpression and knockdown, and *Slc2a4* gene knockout *in vitro* and *in vivo* have been developed to study the insulin-stimulated GLUT4 translocation and glucose homeostasis, which contribute significantly to our understanding of the role of GLUT4[29]. To review the techniques of molecular biology in the study of GLUT4, "GLUT4, molecular biology" and "*SLC2A4*, molecular biology" as keywords were used to search the PubMed database to retrieve relevant articles. We have focused on the techniques used in *Slc2a4* knockout, knockdown and transgenic studies, and results associated with the genetic changes *in vivo* and *in vitro* were analyzed and summarized here. As shown in Figure 1, *Slc2a4* genes have been knocked out and GLUT4 protein has been overexpressed in the whole body and in specific tissues and cells. In addition, GLUT4 protein has been knocked down using shRNA, and its translocation has been studied using fusion or tagged proteins. Various methods such as in situ hybridization, fluorescent microscopy, immunohistochemistry, Western blotting for protein and Northern blot and real-time PCR for mRNA used to determine endogenous or transgenic GLUT4 expressions are also summarized in this review.

Whole-body and tissue specific Slc2a4 knockout studies

Slc2a4 mRNA expression is detected not only in brown and white adipose tissue, skeletal and cardiac muscle, but also in other tissues such as neurons[30]. To study GLUT4 functions, mice with the *Slc2a4* deletion in the whole body or specific tissues or cells have been created. We searched PubMed to retrieve the original articles that initially reported the *Slc2a4* deletions. Table 1 shows the techniques for creating knockouts, experimental animals, methods to confirm the gene deletion and expression, and

Table 1 Methods used to create whole body and tissue specific *Slc2A4* knockout animals, tissues and animals studied, analytic methods included, and observations reported

Methods	Tissues/Animals	Analysis	Observations	Ref.
A construct with a disrupted mouse *Slc2a4* gene was electroporated into WW6/22 ES cells to create deletion, which were microinjected into C57Bl/6 blastocysts	Skeletal muscle/GLUT4-null mice and wild-type control mice	Southern blot for DNA, Northern blot for mRNA, and Western blot for protein measurements	The *Slc2a4-/-*mice have normal glycemia, growth retardation, decreased longevity, cardiac hypertrophy, reduced adipose deposits, postprandial hyperinsulinemia, and lowered insulin sensitivity; The male *Slc2a4-/-*mice have lower and higher blood glucose levels than the controls in fasted and fed states, respectively	[31]
GLUT4-loxP mice were crossed with α-MHC promoter-driven Cre	Heart/Cardiac-selective *Slc2a4-/-*deletion mice (G4H–/– mice) and control mice	Southern blotting and PCR for DNA, and Western blot for GLUT4 levels using various antisera	G4H–/– mice have modest cardiac hypertrophy, normal life span and serum levels of insulin, glucose, FFAs, lactate, and β-hydroxybutyrate, increased basal cardiac glucose transport and GLUT1 expression, and abolished insulin-stimulated cardiac glucose uptake	[33]
GLUT4loxP mice as shown in [33] were crossed with the muscle CK promoter driven Cre transgenic mice to obtain Muscle-G4KO	Skeletal muscle/Muscle-G4KO mice and heterozygous *Slc2a4* deletion mice in the 129SV and C57Bl/6J background	Reverse transcription–PCR for mRNA, and Western blot for GLUT4 protein (anti-GLUT4 AB1346)	Muscle-G4KO mice show a reduction in basal and near-absence of insulin- or contraction-stimulated glucose transport, showing; severe insulin resistance and glucose intolerance from an early age	[34]
GLUT4-null mice were crossed with transgenic mice expressing GLUT 4 driven by MLC promoter[55] to create MLC-GLUT4-null mice	EDL and soleus muscle/MLC-GLUT4-null mice having GLUT4 in the fast-twitch EDL muscle, GLUT4 null mice, and control mice	Western blot for GLUT4 protein (rabbit polyclonal antiserum)	MLC-GLUT4-null mice have less GLUT4 in WAT (females only) and soleus muscle, adipose tissue deposits, adipocyte size, and plasma free fatty acid levels in the fed state than the controls. Glucose uptake in the EDL, but not in the soleus, muscle is restored to normal in male and above normal in female MLC-GLUT4-null mice	[32]
GLUT4–loxP mice were crossed with aP2-driven Cre transgenic mic to obtain G4A-/- mice	Adipose tissue/G4A-/-, and control mice	Western blot for GLUT4 protein in BAT and WAT tissues	G4A-/- mice show impaired insulin-stimulated glucose uptake in adipocytes, glucose intolerance, hyperinsulinemia, and insulin resistance in the muscle and liver	[35]
The G4A-/- mice[35] were crossed with the muscle-G4KO mice[34] to generate AMG4KO mice	Adipose tissue and skeletal muscle/G4A-/-, muscle-G4KO, and AMG4KO mice	Western blot for GLUT4 protein using antibodies from H. Haspel in the Charles River Laboratory	AMG4KO mice develop fasting hyperglycemia and glucose intolerance and are at risk for greater insulin resistance than mice lacking GLUT4 in only one tissue	[37]
The neuron-specific Nestin promoter-driven Cre transgenic mice were crossed with GLUT4-loxP mice (FVB strain) to obtainBG4KO mice	Whole brain/BG4KO and control mice	Western blot for GLUT4 protein in the brain using antibody from Chemicon	BG4KO mice have glucose intolerance, insulin resistance, and impaired glucose sensing, suggesting that the brain GLUT4 may sense and respond to glucose	[36]

α-MHC: α-myosin heavy-chain; AMG4KO: Adipose/muscle-GLUT4 double knockout; BAT: Brown adipose tissue; BG4KO: Brain-specific GLUT4 knockout; Cre: Cre recombinase; CK: Creatine kinase; ES: Embryo stem; EDL: Extensor digitorum longus; GLUT4: Glucose transporter 4; G4A-/-: Adipose tissue-specific GLUT4 knockout; GLUT4-loxP: *Slc2a4* allele with exon 10 flanked by loxP sites; G4KO: GLUT4 knock out; MLC: Myosin light chain; Ref: References; WAT: White adipose tissue.

observations. In the end, seven representative articles that the research groups generated a specific knockout model to study GLUT4 and clearly described the methods of GLUT4 deletion are summarized here as shown in Table 1. The animal models were also used by many other groups.

In1995, the mouse *Slc2a4* locus was disrupted using homologous recombination in embryonic stem cells which generated mice without GLUT4 expression (GLUT4-null) in the whole body[31]. The GLUT4-null mice showed growth retardation, enlarged hearts and complete lack of the white adipose tissue[31]. GLUT4-null mice have normal glucose tolerance and basal glucose turnover rates. However, they are insulin intolerant, suggesting insulin resistance. Later on, the GLUT4-null mice[31] have been used to create mice expressing GLUT4 specifically in the extensor digitorum longus muscle[32].

Tissue specific GLUT4 knockout mice have been created by crossing mice carrying a *Slc2a4* allele with exon 10 flanked by loxP sites with those carrying *Cre* gene expression driven by tissue specific promoters[33-36]. The various phenotypes of these knockout mice help us to understand the roles of GLUT4 in different tissues and glucose metabolism. For example, the muscle-specific GLUT4 knockout mice (muscle-G4KO) were created by breeding mice carrying the *Slc2a4* exon 10 flanked by loxP sites with mice carrying a transgene encoding Cre recombinase under the control of the muscle creatine kinase promoter[34]. Compared with GLUT4-null mice, muscle-G4KO mice have normal body weight and fat pad weight at least before 6 mo of age[34]. The skeletal muscle mass is also normal. The increase in heart weight is consistent with GLUT4-null mice[31] and cardiac-G4KO mice[33]. Compared with the shortened lifespan of GLUT4-null mice, the life span of muscle-G4KO mice is normal. In contrast to GLUT4-null mice and cardiac-G4KO mice, adipose-G4KO mice[35] are similar to muscle-G4KO mice.

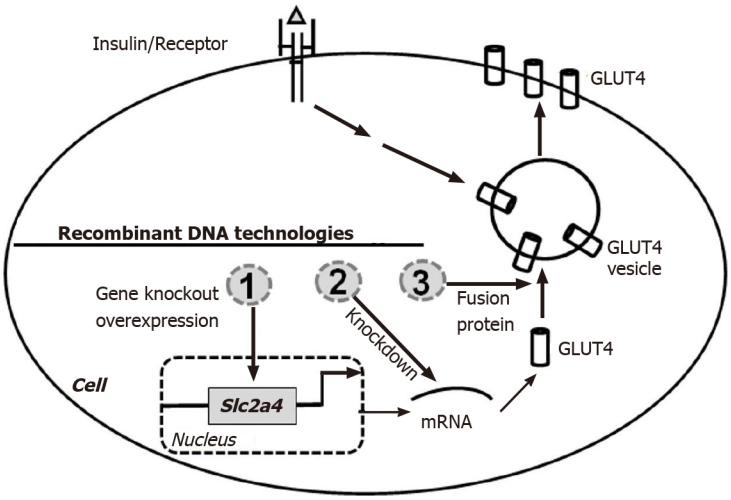

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Figure 1 Recombinant DNA technologies used in the study of glucose transporter 4 functions and its translocation mechanism. *Slc2a4* gene is transcribed into mRNA, which is translated into glucose transporter 4 (GLUT4) protein. The binding of insulin to its receptor leads to the activation of insulin signaling system, which facilitates the movement of GLUT4 from its intracellular location to the cell membrane, and in turn the entry of glucose in the cells. Recombinant DNA technologies have been used to alter gene expression level (1), reduce mRNA translation (2) and tracing intracellular movement of GLUT4 protein (3). 1. *Slc2a4* gene has been deleted in the whole body *via* homologous recombination and in individual tissues or cells *via* Cre-LoxP system driven by tissue specific promoters. In addition, transgenic overexpression of GLUT4 in whole body or specific tissues and cells has been done using mini gene or *SLC2A4* cDNA driven by different promoters, respectively. 2. The GLUT4 protein is knocked down using short-hairpin RNA under the control of different promoters to interfere the translation process. 3. Fusion or tagged GLUT4 has been created to study the insulin-stimulated GLUT4 translocation mechanism using fluorescent microscopy, and immune assays.

However, adipose-G4KO mice have glucose intolerance[35]. Interestingly, unlike other GLUT4 knockout mice, the heart weight of adipose-G4KO mice is normal.

In addition, adipose and muscle *Slc2a4* double knockout (AMG4KO) mice are also created by crossing the respective tissue knockout mice[37]. Interestingly, these AMG4KO mice develop hyperglycemia in the fasting state[37]. It appears that GLUT4 also plays a role in a physiological condition that does not need the insulin-stimulated glucose uptake.

GLUT4 knockdown studies

The deletion of a gene completely stops the genetic information flow. Another way to block the protein expression is to knockdown a gene's expression, which temporarily stops or reduces the expression of the targeted gene. Unlike knockout, gene knockdown involves the methods interfering with RNA molecules (mRNA or non-coding RNA) that bridges DNA and proteins. "GLUT4, knockdown" and "*SLC2A4*, knockdown" as keywords were used to search the PubMed database to retrieve relevant articles. Table 2 summarizes the methods of knockdown and confirmation, cells used, observations of GLUT4 knockdown studies.

Recently, RNAi has emerged as a powerful tool for the study of gene function in mammalian cells [38]. After transfection, the shRNAs molecules are transcribed under promoters in constructs that drive the RNA synthesis within the targeted cells. Oligo nucleotides with sequences of shRNAs may be transfected directly into the cells[38]. In all studies summarized in Table 2, shRNAs method is used to achieve GLUT4 knockdown[39-41], which is delivered *via* recombinant retroviruses. Two of three studies investigated the roles of GLUT4 in 3T3-L1 adipocytes. It appears that GLUT4 expression is needed for the lipogenesis after differentiation in 3T3-L1 cells, but not necessary for lipogenesis during differentiation[41]. In addition, the insulin-regulated aminopeptidase trafficking is not always associated with the GLUT4 movement[40].

Transgenic studies

We have used key words "GLUT4 transgenic" (314 hits) and "GLUT4 overexpression" (609 hit) to search PubMed to retrieve GLUT4 transgenic studies. After going through the titles or abstracts containing "GLUT4 overexpression and GLUT4 transgenic", we found 15 papers that have described their original methods or clearly cited the methods used by them, confirmed the GLUT4 overexpression in mice and provided results. Table 3 summarizes the techniques used to overexpress GLUT4, the methods to confirm the expression and results observed in those animals.

In 1992, a 2.4-kb fragment of 5′ flanking DNA of human *SLC2A4* promoter fused with the bacterial chloramphenicol acetyltransferase (CAT) as a reporter construct was developed and used to show the *SLC2A4* expression profile in mice[42]. In 1993, an 11.5-kb *SLC2A4* mini gene in pHSS6 vector was created and used to overexpress human GLUT4 in the whole body of mice[43]. As shown in Table 3, the

Table 2 Methods used to knockdown glucose transporter 4 and analyze its expression in cell lines, and reported observations

Methods	Cells	Analysis	Observations	Ref.
Recombinant lentivirus was used to express shRNA based on *SLC2A4* sequence (NM_001042.3)	Human head and neck squamous cancer cell lines, HSC-2	Western blot for GLUT4 protein using antibody from Epitomics	The knockdown of GLUT4 expression in HSC-2 cells induced DDX58 and OASL protein expressions, and reduced cell migration in culture	[39]
pSIREN RetroQ system was used to obtain recombinant retroviruses that produce shRNAs corresponding to mouse *Slc2a4* sequence GGTGATTGAACAGAGCTAC (GenBank ID was not provided)	3T3-L1 adipocytes	Immunofluorescence of phase-contrast and epifluorescence images for GLUT4 protein using antibodies (rabbit anti-GLUT4, a gift from Dr. Sam Cushman (National Institutes of Health)	GLUT4 knockdown does not affect IRAP trafficking, showing that IRAP traffics is independent of GLUT4	[40]
Recombinant lentivirus was used to generate shRNA under the control of human H1-RNA promoter using the mouse *Slc2a4* mRNA sequence (GenBank ID not provided)	3T3-L1 adipocytes	Immunofluorescence microscopy and Western blot for GLUT4 using rabbit polyclonal antibody from Chemicon International Inc	GLUT4 knockdown in 3T3-L1 adipocytes reduces insulin-stimulated glucose uptake by 50%-60%, IRAP expression of depending on differentiation stage, and lipogenic capacity of differentiated, but not differentiating cells	[41]

DDX58: DExD/H-Box Helicase 58; GLUT4: Glucose transporter 4; IRAP: Insulin-regulated aminopeptidase; OASL: 2′-5′-Oligoadenylate Synthetase Like; Ref: References; shRNA: Short hairpin RNA.

mouse line containing the 11.5-kb mini gene has been used in seven out of eight papers testing the effects of overexpression of human GLUT4 in the mouse whole body on metabolism[43-49]. CAT activity, *SLC2A4* mRNA and/or GLUT4 protein level in adipose tissue and skeletal muscle and other tissues have been analyzed to confirm the success of transgenic expression[43,44]. In general, the whole-body human GLUT4 overexpression reduces blood glucose in both fasting and fed states and increased glucose uptake in mice, but affects the blood insulin level in wild type mice and diabetic mice differentially[44]. Whole body GLUT4 overexpression does not alter body weight, but can reduce blood glucose level and affect serum insulin level.

GLUT4 has been overexpressed in a tissue specific manner as shows in Table 4. Majority of the studies have been focused on adipose tissues[50-54]. There is one for the skeletal muscle[55] and one for adipocytes[56]. A 6.3-kb genomic DNA fragment of human *SLC2A4* gene driven by the mouse *ap2*[50] promoter has been used to overexpress GLUT4 in mouse adipose tissues. This method was first published in 1993[50] and was used in many other studies in the genetic settings of wild-type and diabetic mice[51-54]. Like the papers summarized in Table 3, a human *SLC2A4* gene under a tissue-specific promoter was used to overexpress GLUT4. Human *SLC2A4* cDNA was also used to overexpress GLUT4 in adipocytes[56], but mouse *Slc2a4* gene was used to express GLUT4 in the hindlimb muscle [55]. All adipose tissue specific GLUT4 overexpression studies[50-55] tested the *SLC2A4* mRNA or GLUT4 protein level to confirm GLUT4 expression, which is found to be expressed in both brown and white adipose tissues. In conclusion, adipose tissue specific GLUT4 overexpression in mice can cause increases in body and adipose tissue weights[50,51]. The adipose tissue specific GLUT4 transgenic mice also have higher glucose disposal rate, may be caused by increased basal and insulin-stimulated glucose transport rate. It is interesting to find out that the elevated expression of GLUT4 in the adipose tissue only can increase glucose transport rate and adipose tissue weight, which is associated with the significant increase in body weight, suggesting the importance of GLUT4 expression in adipose tissue.

CONCLUSION

Conclusion and future perspectives

As summarized in this review, methods such as whole body and tissue specific gene knockout, recombinant viruses, real-time PCR, immunofluorescence, stable cell line and transgenic animals have been used to study GLUT4 system and insulin action in different target cells and tissues. The advantages of using multiple molecular biology methods allow us to confirm the functions of GLUT4 for insulin-stimulated glucose transport in different cells and tissues, and in the regulation of whole-body glucose homeostasis. Interestingly, GLUT4-null mice which do not have a functional *Slc2a4* gene in the whole genome have normal glucose tolerance and basal glucose turnover rates, but they are insulin-intolerant which suggests insulin resistance[31]. AMG4KO mice (adipose and muscle double knockout) have reduced whole body glucose uptake and hyperglycemia[37]. Compared with GLUT4-null mice, AMG4KO mice have more severe glucose homeostasis defects. Although the explanation for this difference is not clear, differences in genetic background and differences in developmental stages, where GLUT4 is deleted have been proposed. More importantly, the hyperglycemia in these double

Table 3 The transgenic studies using the *SLC2A4* mini gene and its promoter for the whole-body expression in mice

Transgenic constructs	Analysis	Observations	Ref.
A 11.5-kb mini gene of human *SLC2A4* starts with a 5.3-kb fragment upstream of transcription start and terminates within exon 10 of the gene followed by the bacterial CAT in pHSS6 vector	RNase protection assay and Western blot were used for SLC2A4 mRNA and GLUT4 protein in BAT, WAT, heart and skeleton muscle, respectively	The transgene expression was detected in WAT and BAT, heart and skeleton muscle of mice. Female transgenic mice have higher GLUT4 protein in the adipose tissue and less *SLC2A4* mRNA in skeleton muscle than male ones. Transgenic mice have higher GLUT4 protein level in adipose tissue, liver, heart and skeleton muscle than the controls	[43]
The 11.5-kb minigene with the CAT reporter as shown in[43]	Reverse transcription PCR was used to measure *SLC2A4* mRNA in cardiac and hindquarter muscle, BAT and WAT. Immunofluorescent test was for GLUT4 translocation	Transgenic mice gained more weight after 15 wk old of age, and have lower blood glucose in both fasting and fed states, lower insulin level in fasting and higher after refeeding, and higher glycogen contents, GLUT4 translocation in cardiac and skeleton muscle than the control mice	[44]
The 11.5 kb minigene with the CAT reporter as shown in[43]	Western blot was used to detect GLUT4 in gastrocnemius muscles	Transgenic mice have lower serum glucose level in both fasting and fed state, higher insulin level during fasting and lower after fed than the control ones	[45]
The 11.5 kb minigene with the CAT reporter as shown in[43]	Western blot was used to detect GLUT4 in the heart	Transgenic mice have higher glucose uptake, glycolysis and glycogen content, and lower insulin-stimulated glycolysis rate and glycogen synthesis in the heart than the control ones. Glucose and fatty acid oxidation remain the same	[46]
The 11.5 kb minigene with the CAT reporter as shown in[43]	Immunofluorescence was used to detect GLUT4 in cardiac myocytes and adipocytes	Transgenic mice have similar body weight, and epididymal adipose tissue weight and adipocyte size as the controls. Transgenic mice have higher levels of triglycerides, β-hydroxybutyrate and free fatty acids, and parametrial fat weight and lower glucose level after an oral glucose challenge and insulin level after an insulin injection than the controls. The insulin-stimulated glucose uptake is impaired in transgenic mice	[47]
A 2.4-kb of 5′ flanking DNA fragment of human *SLC2A4* promoter fused with the CAT as a reporter construct	CAT activity assay and RNase protection assay were used to detect promoter activation and mRNA, respectively	In transgenic mice, CAT activity can be detected in the tissues that generally express GLUT4, including BAT and WAT, and smooth, skeleton and cardiac muscle, but not the liver	[42]
A 2.4-kb of 5′ flanking DNA of human *SLC2A4* promoter fused to CAT as shown in[42]	Western blot was used to detect GLUT4 in adipose and skeleton muscle tissues	Transgenic mice have slower rise of blood glucose (no difference in glucose and insulin levels) during pentobarbital sodium anesthesia, and higher glucose infusion rate (40% increase) during hyper insulinemic euglycemic clamp than the controls	[48]
A 2.4-kb of 5 flanking DNA of human *SLC2A4* promoter fused to CAT as shown in[42]	Only cited previous publications[42]	Transgenic mice have lower blood glucose, higher lactate and β-hydroxybutyrate levels during both fasting and fed states, and better glucose transport in the soleus muscle when fed a high-fat and high-sugar diet than the controls	[49]

BAT: Brown adipose tissue; CAT: Chloramphenicol acetyltransferase; GLUT4: Glucose transporter 4; Ref: References; WAT: White adipose tissue.

knockout mice develops in the fasting state, rather than fed state[37]. This phenomenon appears to indicate that GLUT4 plays an important role in the control of glucose homeostasis during fasting, a state that insulin level is low. The translational value of these observations is that GLUT4's physiological role from the integrated homeostatic point of view may be extended beyond the insulin-stimulated glucose uptake. Of course, more studies are warranted on this line of research.

On the other hand, the GLUT4 knockdown studies used the shRNAs method and have been done in cell lines to reduce GLUT4 expression. This may be helpful for us to understand the GLUT4 functions and the underlying mechanisms in particular cells. It appears that GLUT4 expression is not necessary for lipogenesis during 3T3-L1 cells differentiation. Apparently, it will be helpful when more GLUT4 knockdown studies are done in animals.

The GLUT4 overexpression in transgenic mice at wholebody level reduces blood glucose in both fasting and fed states and increased glucose uptake, glycolysis and glycogen level[44]. Compared to the control mice, overexpression of GLUT4 in adipose tissue in mice leads to lowered blood glucose in the fasting state, and increase in body weight and adipose tissue weight[50]. The expression of GLUT4 in adipose tissue and skeleton muscle affects the rate of whole-body glucose disposal, which may be caused by increased basal and insulin-stimulated glucose transport rates. This lowered blood glucose level in the transgenic mice also indicates that GLUT4 probably plays a role in the basal glucose uptake.

For the tissue specific GLUT4 knockout, Cre-loxP–mediated gene recombination under the control of promoters has been the main method to delete *Slc2a4* gene. Since the development of CRISPR technology, it has not been used to knockout *Slc2a4* in whole body or tissues, which is a limitation in the field. We have used "GLUT4" and "CRISPR", and "*SLC2A4*" and "CRISPR" as key words to search PubMed, and retrieved eight and two published articles, respectively. However, none of the published articles used the CRISPR methods to knockout *SLC2A4* or *Slc2A4* gene in cells or animals. All of them used CRISPR methods to study the components in the exocytosis process of GLUT4 translocation. As

Table 4 Recombinant DNA techniques to create tissue specific glucose transporter 4 overexpression in animals and cells, analysis performed, and observations reported

Techniques	Tissue/analysis	Observations	Ref.
A 6.3-kb genomic DNA fragment of human *SLC2A4* gene is under the control of a 5.4-kb' DNA fragment of mouse ap2 promoter using Gateway cloning	Adipose-specific overexpression/ Western blot was used to detect GLUT4 in BAT and WAT	Transgenic mice have lower glucose level in the fasting, insulin level in the fed state, higher body weight and body fat at 18 to 21 wk of age, and higher basal and insulin-stimulated glucose transport rates in epididymal, parametrial, and subcutaneous adipocytes than the controls	[50]
Same as in[50]	Adipose-specific overexpression/Only cited previous publications[50]	Transgenic mice have higher body weight, parametrial fat pad weight and adipocyte size, and glucose transport in both fasting and fed states, and lower plasma insulin and glucose levels after a glucose challenge than the controls	[51]
Same as in[50]	Adipose-specific overexpression/Only cited previous publications[50]	Transgenic mice have higher glucose disposal rate in a glucose tolerance test, and palmitic acid-hydroxy stearic acid levels in serum, WAT and BAT than the controls	[52]
Same as in[50]	Adipose-specific overexpression/Western blot was used to detect GLUT4 in BAT and WAT	Transgenic mice fed a high-fat diet have higher glucose disposal rate than those fed a low-fat diet, and stable GLUT4 expression in fat and no increase in body fat	[53]
Same as in[50]	Adipose-specific overexpression/Western blot was used to detect GLUT4 in BAT and WAT	Transgenic mice have higher gonadal adipose weight, basal and maximum insulin stimulated glucose transport in isolated adipocytes, glucose transport rate, triglyceride synthesis and CO_2 production than the controls	[54]
A 4.5-kb DNA fragment of the mouse *Slc4a2* gene is under the control of a 3-kb fragment of the mouse myosin light chain gene promoter	Hindlimb muscle overexpression/Northern blot and Western blot were used to detect *Slc4a2*mRNA and GLUT4 in different tissues respectively	Transgenic mice have higher basal and insulin-stimulated glucose uptake and turnover, higher glycogen content in the skeleton muscle, higher insulin sensitivity, higher levels of free fatty acid and ketone in both fasting and fed state, and lower fasting glucose level than the controls	[55]
The human *SLC2A4* cDNA is driven by the CMV promoter in pCIS2 vector	Rat adipocytes overexpression/Immunofluorescence was used to detect GLUT4 overexpression	Rat adipose cell transfected with the GLUT4 construct had significantly higher antibody binding after insulin stimulation than the control cells	[56]

BAT: Brown adipose tissue; CMV: Cytomegalovirus; GLUT4: Glucose transporter 4; Ref: References; WAT: White adipose tissue.

CRISPR has been developed and used widely, GLUT4 knockout/knockdown through this system may be worth to be done. This may provide us another tool to manipulate the GLUT4 expression in the whole body or in tissue specific manners.

In addition, results of glucose tolerance are different between mice with whole body and tissue specific GLUT4 knockout. Therefore, whether the loss of GLUT4 in a specific tissue (muscle or fat) or the expression of GLUT4 in other tissues without gene deletion plays a role in this difference is worth to be investigated. It is safe to say that more research works are anticipated in the future to precisely define the role of GLUT4 in the control of glucose homeostasis at whole body and tissue levels. In so doing, we develop effective ways to prevent and treat type 2 diabetes mellitus.

FOOTNOTES

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META-ANALYSIS

Hepatitis C virus among blood donors and general population in Middle East and North Africa: Meta-analyses and meta-regressions

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Abstract

BACKGROUND

Despite the Middle East and North Africa (MENA) Region reported to have the highest prevalence of hepatitis C virus (HCV) globally, HCV infection levels in the majority of MENA countries remain inadequately characterized. Blood donor data have been previously used as a proxy to assess levels and trends of HCV in the general population, however, it is unclear how comparable these populations are in MENA and whether blood donors provide an appropriate proxy.

AIM

To delineate HCV epidemiology among blood donors and the general population in the MENA.

METHODS

The data source was the systematically gathered MENA HCV Epidemiology Synthesis Project Database. Random-effects meta-analyses and meta-regressions were conducted. For comparison, analyses were conducted for Europe, utilizing the Hepatitis C Prevalence Database of the European Centre for Disease Prevention and Control.

RESULTS

One thousand two hundred and thirteen HCV antibody prevalence measures and 84 viremic rate measures were analyzed for MENA. Three hundred and seventy-seven antibody prevalence measures were analyzed for Europe. In MENA, pooled mean prevalence was 1.58% [95% confidence interval (CI): 1.48%–1.69%] among blood donors and 4.49% (95%CI: 4.10%–4.90%) in the general population. In Europe, pooled prevalence was 0.11% (95%CI: 0.10%–0.13%) among blood donors and 1.59% (95%CI: 1.25%–1.97%) in the general population. Prevalence in the

general population was 1.72-fold (95%CI: 1.50–1.97) higher than that in blood donors in MENA, but it was 15.10-fold (95%CI: 11.48–19.86) higher in Europe. Prevalence was declining at a rate of 4% per year in both MENA and Europe [adjusted risk ratio: 0.96 (95%CI: 0.95–0.97) in MENA and 0.96 (95%CI: 0.92–0.99) in Europe]. Pooled mean viremic rate in MENA was 76.29% (95%CI: 67.64%–84.02%) among blood donors and 65.73% (95%CI: 61.03%–70.29%) in the general population.

CONCLUSION

Blood donor data provide a useful proxy for HCV infection in the wider population in MENA, but not Europe, and could improve HCV burden estimations and assess progress toward HCV elimination by 2030.

Key Words: Hepatitis C virus; Viral hepatitis; Blood donors; General population; Middle East and North Africa; Meta-analysis; Meta-regression

Core tip: We investigated hepatitis C virus (HCV) epidemiology among blood donors and the wider general population in Middle East and North Africa (MENA). For comparison, similar analyses were performed for Europe. Our results indicated that HCV antibody prevalence in the population of MENA and Europe appears to be declining by 4% per year. Blood donor data in MENA (but not in Europe) were found to provide a useful proxy for HCV infection levels and trends in the general population. Thus, the data can be utilized in HCV estimates and to assess, track and validate progress towards World Health Organization elimination goals for HCV.

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INTRODUCTION

In the Middle East and North Africa (MENA) an estimated 15 million individuals are chronically infected with hepatitis C virus (HCV), making it the global region most affected by HCV infection[1]. Left untreated, chronic HCV infection may lead to several morbidities, including liver cancer, fibrosis, and cirrhosis[2]. Prompted by development of highly efficacious direct-acting antivirals (DAAs), the World Health Organization (WHO) has set a global target to eliminate HCV as a public health problem by 2030[3].

Despite disproportionally high HCV infection levels in specific MENA countries, *e.g.*, Egypt[4-7] and Pakistan[8-11], relative to global levels[1,12], only three countries in this region have conducted nationally representative population-based surveys[13-15]. HCV infection levels in the remaining countries remain inadequately characterized[1].

Blood donors have been used as a proxy population to provide a crude estimate of HCV infection levels in the general population[16,17]. However, in developed countries, such as the United States[18] and countries of the European Union[16], blood donors are not considered representative of the wider general population. In these countries, strict donor selection and blood safety regulations[19] have resulted in a large disparity in HCV infection levels between blood donors and the general populations. This raises two questions: How comparable are HCV infection levels between blood donors and the general population in MENA? Are blood donor data, which are readily available, thanks to blood screening, an appropriate proxy for the general population in this region?

In this context, objectives of this study were to delineate HCV epidemiology in blood donors and general populations in MENA, and to assess how representative blood donor data are of HCV antibody (Ab) prevalence in the general population of this region. The study was also conducted to infer programmatic implications on blood safety in the region. These objectives were accomplished through analyses of a large, systematically gathered database, including 2622 HCV Ab prevalence measures on 49.8 million individuals by: (1) Estimating the pooled mean prevalence among blood donors and in general populations (henceforth the general population); and (2) Identifying predictors and trends of prevalence in these populations and sources of between-study heterogeneity. We further conducted

similar analyses for Europe, a region in which stringent donor selection and blood safety processes have been implemented[19], for comparison. We did so by utilizing a large systematically gathered database including 419 HCV Ab prevalence measures for 25.7 million individuals[20], to compare outcomes with results for MENA.

MATERIALS AND METHODS

Data sources

This study was conducted as part of the MENA HCV Epidemiology Synthesis Project[1], an ongoing project with the aim of delineating HCV epidemiology and informing key public health research, policy, and programming priorities in MENA. The source of data was the MENA HCV Epidemiology Synthesis Project Database[1]. The database included 685 HCV Ab prevalence measures on 46 634 214 blood donors and 528 measures on 2 358 944 individuals of the general population, such as pregnant women, healthy adults, and children. The database also included eight HCV viremic rate measures on 58 986 blood donors and 76 measures on 14 936 individuals of the general population. HCV viremic rate was defined as the proportion of those who had tested Ab positive that are subsequently confirmed to be chronically infected by testing positive for HCV RNA – the proportion of those HCV RNA positive among HCV Ab-positive individuals[21,22].

The database was populated through a series of systematic reviews for HCV infection across MENA that were previously conducted as part of this project[5,6,8,23-28]. All reviews followed a standardized methodology, and specific details such as literature search strategy, databases searched, and eligibility criteria can be found in each of these reviews[5,6,8,23-28]. The methodology used for these reviews was informed by the Cochrane Collaboration Handbook[29], and all findings were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[30]. Literature searches were conducted to identify primary data on HCV measures in international and national/regional databases, the MENA HIV/AIDS Epidemiology Synthesis Project Database[31,32], abstract archives of international conferences, and grey literature, including public health reports and routine data reporting. Literature searches were broad, with no language restrictions to ensure inclusiveness. All records reporting HCV measures after 1989, the year in which the virus was officially identified[33], were included in the reviews[5,6,8,23-28].

Blood donors are typically a diverse group with different rates of HCV Ab prevalence depending on the rigor of the donor selection process[19]. The vast majority of HCV Ab prevalence studies in MENA did not specify the type of blood donors, and therefore the term blood donors in the present analysis encompassed the different blood donor types, including regular voluntary nonremunerated donors, one-time voluntary nonremunerated donors, family replacement donors, and paid donors.

For the MENA HCV Epidemiology Synthesis Project, the MENA region was defined to include 24 countries (Figure 1). Given the distinctive nature of the HCV epidemics in Egypt[4-7] and Pakistan[8-11], relative to other MENA countries, separate analyses were performed for each of these countries.

HCV measures in blood donors and the general population were also analyzed for Europe, a region in which stringent donor selection and blood safety regulations have been implemented for decades [19], for comparison with MENA outcomes. Europe's HCV Ab prevalence measures were retrieved from the Hepatitis C Prevalence Database of the European Centre for Disease Prevention and Control [20]. The database was populated through a systematic review[16] and multiple reports[34,35]. The database included 257 HCV Ab prevalence measures on 25 232 790 blood donors and 120 measures on 410 444 individuals of the general population, such as pregnant women and healthy adults.

Pooled mean HCV Ab prevalence and viremic rate

Meta-analyses for countries and subregions were performed to pool HCV Ab prevalence in blood donors and the general population, whenever three or more measures were available, and a minimum sample size of 25 participants was met. Random-effects meta-analyses were performed using the DerSimonian–Laird method[36], with inverse-variance weighting to pool measures[36]. Freeman–Tukey type arcsine square-root transformation was used to stabilize the variance of each measure, factoring knowledge regarding the applicability of this transformation[37,38]. Heterogeneity was formally assessed[36]. Forest plots were generated and examined visually, and Cochran's Q-test was conducted. Statistical significance of heterogeneity was indicated whenever P was < 0.10[36,39]. The I^2 and its confidence interval (CI) were calculated to assess the percentage of variance that is explained by true differences in prevalence across studies, rather than chance[36]. Prediction intervals were also determined to describe the distribution of prevalence around the pooled mean estimate[36]. Meta-analyses were also used to estimate the pooled mean HCV viremic rate among blood donors and in the general population. Meta-analyses and forest plots were generated using R version 3.4.3.

Predictors, trends, and sources of between-study heterogeneity

Univariable and multivariable random-effects meta-regressions were conducted following established methodology[29]. A priori relevant independent variables in meta-regressions included subpopulation

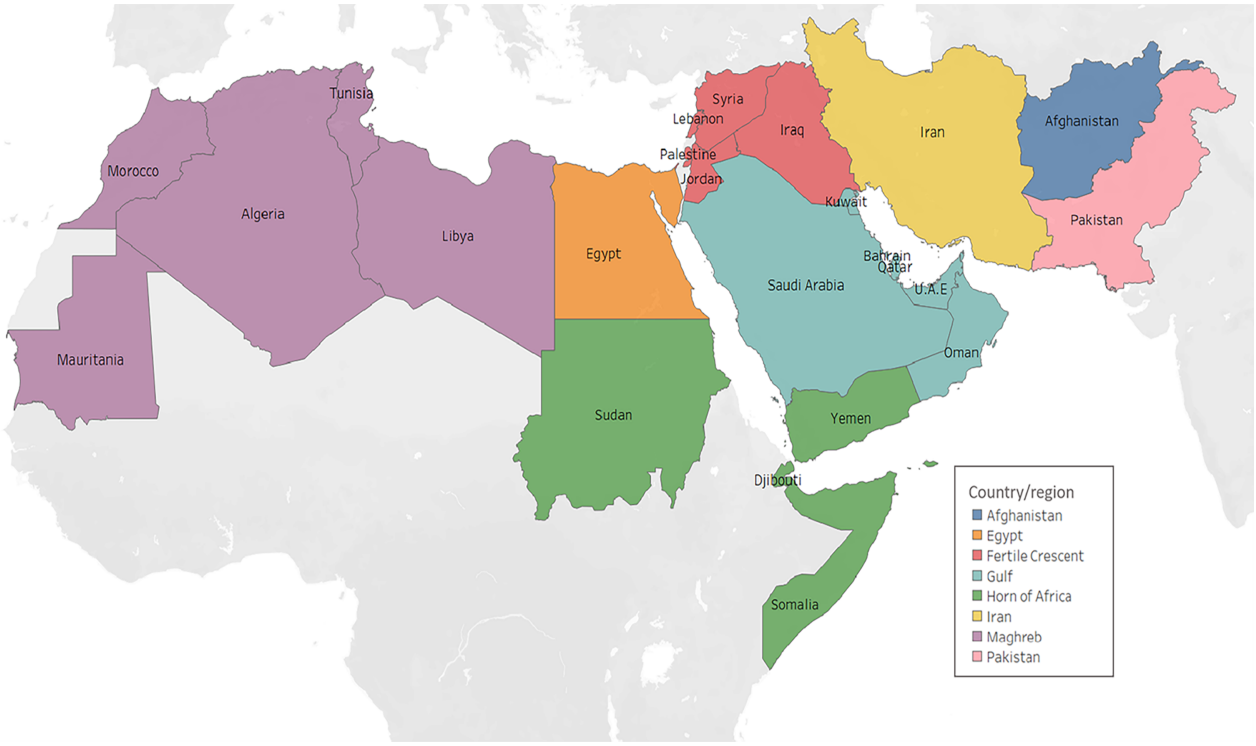

Figure 1 Map of the countries and subregions included in the Middle East and North Africa Region.

(blood donors *vs* the general population), country/subregion, and year of data collection. Factors associated with HCV Ab prevalence at $P \leq 0.20$ in the univariable analysis qualified for inclusion in the multivariable analysis. Here, an adjusted relative risk (ARR) $P \leq 0.05$ was considered to indicate strong evidence for an association.

In studies in which the year of data collection variable was missing, the variable was imputed. This was done by first subtracting the year of data collection (when available) from the year of publication for each study, and using the median of these values in imputing the year of data collection. Sensitivity analysis was performed without the imputed observations to determine the impact of the imputation on the results, confirming the results of the original meta-regression. Meta-regressions were performed on STATA version 13 using the *metan* command.

RESULTS

HCV Ab prevalence among blood donors and the general population in MENA

Studies on HCV Ab prevalence among blood donors and the general population in MENA are listed in Supplementary Tables 1 and 2. HCV Ab prevalence data were available for 23 of the 24 MENA countries. The largest number of data points were retrieved from Egypt, followed by the Gulf and Fertile Crescent Subregions. HCV Ab prevalence in blood donors ranged from 0 to 38.20%, with a median of 0.86% (Table 1). Studies reporting the highest HCV Ab prevalence were reported from parts of Egypt in the 1990s, a period during which HCV infection was widespread following the parenteral antischistosomal therapy (PAT) campaigns that contributed in a major way to the HCV epidemic in Egypt[5-7,40]. The pooled mean prevalence was 1.58% (95%CI: 1.48%–1.69%). It was lowest in the Fertile Crescent Subregion at 0.21% (95%CI: 0.18%–0.25%) and highest in Egypt at 10.40% (95%CI: 9.59%–11.23%), followed by Pakistan at 3.47% (95%CI: 2.96%–4.02%). HCV Ab prevalence in the general population ranged from 0 to 73.38%, with a median of 3.14%. The pooled mean prevalence was 4.49% (95%CI: 4.10%–4.90%). It was lowest in Iran at 0.33% (95%CI: 0.21%–0.47%) and highest in Egypt at 13.08% (95%CI: 11.51%–14.73%), followed by Pakistan at 8.81% (95%CI: 7.62%–10.06%). All outlier high HCV Ab prevalence measures were investigated and found to reflect blood donors or general populations in specific settings that were affected by high exposure to the virus, such as specific villages in the Nile delta in Egypt following the PAT era[5-7,40]. There was strong evidence for heterogeneity in HCV Ab prevalence in all meta-analyses ($P < 0.01$), with almost all variation being attributed to true variation in prevalence across studies rather than chance ($I^2 > 99.4\%$). Heterogeneity was also confirmed by the estimated prediction intervals (Table 1).

Table 1 Results of meta-analyses on studies reporting HCV Ab prevalence among blood donors and in the general population in Middle East and North Africa

Population	Studies	Samples	HCV Ab prevalence		Pooled HCV Ab prevalence		Heterogeneity measures		
	Total (*n*)	Total (*n*)	Range (%)	Median (%)	Mean (%)	95%CI	Q (*P* value)[1]	I^2 (confidence limits)[2]	Prediction interval (%)[3]
Blood donors									
Afghanistan	40	737407	0.00-7.19	0.60	0.75	0.57-0.96	3046.03 (*P* < 0.01)	98.7% (98.6%-98.9%)	0.02-2.41
Egypt	116	1566669	0.00-38.20	10.97	10.40	9.59-11.23	24513.7 (*P* < 0.01)	99.5% (99.5%-99.6%)	3.64-19.96
Fertile Crescent[4]	157	3488952	0.00-3.95	0.27	0.21	0.18-0.25	3674.2 (*P* < 0.01)	95.8% (95.4%-96.1%)	0.00-0.67
Gulf[5]	156	20891379	0.00-27.19	0.89	0.78	0.71-0.86	29882.0 (*P* < 0.01)	99.5% (99.5%-99.5%)	0.20-1.69
Horn of Africa[6]	22	48076	0.0-6.03	1.0	0.97	0.57-1.45	327.8 (*P* < 0.01)	93.6% (91.5%-95.2%)	0.00-3.78
Iran	73	15971802	0.00-3.13	0.24	0.31	0.22-0.40	55740.9 (*P* < 0.01)	99.9% (99.9%-99.9%)	0.00-1.43
Maghreb[7]	49	2145044	0.11-6.58	0.65	0.68	0.49-0.91	13475.9 (*P* < 0.01)	99.6% (99.6%-99.7%)	0.00-2.82
Pakistan	73	1797644	0.01-20.79	3.00	3.47	2.96-4.02	24753.7 (*P* < 0.01)	99.7% (99.7%-99.7%)	0.38-9.32
All countries/subregions	686	46646973	0.00-38.2	0.86	1.58	1.48-1.69	481819.0 (*P* < 0.01)	99.9% (99.9%-99.9%)	0.01-5.18
General population									
Afghanistan	6	12048	0.00-4.03	0.88	0.61	0.20-1.18	21.7 (*P* < 0.01)	76.9% (48.5%-89.6%)	0.00-2.68
Egypt	147	110603	0.00-54.10	11.82	13.08	11.51-14.73	8457.0 (*P* < 0.01)	98.3% (98.1-98.4%)	0.62-36.45
Fertile Crescent[4]	64	189456	0.00-8.87	0.19	0.42	0.24-0.64	1117.8 (*P* < 0.01)	94.4% (93.4%-95.2%)	0.00-2.39
Gulf[5]	85	222829	0.00-22.54	0.83	1.41	1.0-1.88	5343.3 (*P* < 0.01)	98.4% (98.3%-98.6%)	0.00-7.66
Horn of Africa[6]	27	29552	0.00-8.50	1.53	1.86	1.26-2.57	262.0 (*P* < 0.01)	90.1% (86.8%-92.6%)	0.00-6.13
Iran	50	101677	0.00-2.35	0.45	0.33	0.21-0.47	206.9 (*P* < 0.01)	76.3% (69.0%-81.9%)	0.00-1.25
Maghreb[7]	42	1378206	0.00-6.16	0.62	0.87	0.55-1.26	7595.3 (*P* < 0.01)	99.5% (99.5%-99.5%)	0.00-4.38
Pakistan	106	301814	0.44-73.38	6.82	8.81	7.62-10.06	13619.0 (*P* < 0.01)	99.2% (99.2%-99.3%)	0.60-24.62
All countries/subregions	527	2346185	0.00-73.38	3.14	4.49	4.10-4.90	83750.3 (*P* < 0.01)	99.4% (99.4%-99.4%)	0.00-16.88

[1]Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in effect size (here, HCV Ab prevalence) across studies.
[2]I^2: A measure assessing the magnitude of between-study variation that is due to true differences in effect size (here, HCV Ab prevalence) across studies rather than chance.
[3]Prediction interval: a measure estimating the 95% interval of the distribution of true effect sizes (here, HCV Ab prevalence).
[4]Countries include Iraq, Jordan, Lebanon, Palestine, and Syria.
[5]Countries include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates.
[6]Countries include Djibouti, Somalia, Sudan, and Yemen.
[7]Countries include Algeria, Libya, Mauritania, Morocco, and Tunisia. Ab: Antibody; CI: Confidence interval; HCV: Hepatitis C virus.

HCV Ab prevalence among blood donors and the general population in Europe

HCV Ab prevalence data were available for 30 countries in Europe. HCV Ab prevalence in blood donors ranged from 0 to 3.28%, with a median of 0.06% (Table 2). The pooled mean prevalence was 0.11%

Table 2 Results of meta-analyses on studies reporting HCV Ab prevalence among blood donors and in the general population in Europe

Subpopulation	Studies	Samples	HCV Ab prevalence		Pooled HCV Ab prevalence		Heterogeneity measures		
	Total (*n*)	Total (*n*)	Range (%)	Median (%)	Mean (%)	95%CI	Q (*P* value)[1]	I^2 (confidence limits)[2]	Prediction interval (%)[3]
Blood donors	257	25232790	0.0-3.28	0.06	0.11	0.10-0.13	35657.5 ($P < 0.01$)	99.3 (99.3-99.3)	0.00-0.51
The general population	120	410444	0.0-16.83	1.11	1.59	1.25-1.97	9176.9 ($P < 0.01$)	98.7 (98.6-98.8)	0.0-7.57

[1]Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in effect size (here, HCV Ab prevalence) across studies.
[2]I^2: a measure assessing the magnitude of between-study variation that is due to true differences in effect size (here, HCV Ab prevalence) across studies rather than chance.
[3]Prediction interval: a measure estimating the 95% interval of the distribution of true effect sizes (here, HCV Ab prevalence). Ab: Antibody; CI: Confidence interval; HCV: Hepatitis C virus.

(95%CI: 0.10%–0.13%). Prevalence in the general population ranged from 0 to 16.83%, with a median of 1.11%. The pooled mean prevalence was 1.59% (95%CI: 1.25%–1.97%). There was strong evidence for heterogeneity in HCV Ab prevalence ($P < 0.01$), with the majority of variation being attributed to true variation in prevalence across studies rather than chance ($I^2 > 98.7\%$).

HCV viremic rate of blood donors and the general population

The HCV viremic rate of blood donors in different MENA countries ranged from 61.84% to 93.33%, with a median of 70.78% (Supplementary Table 3). The pooled mean for the entire MENA region was 76.29% (95%CI: 67.64%–84.02%), indicating that approximately three-quarters of Ab-positive blood donors are chronically infected. The viremic rate ranged from 22.73% to 100% in the general population in different MENA countries, with a median of 68.27% (Supplementary Table 3). The pooled mean for the entire MENA region was 65.73% (95%CI: 61.03%–70.29%). There was strong evidence for heterogeneity in the viremic rates ($P < 0.01$), with most variation being attributed to true variation in the viremic rate across studies rather than chance ($I^2 > 77.4\%$).

Predictors and trends of HCV Ab prevalence in MENA

The meta-regressions for MENA indicated that HCV Ab prevalence in the general population was 1.72-fold (95%CI: 1.50–1.97) higher than that in blood donors (Table 3). They also indicated substantial variation in prevalence by country and subregion with Egypt and Pakistan having a higher prevalence than the rest of MENA countries. Importantly, the analyses indicated that HCV Ab prevalence has been declining over the last three decades at an average rate of 4% per year (ARR of 0.96; 95%CI: 0.95–0.97). Subgroup analyses were conducted on the above results. The same regressions were repeated, but for Egypt, Pakistan and other MENA countries individually (Table 4). These analyses indicated that HCV Ab prevalence in the general population was 1.30-fold (95%CI: 1.07–1.59) higher than that among blood donors in Egypt, 2.52-fold (95%CI: 1.89–3.36) higher in Pakistan, and 1.73-fold (95%CI: 1.42–2.11) higher in the remaining MENA countries. The analyses also confirmed the same rate of decline for prevalence at 4% in the rest of MENA countries. The rate of decline was slightly higher in Egypt at 6%. There was no evidence for a decline in prevalence, however, in Pakistan.

In a sensitivity analysis, the same regressions were also repeated, but excluding all blood donor data (not shown). The analyses indicated that HCV Ab prevalence in MENA is declining at a rate of 5% per year (ARR of 0.95; 95%CI: 0.93–0.97), indicating a marginally higher rate of decline in the general population.

Predictors and trends of HCV Ab prevalence in Europe

The meta-regressions for Europe indicated that HCV Ab prevalence in the general population is 15.10-fold (95%CI: 11.48–19.86) higher than that in blood donors (Table 5). The analyses indicated further that HCV Ab prevalence has been declining over the last three decades at a similar rate to that of MENA, at 4% per year (ARR of 0.96; 95%CI: 0.92–0.99).

A sensitivity analysis was conducted on the above results. The same regressions were repeated, but excluding all blood donor data (not shown). The analyses indicated that HCV Ab prevalence in Europe is declining at a rate of 10% per year (ARR of 0.90; 95%CI: 0.85–0.96), higher than that in MENA.

Table 3 Univariable and multivariable meta-regression models for HCV Ab prevalence among blood donors and the general population in Middle East and North Africa

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total (*n*)	Total (*n*)	RR (95%CI)	*P* value	F *P* value[a]	Variance explained R^2 (%)	ARR (95%CI)	*P* value
Subpopulations								
Blood donors	686	46646973	1	-			1	-
The general population	527	2346185	2.92 (2.41-3.55)	< 0.001	< 0.001	10.73	1.72 (1.50-1.97)	< 0.001
Country/subregion								
Afghanistan	46	749455	1	-			1	-
Egypt	263	1677272	14.89 (10.2-21.8)	< 0.001			9.48 (6.54-13.75)	< 0.001
Fertile Crescent[1]	221	3678408	0.52 (0.35-0.77)	< 0.001			0.49 (0.34-0.72)	< 0.001
Gulf[2]	241	21114208	1.24 (0.84-1.82)	0.280			0.82 (0.56-1.19)	0.398
Horn of Africa[3]	49	77628	2.05 (1.25-3.37)	0.005			1.33 (0.82-2.15)	0.244
Iran	123	16073479	0.50 (0.33-0.77)	< 0.001			0.42 (0.28-0.63)	< 0.001
Maghreb[4]	91	3523250	1.02 (0.66-1.56)	0.936			0.77 (0.51-1.16)	0.207
Pakistan	179	2099458	6.96 (4.71-10.29)	< 0.001	< 0.001	58.39	5.44 (3.73-7.93)	< 0.001
Year of data collection	1213	48993158	0.95 (0.94-0.97)	< 0.001	< 0.001	3.71	0.96 (0.95-0.97)	< 0.001

[1]Countries include Iraq, Jordan, Lebanon, Palestine, and Syria.
[2]Countries include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates.
[3]Countries include Djibouti, Somalia, Sudan, and Yemen.
[4]Countries include Algeria, Libya, Mauritania, Morocco, and Tunisia.
[a]Variables with $P \leq 0.2$ were eligible for inclusion in the multivariable analysis.
[b]The adjusted R-squared for the full model was 62.65%.
Ab: Antibody; ARR: Adjusted relative risk; CI: Confidence interval; RR: Relative risk.

DISCUSSION

Levels and trends of HCV Ab prevalence in blood donors and in the general population of MENA were assessed using a large standardized database. There was large variability in HCV Ab prevalence by country and subregion, with Egypt and Pakistan, the largest countries in MENA by population size, having several fold higher prevalence than the rest of MENA countries. HCV Ab prevalence in the remaining MENA countries was at about 1% or less, similar to that in Europe and most other countries globally[12,41]. These results confirm our understanding of HCV epidemiology across MENA countries and subregions[4-11,21-28,42-49].

Strikingly, HCV Ab prevalence is declining rapidly in both MENA and Europe, and at a similar rate of about 4% per year. The exception to this downward trend was Pakistan where there was no evidence for a decline. These declines may be reflective, in part, of the declining incidence of HCV infection within these regions through improvements to infection control following the discovery of this virus three decades ago, and scale-up of HCV treatment worldwide[3]. They also may reflect the progressive improvement in effective blood donor selection, such as by motivating and retaining voluntary nonremunerated donors to donate regularly[19].

A major finding of this study is that HCV Ab prevalence in blood donors in MENA was similar to HCV Ab prevalence in the general population; unlike the situation in Europe. While HCV Ab prevalence in the general population was almost twofold higher than that of HCV Ab prevalence in blood donors in MENA, it was 15-fold higher in Europe (Table 3 *vs* Table 5). HCV Ab prevalence in blood donors in MENA appears to closely reflect the background prevalence in the wider population. Of note that HCV Ab prevalence in blood donors is a function of not only the prevalence in the general

Table 4 Subgroup analyses: Univariable and multivariable meta-regression models for HCV Ab prevalence among blood donors and the general population in Egypt, Pakistan, and rest of Middle East and North Africa countries

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total (*n*)	Total (*n*)	RR (95%CI)	*P* value	F *P* value[a]	Variance explained R^2 (%)	ARR (95%CI)	*P* value
Egypt								
Subpopulations								
Blood donors	116	1566669	1	-			1	-
The general population	147	110603	1.25 (1.00-1.57)	0.049	0.087	2.05	1.30 (1.07-1.59)	0.008
Year of data collection	263	1677272	0.94 (0.93-0.95)	< 0.001	< 0.001	24.48	0.94 (0.93-0.95)	< 0.001
Pakistan								
Subpopulations								
Blood donors	73	1797644	1	-			-	-
The general population	106	301814	2.52 (1.89-3.36)	< 0.001	< 0.001	19.03	-	-
Year of data collection	179	2099458	1.00 (0.98-1.03)	0.648	0.648	0.00	-	-
Rest of MENA countries								
Subpopulations								
Blood donors	497	43282660	1	-	-		1	-
The general population	274	1933768	1.80 (1.47-2.21)	< 0.001	< 0.001	5.44	1.73 (1.42-2.11)	< 0.001
Country/subregion								
Afghanistan	46	749455	1	-	-		1	-
Fertile Crescent[1]	221	3678408	0.53 (0.35-0.81)	0.003			0.50 (0.33-0.75)	0.001
Gulf[2]	241	21114208	1.26 (0.83-1.91)	0.273			0.86 (0.56-1.30)	0.462
Horn of Africa[3]	49	77628	2.08 (1.22-3.54)	0.007			1.37 (0.81-2.32)	0.247
Iran	123	16073479	0.51 (0.33-0.81)	0.004			0.43 (0.28-0.67)	< 0.001
Maghreb[4]	91	3523250	1.04 (0.65-1.64)	0.883	< 0.001	11.48	0.79 (0.50-1.24)	0.298
Year of data collection	771	45216428	0.95 (0.94-0.96)	< 0.001	< 0.001	6.22	0.96 (0.95-0.98)	< 0.001

[1]Countries include Iraq, Jordan, Lebanon, Palestine, and Syria.
[2]Countries include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates.
[3]Countries include Djibouti, Somalia, Sudan, and Yemen.
[4]Countries include Algeria, Libya, Mauritania, Morocco, and Tunisia.
[a]Variables with a *P* value ≤ 0.2 were eligible for inclusion in the multivariable analysis. No multivariable analysis was conducted for Pakistan, as only one variable qualified for inclusion in the model.
[b]The adjusted R-squared was 27.35% for the multivariable model for Egypt and 17.92% for the multivariable model for rest of MENA countries. Ab: Antibody; ARR: Adjusted relative risk; CI: Confidence interval; RR: Relative risk.

population, but also of the effectiveness of blood donation programs to collect blood from regular voluntary nonremunerated blood donors[19]. This finding suggests that risk reduction strategies through selection and retention of safer blood donors (regular voluntary nonremunerated blood donors) are not yet effectively implemented widely in MENA as in Europe[19], where the source of blood largely comes from such donors. Indeed regulatory framework (including legislation, regulation, policies and standards) and a functioning regulatory authority to enforce the regulatory framework is largely at its infancy in MENA[19], where, as of 2016, only 55% of MENA countries had legislation covering safety and quality of blood transfusions, and only two countries had achieved 100% voluntary nonremunerated blood donations[19,50]. Furthermore, HCV Ab prevalence in blood donors may be reflective of people in the general population unaware of their HCV infection status, in the context of which an individual aware of their positive HCV infection status would not donate blood.

Nevertheless, contingent on the quality of blood donor management systems implemented within countries of MENA, this finding indicates that HCV Ab prevalence in blood donors in MENA (unlike in North America[18] and Europe[16]) can be used for the time being as a proxy to estimate infection levels in the general population. This outcome has important consequences. With the lack of nationally repres-

Table 5 Univariable and multivariable meta-regression models for HCV Ab prevalence among blood donors and the general population in Europe

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total (*n*)	Total (*n*)	RR (95%CI)	*P* value	F *P* value[a]	Variance explained R^2 (%)	ARR (95%CI)	*P* value
Subpopulations								
Blood donors	257	25232790	1				1	
The general population	120	410444	15.57 (11.83-20.49)	< 0.001	< 0.001	53.62	15.10 (11.48-19.86)	< 0.001
Year of data collection	377	25643234	0.93 (0.88-0.98)	0.004	0.005	2.17	0.96 (0.92-0.99)	0.020

[a]Variables with $P \leq 0.2$ were eligible for inclusion in the multivariable analysis.
[b]The adjusted R^2 for the full model was 54.27%.
Ab: Antibody; ARR: Adjusted relative risk; CI: Confidence interval; RR: Relative risk.

entative population-based surveys in most countries of this region, blood donor data, which are readily available, can be easily used to assess levels and trends of this infection in the wider population. They can also be used to generate other estimates, such as those related to the disease burden of HCV sequelae, and can be leveraged to assess, track and validate progress toward the WHO elimination goals for this infection[3]. The present study also provides adjustment factors to improve use of blood donor data (Table 2), so that they better reflect HCV levels in the wider population. These adjustment factors can be used at a regional level, or can be fine-tuned so as to be specific for individual countries.

This study had several limitations. Availability of data varied across MENA, with HCV Ab prevalence data being unavailable for Bahrain. The majority of HCV viremia data were collected at times before the launch of DAA treatment programs (Supplementary Table 3); thus, they may not represent the current viremic rate in blood donors and in the general population. Analysis for the different blood donor types was not conducted as the specification of blood donor type was not available for the vast majority of HCV Ab prevalence measures. The sample size of blood donors was larger than that of the general population; however, the sample size in the general population was still substantial at 2.3 million. Despite these limitations, an immense volume of data was acquired, allowing various analyses and an array of consequential inferences to be drawn. While high heterogeneity was found, most (63%) of it was subsequently explained in meta-regression analyses in terms of prevalence variation by country and subregion within MENA.

CONCLUSION

HCV Ab prevalence in the wider population of MENA and Europe appears to be rapidly declining by 4% per year. Blood donor data in MENA (but not in Europe) provide a useful proxy for HCV infection levels and trends in the general population; at least in countries where effective blood donor selection and blood donor management programs are not in place. Thus, the data can be utilized in HCV infection and disease burden estimates and to assess, track and validate progress toward WHO elimination goals for this infection. While these findings are specific for MENA, they may also apply to resource-limited countries of other regions.

ARTICLE HIGHLIGHTS

Research background

The Middle East and North Africa (MENA) Region is the most affected by hepatitis C virus (HCV) infection, with approximately 20% of the global chronically infected individuals residing in this region. Despite this, only three countries conducted national population-based surveys to delineate HCV infection levels in the general population.

Research motivation

HCV infection in blood donors have been used as a proxy for HCV infection levels in the general population. However, it is unclear how comparable blood donors are to the general population in countries in MENA and whether they are a suitable proxy population.

Research objectives
To delineate HCV epidemiology in blood donors and in the general population in MENA.

Research methods
The MENA HCV Epidemiology Synthesis Project Database was used as a data source. Studies reporting HCV in blood donors and in the general population were retrieved, and random-effects meta-analyses and random-effects meta-regressions were performed. For regional comparison, similar analyses were performed for countries in Europe, using the Hepatitis C Prevalence Database from the European Centre for Disease Prevention and Control (ECDC).

Research results
A total of 1213 HCV Ab prevalence measures and 84 viremic rate measures were retrieved from the MENA HCV Epidemiology Synthesis Project, and 377 HCV Ab prevalence measures were retrieved from the ECDC. The pooled mean prevalence in MENA was 1.58% [95% confidence interval (CI): 1.48%–1.69%] in blood donors and 4.49% (95%CI: 4.10%–4.90%) in the general population, and in Europe was 0.11% (95%CI: 0.10%–0.13%) among blood donors and 1.59% (95%CI: 1.25%–1.97%) in the general population. In MENA, the prevalence in the general population was 1.72-fold (95%CI: 1.50–1.97) higher than that in blood donors, and in Europe it was 15.10-fold (95%CI: 11.48–19.86) higher. HCV prevalence appeared to be declining by 4% annually in both MENA and Europe.

Research conclusions
Blood donor data in MENA (but not in Europe) appears to be comparable with that in the general population and therefore can be used as a useful proxy for HCV infection levels and trends in the general population, at least in countries where effective blood donor selection and blood donor management programs are not yet firmly in place. Blood donor data may be used to estimate HCV infection and disease burden and to assess, track, and validate progress toward World Health Organization elimination goals for this infection.

Research perspectives
With the lack of nationally representative population-based surveys in most countries in MENA and beyond, blood donor data, which are readily available, can be easily used to assess levels and trends of this infection in the wider population. The study rationalizes and facilitates generation of estimates at low costs and demands for resources, even in resource-limited settings where population-level data are most scarce. While these findings are specific for MENA, they may also apply and be of relevance to other global regions.

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FOOTNOTES

Author contributions: Mahmud S conducted data extraction and analysis, and wrote the first draft of the paper; Abu-Raddad L conceived and led the design of the study, analyses, and drafting of the article; All authors contributed to data collection and acquisition, and/or database development, and/or discussion and interpretation of the results, and to the writing of the manuscript.

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META-ANALYSIS

Effects of dexmedetomidine on cardioprotection and other postoperative complications in elderly patients after cardiac and non-cardiac surgerie

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Abstract

BACKGROUND

After cardiac and non-cardiac surgeries, elderly patients have a high probability of developing cardiac complications and postoperative delirium. Although several clinical trials have investigated whether perioperative intravenous dexmedetomidine can protect the heart and reduce postoperative complications such as delirium in elderly patients, the obtained results have been inconsistent. We conducted a meta-analysis to investigate the effects of dexmedetomidine on cardioprotection and other postoperative complications in elderly patients undergoing cardiac or non-cardiac surgery.

AIM

To investigate the effects of dexmedetomidine on cardiac complications and delirium in elderly patients undergoing cardiac or non-cardiac surgery.

METHODS

The PubMed, Cochrane Library, web of science, and other sources were comprehensively searched for all randomized controlled trials published before May 2021 that investigated the efficacy of dexmedetomidine in the prevention of cardiac and postoperative delirium (POD).

RESULTS

In total, 18 studies involving 1025 patients were included in the meta-analysis. Intravenous dexmedetomidine significantly reduced cardiac troponin I (cTnI) and the inflammatory factor tumor necrosis factor-α (TNF-α) was comparable to the control group. Dexmedetomidine also reduced the POD and mortality rates. However, patients in the dexmedetomidine group were more likely to have a

decreased heart rate (within the normal range) and hypotension during dexmedetomidine administration than those in the control group. There was no difference in the occurrence of myocardial infarction, bradycardia, or stroke between the two groups. Dexmedetomidine significantly shortened the time to extubate; however, it did not shorten the length of stay in the intensive care unit.

CONCLUSION

The administration of dexmedetomidine during cardiac and non-cardiac surgeries can provide myocardial protection by inhibiting inflammation and cTnI, which may be beneficial for the rapid recovery of patients. Meanwhile, the administration of dexmedetomidine reduced the incidence of POD and decreased mortality (in-hospital).

Key Words: Dexmedetomidine; Cardioprotection; Postoperative delirium; Complication; Meta-analysis

Core Tip: After cardiac and non-cardiac surgeries, elderly patients have a high probability of developing cardiac complications and postoperative delirium. Although several clinical trials have investigated whether perioperative intravenous dexmedetomidine can protect the heart and reduce postoperative complications such as delirium in elderly patients, the obtained results have been inconsistent. We conducted a meta-analysis to investigate the effects of dexmedetomidine on cardioprotection and other postoperative complications in elderly patients undergoing cardiac or non-cardiac surgery.

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INTRODUCTION

Elderly patients (> 65 years old) have decreased organ functions and are prone to hemodynamic fluctuations and increased cardiac oxygen consumption, which induces or aggravates myocardial ischemia and hypoxia, leading to severe adverse cardiac events[1]. Postoperative delirium (POD) in elderly patients undergoing major operations, including heart surgery, is a relatively common and serious complication, which is associated with higher morbidity and mortality, cognitive dysfunction, increased length of hospital stay, and increased medical costs[2]. In addition, POD, infection, acute renal failure, major adverse cardiac events, and neurological complications, including permanent or transient stroke, coma, perioperative myocardial infarction (MI), heart block, and cardiac arrest, are major complications [3,4]. However, POD is the most common surgical complication in elderly patients aged 65 years and older[5,6]. The occurrence of delirium may significantly extend the length of hospitalization, delayed recovery, delayed cognitive dysfunction, and increased mortality[4]. Dexmedetomidine can reduce the occurrences of POD postoperative pain, nausea, and vomiting[4,7]. Meanwhile, dexmedetomidine can provide rapid and stable recovery and early extubation after surgery by maintaining the patient's hemodynamics[8].

Dexmedetomidine, a derivative of medetomidine, is a highly selective α2 adrenergic receptor agonist [9] that can inhibit the sympathetic nervous system and act on the noradrenergic glands in the locus coeruleus of the pons to inhibit the release of norepinephrine[6,10]. The dorsal vagus nucleus and suspicious nucleus are the human parasympathetic nerve center, and the central area of the parasympathetic nerve is directly controlled by the nucleus tractus solitarius. Because the nucleus tractus solitarius is abundant in α2 adrenergic receptors, the combination of dexmedetomidine and the nucleus tractus solitarius α2 adrenergic receptors can increase the activity of the vagus nerve and reduce the myocardial cAMP production and L-type calcium channel current, which slows down the heart rate, increases coronary blood flow, and plays a role in myocardial protection[1]. In addition, the anxiolytic, sedative/hypnotic, and analgesic effects of dexmedetomidine[2,11], including the intraoperative hemostatic effect, also enhance cardioprotection[12]. Regarding inflammation, dexmedetomidine can block the accumulation of inflammatory cells in the nervous system[10], reduce neuronal damage caused by immune responses, and reduce surgical complications such as stress response and postoperative cognitive impairment to exert its neuronal protection[9,10]. However, high-dose dexmedetomidine can cause adverse reactions such as hypertension, decreased reflex heart rate,

decreased cardiac output, and decreased drug tolerance in elderly patients, requiring special attention to drug dosage[1].

MATERIALS AND METHODS

This meta-analysis was reported according to the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13]. In addition, this study was not registered with the PROSPERO.

Search strategy

We performed this meta-analysis according to PRISMA guidelines. PRISMA is the minimum set of evidence-based items used for reporting in systematic reviews and meta-analyses, and can be adopted as the basis for systematic reviews for reporting different types of research. We searched 1025 studies from PubMed, Cochrane Library, and Web of Science that were published before May 2021; other search systems focused on 10 studies (Google) to confirm further eligible studies.

We manually screened whether the studies we included met our final research criteria, and then selected 18 of them for research. The basic search strategy included the following words: ("dexmedetomidine"[MeSH Terms] OR"dexmedetomidine"[All Fields]) AND ("cardiac"[MeSH Terms] OR"cardiac"[All Fields]) AND ("aged"[MeSH Terms] OR"aged"[All Fields] OR"elderly"[All Fields]). No language restrictions were applied during the search.

Bradycardia, hypertension, and hypotension were defined as HR < 60 bpm, SBP > 160 mmHg or 20% of baseline, and SBP < 90 mmHg or 20% of baseline, respectively.

Eligibility criteria

We included the following standard studies: (1) Elderly patients (> 65 years old) undergoing cardiac or non-cardiac surgery; (2) We selected a dexmedetomidine group combined with normal saline or other anesthetics, regardless of the initial administration time, dose, duration, or dose; (3) The research content type was randomized controlled clinical trial (RCT); and (4) The research results included hypertension, hypotension, heart rate, cardiac status, complications, POD, stroke, mortality, extubation time, intensive care unit (ICU) time, and cardiac enzyme markers.

Exclusion criteria

Non-randomized controlled trials, case reports, meeting abstracts, and comments were excluded.

Including non-elderly surgery and no results of our study were also excluded.

Study selection and data collection process

Two authors (Yang and Hu) independently conducted qualified research selection and data extraction. Disagreements between the two authors were discussed with the third author (Duan) to arrive at the final solution. The extracted data were as follows: first author, annual publication, type of surgery, number of patients, dose of dexmedetomidine, method of anesthesia, hypotension, hypertension, heart rate, myocardial infarction, bradycardia, delirium, stroke, mortality, extubation time, ICU duration, and myocardial enzyme markers.

Risk of bias in individual studies

Two examiners (Yang and Hu) independently used version 2 of the Cochrane tool to assess RCT deviation risk for methodological quality assessment. When the two examiners disagreed, the disagremments were resolved *via* discussions with a third examiner (Duan).

Statistical analysis

We employed a Review Manager 5.0 software (Cochrane Collaboration Company) for rigorous statistical analysis. Risk ratios (RRs) with 95% confidence intervals (CIs) and the Mantel-Haenszel method (fixed or random model) were adopted to analyze dichotomous data. For continuous outcomes, the mean differences (MD) or standardized mean differences (SMD) with 95%CIs were calculated. If significant heterogeneity existed (I^2 > 50%), sensitivity analysis was performed, each study was ignored separately, and a random effects model was selected.

RESULTS

As illustrated in Figure 1. We initially identified 1035 studies by searching the database. After screening out duplicate studies, 486 studies entered the next step of screening: 443 studies were excluded because the focused on non-elderly patients, were non-RCT, were unable to obtain full-text qualifications or not published, *etc.* (Google search); 25 excluded studies did not comply with the statistical data in this

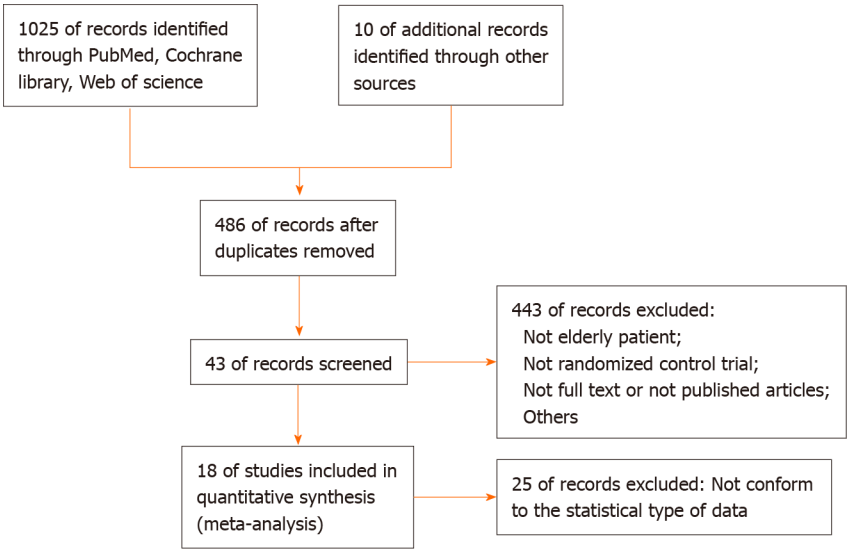

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Figure 1 Flow chart of study selection.

article. Finally, we included 18 studies that met all eligibility criteria (Figure 1). The basic characteristics of the enrolled studies are presented in Table 1. A summary of the risk of bias is presented in Figure 2. Regarding the blindness of patients, researchers, and evaluators, 11 trials were rated as double-blind low-risk trials, and seven trials were rated as high-risk or unclear-risk trials because related articles were not clear about blindness.

Meta-analysis of intraoperative data

We determined that there was no significant difference in hypertension between the dexmedetomidine and control groups (Figure 3, RR: 0.99, 95%CI: 0.78-1.25, $P = 0.92$, $I^2 = 21\%$). However, 426 patients had hypotension among the 2025 patients, of whom 265 and 161 were in the dexmedetomidine and control groups, respectively. Therefore, it could be inferred that dexmedetomidine had a significant effect on lowering blood pressure (Figure 3, RR: 1.63, 95%CI: 1.40-1.90, $P < 0.001$, $I^2 = 2\%$).

HR was significantly lower in the dexmedetomidine group than in the control group (Figure 4, MD: -8.46, 95%CI: -12.56 to -4.36, $P < 0.001$). However, heterogeneity I^2 was as high as 87%. Further sensitivity analysis indicated that the heterogeneity decreased to 45% after excluding Shokri and Ali 2020[7], Tosun *et al*[12] 2013, and Zhou *et al*[14] 2019. This study was relatively unstable, and the number of included studies needs to be increased in the future.

Meta-analysis of other cardiac complications

In total, six studies investigated the occurrence of MI. In these studies, 26 patients developed MI in the dexmedetomidine group (Figure 5, RR: 0.74, 95%CI: 0.49-1.13, $P = 0.16$, $I^2 = 0\%$). However, there was no statistically significant difference between the dexmedetomidine and control groups. In addition, five studies participated in the study of bradycardia, and there was no significant statistical difference between the dexmedetomidine and control groups (Figure 5, RR: 1.51, 95%CI: 0.79-2.89, $P = 0.21$, $I^2 = 63\%$). However, we performed a sensitivity analysis by excluding Turan 2020 and Zhang 2020, and the heterogeneity decreased to zero ($P = 0.004$).

Meta-analysis of cardiac troponin I and tumor necrosis Factor-α

The level of cardiac troponin I (cTnI) in elderly patients after surgery was analyzed. The obtained results indicated that the level of cTnI in the dexmedetomidine group was lower than that in the control group after surgery (Figure 6, SMD: -3.14, 95%CI: -5.16 to -1.11, $P = 0.002$, $I^2 = 97\%$). Statistical heterogeneity was absent when the studies conducted by Elgebaly 2020 and Shen 2017 were excluded, and the obtained results were statistically significant (SMD: -1.00, 95%CI: -1.37 to -0.63, $P < 0.001$, $I^2 = 0\%$).

As illustrated in Figure 6, the level of Factor-α (TNF-α) in the dexmedetomidine group was lower (SMD: -0.72, 95%CI: -1.30 to -0.13, $P = 0.02$, $I^2 = 52\%$) after surgery than that of the control group. Sensitivity analysis and subgroup analysis failed to eliminate the heterogeneity; therefore, a random-effects model was adopted.

Meta-analysis of other complications

Seven studies have demonstrated that the use of dexmedetomidine use is associated with POD. The occurrence of POD was reported in all the RCTs. Notably, the occurrence of POD in the

Table 1 Study characteristics

Ref.	No. of patients in study		DEX dose		Surgical procedure	Anesthesia	Outcome parameters
	DEX	Control	Loading dose (μg.kg^{-1})	Infusion rate (μg.kg^{-1}.hr^{-1})			
Aouad *et al*[26], 2019	48	50	1	N/A	Elective surgery	GA	Hypotension; HR
Cheng *et al*[25], 2016	222	283	N/A	0.24-0.6	Cardiac Surgery	GA	Delirium; MI; Mortality; Stroke
Chi *et al* [21], 2016	34	33	1	0.6	Off-pump coronary artery bypass graft surgery	GA	Hypertension; ICU time
Elgebaly *et al*[8], 2020	30	30	N/A	0.4	Open-heart surgery	GA	HR; cTnI; ET; Length of ICU stay
Ji *et al*[3], 2013	568	566	N/A	0.24-0.6	CABG or valve surgery or CABG or valve surgery combined with other procedures. patients excluded were those undergoing emergency surgery, off-pump or robotic surgery, surgery requiring deep hypothermic circulatory arrest, or surgery involving the thoracic aorta	GA	Delirium; Mortality stroke; MI
Lee *et al* [18], 2016	20	20	1	0.5	Orthopedic surgery in supine position	GA	HR; Hypertension
Lee *et al* [2], 2018	95	109	1	0.2-0.7	Laparoscopic major non-cardiac surgery	GA	Incidence of delirium
Li *et al* [20], 2020	309	310	0.6	0.5	Major non-cardiac surgery	GA	Delirium: Length of ICU stay (h)
Ríha *et al* [11], 2012	17	21	1	0.5-1.5	Elective CABG procedures with the use of cardiopulmonary bypass to treat coronary artery disease	GA	Length of ICU stay; MI; ET
Shen *et al* [1], 2017	30	30	0.5	0.5	Coronary heart disease and underwent gastric cancer operation	GA	Hypotension; cTnI; MI; Bradycardia
Shokri *et al*[7], 2020	144	142	N/A	0.7-1.2	Coronary artery bypass grafting	GA	Delirium; Hypotension; HR; Bradycardia; ET; Mortality
Soliman *et al*[27], 2016	75	75	1	0.3	Aortic vascular surgery	GA	Hypertension; HR; MI; Bradycardia; Mortality
Sun *et al* [5], 2019	281	276	N/A	0.1	Major elective noncardiac surgery	GA	Delirium; Hypotension; Hypertension; Mortality
Tosun *et al* [12], 2013	18	20	0.5	0.5	Coronary artery bypass graft surgery	GA	HR
Turan *et al* [15], 2020	398	396	0.1	0.2	Cardiac surgery	GA	Hypotension; MI; Bradycardia; mortality; ICU time; Stroke
Zhang *et al*[16], 2020	120	120	0.5	0.3	Hip Fracture Operation	GA	Delirium; Hypotension; Hypertension; Bradycardia
Zhou *et al* [22], 2019	14	14	0.5	0.5	Valve replacement surgery	GA	cTnI
Zhou *et al* [14], 2019	53	47	N/A	0.2-0.7	Cardiac surgery	GA	HR; ET; cTnI

CABG: Coronary artery bypass grafting; cTnI: Cardiac troponin I; ET: Extubation time; N/A: Not applicable; DEX: Dexmedetomidine; GA: General Anesthesia; MI: Myocardial infarction; ICU: Intensive care unit.

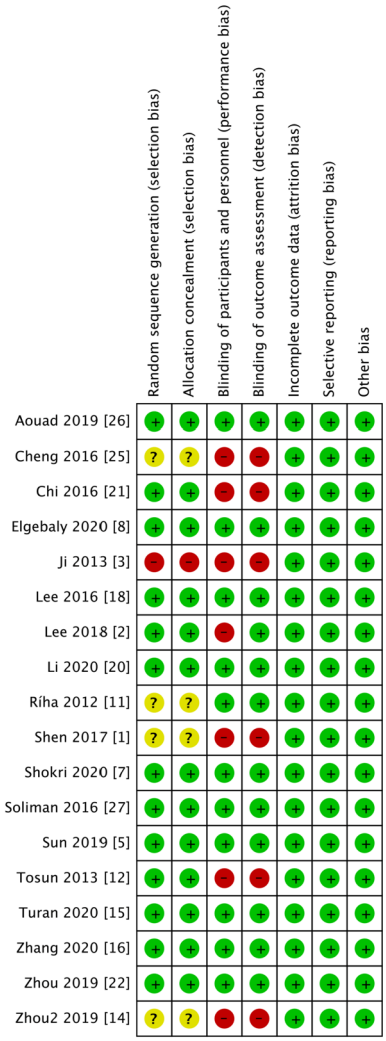

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Figure 2 Risk of bias assessment according to cochrane risk of bias methods.

dexmedetomidine group was significantly lower than that in the control group (Figure 7, RR: 0.63, 95%CI: 0.51-0.76, $P < 0.001$, $I^2 = 0\%$). Low heterogeneity was observed, which we rated as high-quality evidence. We conclude that dexmedetomidine may significantly reduce delirium.

Among the 18 high-quality studies, three studies demonstrated that there was no correlation between the use of dexmedetomidine and postoperative stroke (Figure 7, RR: 1.19, 95%CI: 0.59-2.40, $P = 0.62$, $I^2 = 0\%$). In addition, regarding mortality, the results indicated that the dexmedetomidine group had lower postoperative mortality than the control group (Figure 7, RR: 0.32, 95%CI: 0.18-0.58, $P = 0.0002$). There was low heterogeneity among the studies regarding mortality outcomes ($I^2 = 0$).

Meta-analysis of extubation time and ICU length of stay

Extubation time (ET) was recorded in 4 studies including 484 patients. The results demonstrated that the use of dexmedetomidine in the perioperative period can shorten ET in patients compared to control patients (Figure 8, MD: -2.03, 95%CI: -2.87 to -1.18, $P < 0.001$). With low heterogeneity ($I^2 = 38\%$), it can be deduced that dexmedetomidine shortens extubation time after surgery without subgroup analysis. However, regarding ICU length of stay, there was no statistical difference between the dexmedetomidine and control groups (Figure 8, MD: 0.05, 95%CI: -9.11 to -9.21, $P = 0.99$), and heterogeneity I^2 was also higher at 98%.

DISCUSSION

Dexmedetomidine is a highly selective and effective α2-adrenergic receptor agonist that can provide dose-dependent sedation, anti-anxiety, and moderate analgesia[15], with minimal inhibition of respiratory functions. The central sympathetic nervous system reduces the systemic inflammatory response after surgery and regulates the immune system[5,16,17].

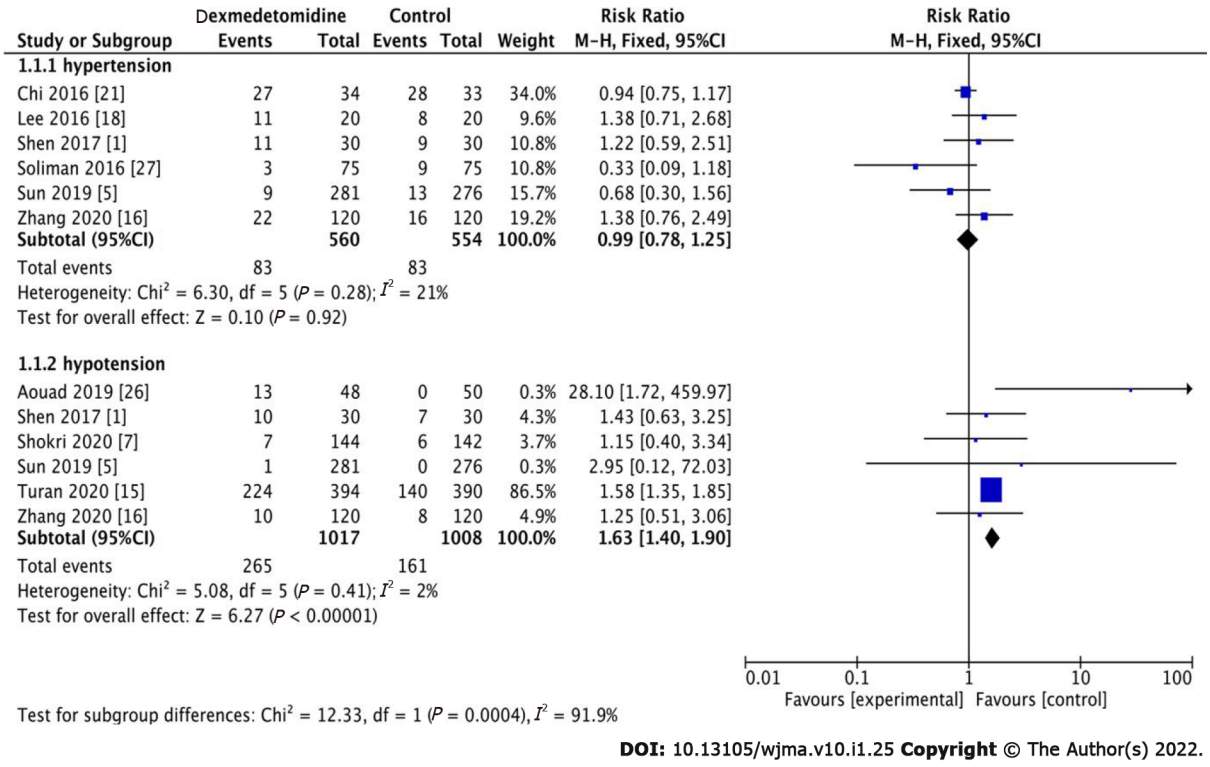

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Figure 3 Meta-analysis of the incidence of hypertension and hypotension during the operation.

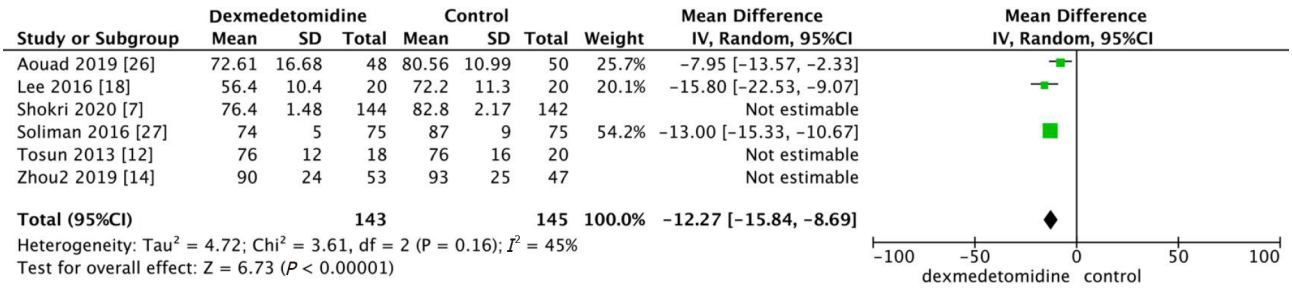

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Figure 4 Meta-analysis of heart rate.

First, we compared the occurrence of intraoperative hypertension and hypotension, and determined that dexmedetomidine could increase the risk of intraoperative hypotension; however, it could also lower than the HR within the normal range. This was attributed to the fact that dexmedetomidine stimulates vascular smooth muscle α2 receptors, thereby resulting in a transient increase in blood pressure and a decrease in HR[18]. Studies have shown that dexmedetomidine has an effective sedative effect in heart and vascular surgeries, minimizes the variability of heart rate and blood pressure, and reduces the response of tachycardia to painful stimulation[6,8,19].

Second, we explored cardiac complications and inferred that dexmedetomidine did not increase the occurrence of myocardial infarction and bradycardia[20]; however, it reduced the expression of cTnI and improved the protection of the myocardium. Studies have demonstrated that more bradycardia was observed in dexmedetomidine, which was the expected result of α2-adrenergic receptor agonists; however, considering that the occurrence of bradycardia was transient, intervention was required, and the proportion of patients was low[21]. In clinical practice, postoperative administration of small doses of dexmedetomidine might be an acceptable and safe strategy for patients in general surgery wards[5].

cTnI is a highly sensitive and specific marker that is adopted as the gold standard diagnostic marker for myocardial infarction in coronary artery bypass grafting (CABG); cTnI is also a significant predictor of the prognosis of patients with heart diseases[14]. The low postoperative cardiac biomarker cTnI exhibited cardioprotective effects of dexmedetomidine[8]. Regarding inflammation, our study determined that dexmedetomidine reduced the expression of TNF-α compared to the control group. Dexmedetomidine provides end-organ protection *via* anti-inflammatory, antioxidant, and anti-apoptotic effects[15]. With several basic effects such as surgical intervention, systemic inflammation, and oxidative

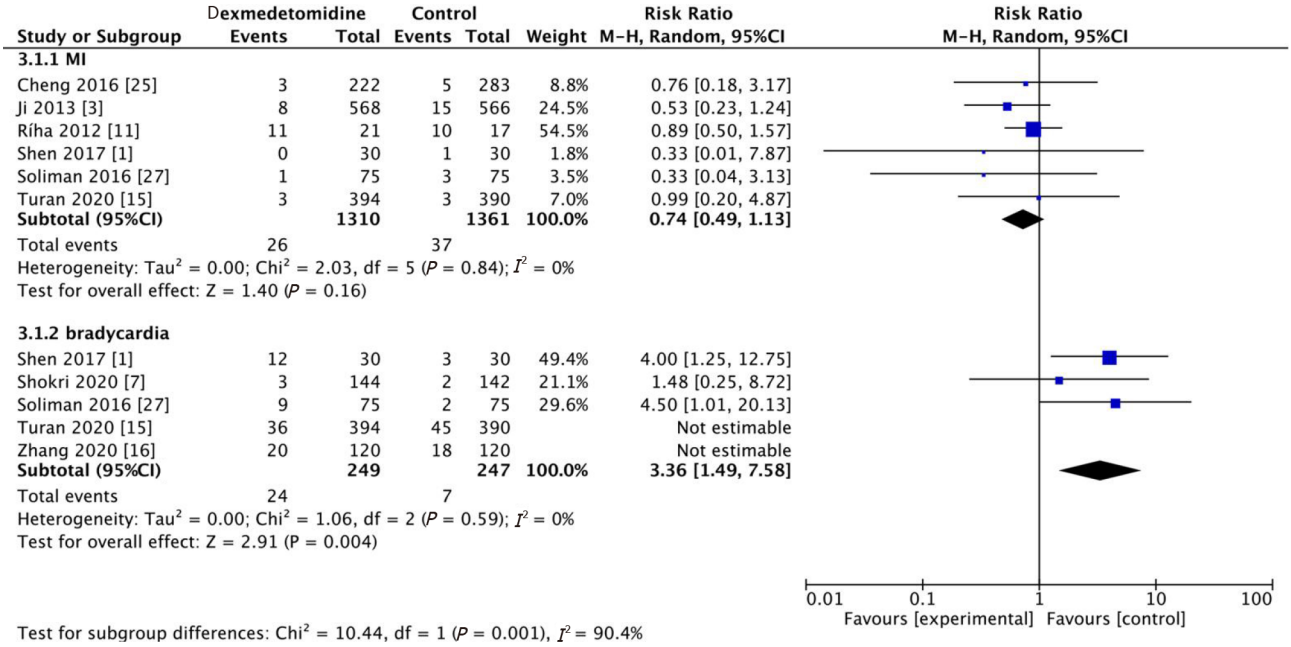

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Figure 5 Meta-analysis of cardiac complications (myocardial infarction and bradycardia). MI: Myocardial infarction.

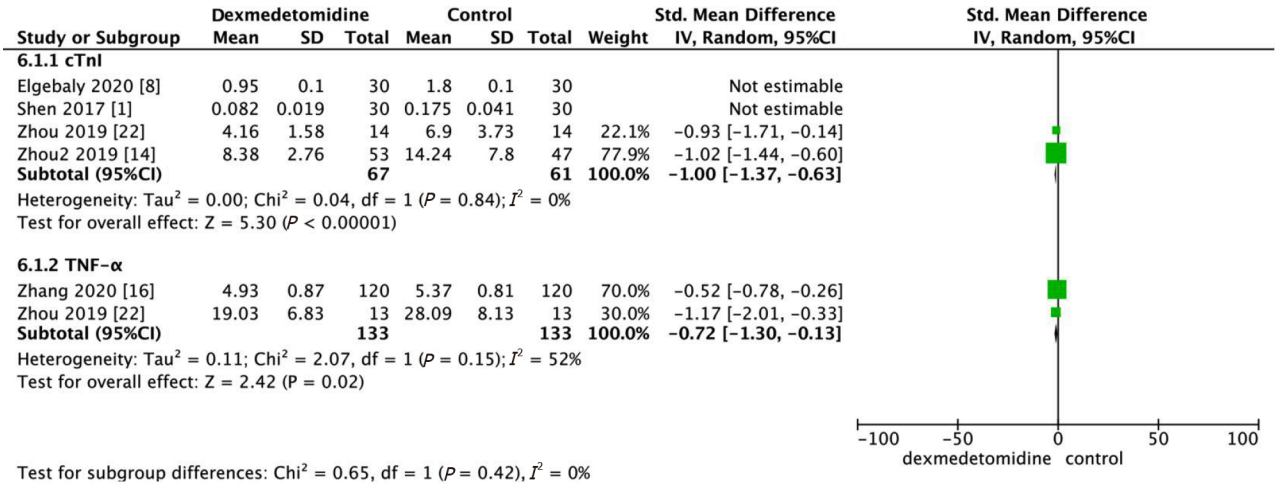

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Figure 6 Meta-analysis of cardiac troponin I (cTnI) (mg/L) and TNF-α (tumor necrosis factor-α) (μl/L).

stress, reperfusion after myocardial ischemia increases myocardial injury and leads to myocardial cell apoptosis[22]. The most well-known mechanisms by which dexmedetomidine reduces inflammation include the NF-kB pathway, Toll-like receptors, and several inflammatory mediators[22], which in turn reduce the demand for opioids and benzodiazepines[15]. Several studies have shown that postoperative inflammation may be the cause of POD[2,15]. We also determined that the occurrence of POD reduced more significantly in the dexmedetomidine group than in control group after surgery. In addition, POD occurs within 3 d after the operation and is affected by memory loss and impaired comprehension[6,23]. Delirium is a frequent postoperative complication in elderly patients after non-cardiac surgery that caused by several stressors, including neurotransmitter imbalance (especially cholinergic deficiency), inflammation, and electrolyte or metabolic disorders[7,15,24]. It has been reported that the incidence of POD in patients undergoing cardiac surgery is 20%-50%, especially in elderly patients admitted to the ICU and patients undergoing orthopedic surgery. This is associated with higher morbidity and mortality, while the longer length of hospital stay is related to ICU time, increased economic burden, and hospital-acquired complications[6,23]. This study also demonstrated that although the use of dexmedetomidine could reduce the postoperative mortality of patients, it did not reduce the risk of postoperative stroke. Studies have also shown that the mortality rate of patients receiving dexmedetomidine in the hospital, 30 d and 1 year later, was significantly reduced[3]. Stroke is a

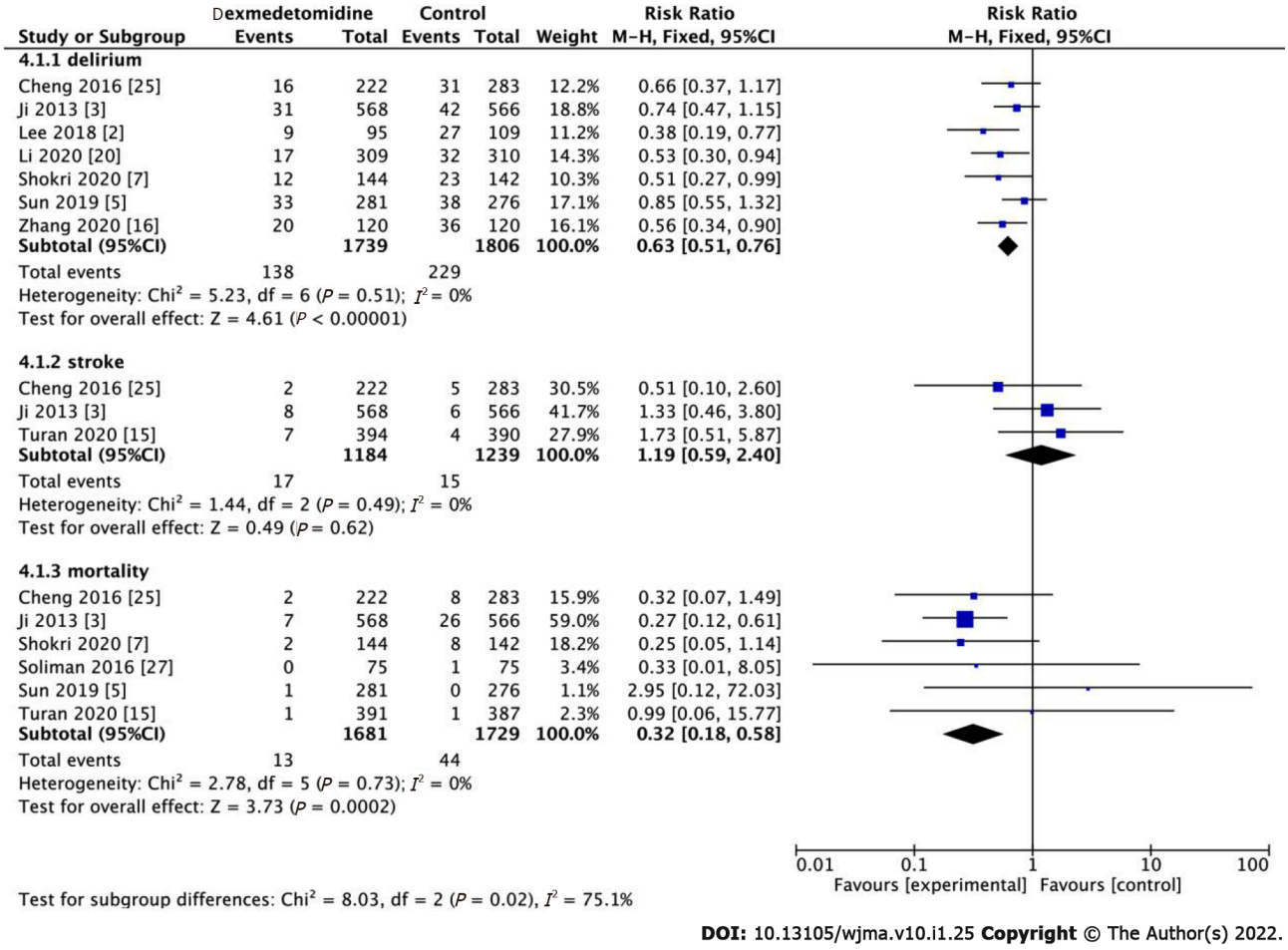

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Figure 7 Meta-analysis of postoperative delirium, stroke, and mortality (In-hospital). POD: Postoperative delirium.

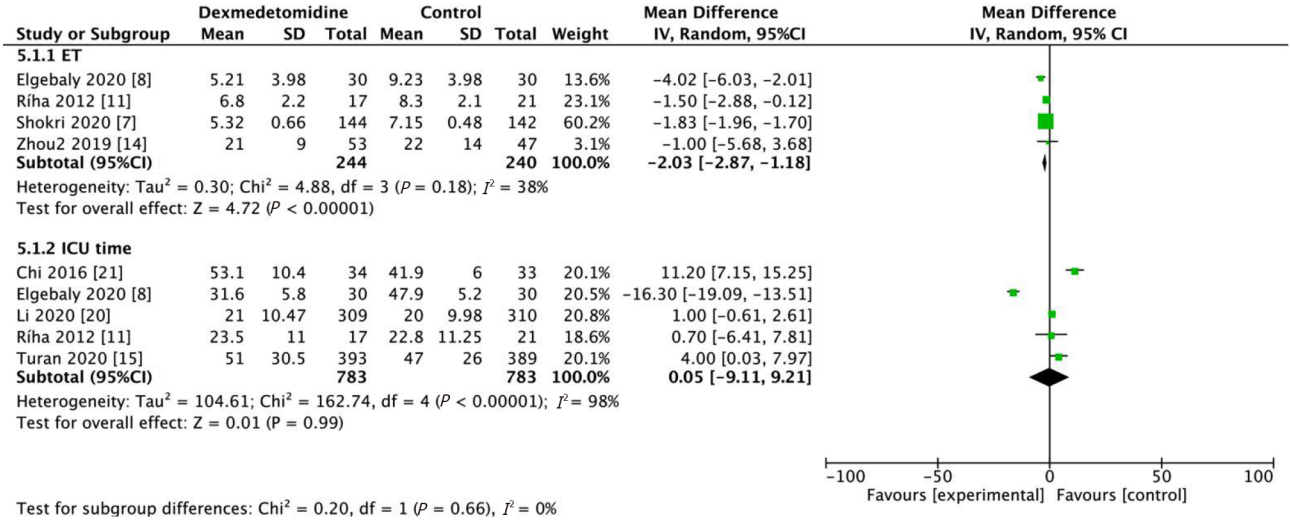

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Figure 8 Meta-analysis of extubation time (h) and intensive care unit length of stay (h). ET: Extubation time; ICU: Intensive care unit.

devastating complication of cardiac surgery. Among patients undergoing different cardiac surgeries, the prevalence of stroke is 1.6%-5.25%[25]; however, the exact cause of postoperative stroke remains unclear. Finally, we found that although the patients receiving dexmedetomidine had a significantly shorter postoperative extubation time than control patients, dexmedetomidine did not significantly shorten the time spent in the ICU. Dexmedetomidine can shorten the time of extubation, which can promote the rapid recovery of heart function in patients[8,9,25-27], reduce the use of psychotropic

drugs, and facilitate recovery from activities as soon as possible.

CONCLUSION

The administration of dexmedetomidine during cardiac and non-cardiac surgeries can provide myocardial protection by inhibiting inflammation and cTnI, which could be beneficial to the rapid recovery of patients. Furthermore, intravenous dexmedetomidine reduces POD and mortality in patients.

ARTICLE HIGHLIGHTS

Research background

There was also a consistent conclusion on whether dexmedetomidine had a protective effect on the heart and improved postoperative complications, for which we conducted a meta-analysis.

Research motivation

It has guiding significance for clinical application of dexmedetomidine on the heart and postoperative complications in elderly patients undergoing cardiac or non-cardiac surgery.

Research objectives

Our main goal is to investigate the effects of dexmedetomidine on cardiac complications and delirium in elderly patients undergoing cardiac or non-cardiac surgery.

Research methods

We collected references to randomized controlled trials examining the efficacy of dexmedetomidine in the treatment of cardiac and postoperative complications.

Research results

Dexmedetomidine significantly reduced the cardiac troponin I and he inflammatory factor tumor necrosis factor-α, and reduced the extubation time, postoperative delirium and mortality. It really brings benefits to patients.

Research conclusions

Dexmedetomidine has cardioprotective effects and improves patient postoperative complications.

Research perspectives

In clinical practice, we will study the effect of dexmedetomidine at an appropriate dose on the heart and postoperative complications which will have certain guiding significance.

FOOTNOTES

Author contributions: Yang YL conceived and designed the study; Yi J, Hu BJ and Duan HW collected the data and performed the literature search; Yang YL was involved in the writing of the manuscript; Pan MZ and Xie PC contributed equally to this work; all authors have read and approved the final manuscript.

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META-ANALYSIS

Leptin levels in women with unexplained infertility: A systematic review and meta-analysis

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Abstract

BACKGROUND

Unexplained infertility (UI) is usually used for any heterosexual couple who failed to have a successful clinical pregnancy without identifying clear causes after they undergo all standard fertility tests. Evidence shows that leptin is one of the most accurate biomarkers for UI. Nevertheless, conflicting results regarding leptin levels in women with UI have been reported.

AIM

To find the serum leptin levels in women with UI.

METHODS

All studies written in English and conducted before April 30, 2021 from PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar, OpenGrey, OATD, and the infertility conference abstract were included. Studies were found eligible if they provided the mean and standard deviation of leptin for the case group and control group. The quality assessment of individual studies was evaluated using the Joanna Briggs Institute Quality Assessment Tool. Data synthesis and statistical analysis were done using STATA software version 16.

RESULTS

A total of 378 studies were reviewed, and just six studies that fulfilled the eligibility criteria were included in this meta-analysis. The pooled result showed that leptin levels were significantly higher in women with UI compared to fertile women, with a standardized mean difference of 0.97 (95% confidence interval: -0.49-2.43). However, heterogeneity across studies was highly significant ($P < 0.00001$; $I^2 = 98.8\%$).

CONCLUSION

The results of this study suggest that leptin levels are elevated in women with UI compared with fertile women; hence, leptin could be a potential biomarker for UI in women, and it may be useful for identifying women with a high risk of infertility.

Key Words: Leptin; Meta-analysis; Serum level; Unexplained infertility; Women

Core Tip: A comprehensive systematic review and meta-analysis was conducted to find the serum leptin levels in women with unexplained infertility. Six studies were included in this meta-analysis, after passing all quality checkups. The pooled result showed that leptin levels were significantly higher in women with unexplained infertility compared to fertile women, with a standardized mean difference of 0.97. Leptin could be a potential biomarker for unexplained infertility in women, and it may be useful for identifying women with a high risk of infertility.

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INTRODUCTION

Reproductive medicine has made many breakthroughs in the field of infertility diagnosis and treatment. Following this breakthrough, many untreated infertility cases now can be treated using one of the advanced reproduction methods such as assisted reproductive technologies[1]. Despite this, some infertility cases cannot still be diagnosed or treated using the current methods, especially in developing countries[2]. This type of infertility is widely known as unexplained infertility (UI)[3].

UI is usually used for any heterosexual couple who failed to have a successful clinical pregnancy without clear causes after they undergo all standard fertility tests[4]. Worldwide, the prevalence of UI ranges from 10% to 37%[2,5-7], and females are found to be responsible for at least 50%. The complexity of the reproductive process especially in females[8], makes it very hard to identify the source of UI. Despite this, many studies have been done to find the pathophysiologic basis and the possible relationship between obesity, endocrinological imbalance, genetic factors, immunological factors, and UI[7,9,10], but unfortunately, till now, the pathophysiology and exact role of these factors and how they contribute to UI have not been fully understood. To overcome this diagnostic issue, many serum biomarkers have been used as predictive markers for UI in females. Out of these biomarkers, leptin was found to be one of the most accurate biomarkers[10,11].

Leptin is an adipokinetic hormone that plays a key role in energy homeostasis and body weight regulation, and acts as a neuroendocrine mediator in different body systems, including the reproductive system[12-15]. Leptin is secreted mainly from adipocyte cells in the white adipose tissues, and altered with obesity[16]. Also, it can be produced from other cells related to the reproductive system in both males and females, such as placental syncytiotrophoblast cells, hypothalamus cells, and pituitary cells [12]. Evidence shows that leptin receptors can be found along the hypothalamic-pituitary-ovarian (HPO) axis of females. Therefore, leptin has direct regulatory effects, both inhibitory and stimulatory depending on its concentration, on all parts of the HPO axis, and all stages of the reproductive process starting from puberty, menstrual cycle, pregnancy, early embryo development, and lactations[13,17].

In the context of reproduction, several scholars have tried to find a relationship between adipose tissue hormones (adipokines) and the female reproductive system in general, and especially between leptin and ovarian functions. Findings have shown that high leptin concentration inhibited ovarian steroidogenesis, folliculogenesis, and oogenesis. The high level of leptin is associated with low levels of ovarian hormones, estradiol, and progesterone, and the poor quality of produced ova[18-20]. Therefore, it may be considered that the concentration of leptin is related to female infertility, and it could explain some cases of female UI. Meanwhile, studies on the association between leptin and UI reported

conflicting results. Some studies showed that serum leptin levels were higher in women with UI compared with the fertile women[11,19-21], whereas other studies showed that there was no significant difference in leptin in women with UI compared to fertile women[22,23]. Thus, this study was aimed to find serum leptin levels in women with UI by conducting a systematic review and meta-analysis in order to quantitatively pool all findings from the relevant studies.

MATERIALS AND METHODS

Inclusion and exclusion criteria

All studies that defined UI based on the World Health Organization standard definition and reported the plasma level of leptin in women with UI and fertile women were eligible for this study. Studies were not eligible for this study if: (1) They were reviews, letters, editorials, or studies using animals or cell lines; (2) No healthy control group was included; or (3) The study enrolled participants who had diseases other than UI, and/or were on any kind of medication.

Information sources

The current study was performed according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[24]. The information was retrieved from electronic and non-electronic database sources. Electronic sources included: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Non-electronic sources included: Direct Google search, Google Scholar, OpenGrey, OATD, WorldCat.org, American Society for Reproductive Medicine and Canadian Fertility and Andrology Society (ASRM/CFAS) Conjoint Annual Meeting, Abstracts of the Scientific Oral and Poster Sessions, and European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting, Abstracts of the Scientific Oral and Poster Sessions. All those databases were searched from their inception to April 30, 2021, for human studies published in English.

Search strategy

The terms AND, OR, and NOT were used as Boolean search terms to develop the research strategy, and the final search strategy included the use of Title/Abstract related to (Women with Unexplained Infertility) AND (Leptin) taken from the study questions. Non-electronic sources were used combined with direct Google search, Google Scholar, OpenGrey, OATD, and WorldCat.org, American Society for Reproductive Medicine and Canadian Fertility and Andrology Society (ASRM/CFAS) Conjoint Annual Meeting, Abstracts of the Scientific Oral and Poster Sessions, and ESHRE Annual Meeting, Abstracts of the Scientific Oral and Poster Sessions. In addition, a manual search by the investigators was done for the grey literature and unpublished thesis/papers.

Selection process

The selection of the studies was done following these steps: (1) All retrieved studies were exported to the EndNote X9 citation manager, to check for duplication, and then the duplicated articles were removed; (2) Three authors (AA, MA, and SO) screened and evaluated the remaining studies independently by carefully reading the title and abstract, and all studies that mentioned the outcomes of the review [(Women with Unexplained Infertility)/Leptin] in their titles and abstracts were considered for further evaluation based on the objectives, methods, participants, and the key findings, serum levels of leptin in women with UI; (3) Two authors (AA and MA) independently evaluated the quality of the relevant studies against the checklist; and (4) Any discrepancy was resolved by discussion between the two authors (AA and MA), or by asking a third reviewer if consensus could not be reached. The selection process of the studies is presented using PRISMA statement flow diagram (Figure 1).

Data collection process

After the selection of all appropriate articles for this study, the relevant data were extracted by two investigators independently (AA and MA) using a data extraction template and presented using Microsoft Word 2016. The investigators contacted the authors of any study who did not report the aforementioned data (*via* email) to obtain the original data and after the expiration of the 2-wk timeline, the studies with the missing data that could not be obtained were removed. The extraction template contained author name, year of publication, study design, method of serum leptin measurement, body mass index (BMI), age, sample size, leptin concentration, and the LH/FSH ratio (Table 1). The data extraction accuracy was verified by comparing the data extraction results from the two investigators (AA and MA), who independently extracted the data in a randomly selected subset of papers (30% of the total).

Data items

The main outcome of this study was the serum leptin levels in women with UI, and it was measured by the direct report from the individual studies. To quantify the outcome "serum leptin levels in women

Table 1 Main characteristics of studies included in the meta-analysis

Ref.	Region	Study design	Method	BMI (kg/m²)		Age, years		Sample size		Leptin (mean + SD), ng/mL		LH/FSH ratio
				UI	Controls	UI	Controls	UI	Controls	UI	Controls	
Tafvizi and Masomi[20], 2016	Iran	Case–control	EIA	23.6 ± 0.27	23.66 ± 0.33	29.3 ± 4.2	31.03 ± 3.76	40	30	31.20 ± 2.83	24.89 ± 2.94	0.85
Al-Fartosy *et al* [21], 2019	Iraq	RCT	EIA	22.3 ± 3	21.7 ± 1.4	29.45 ± 6.38	30.92 ± 5.90	63	33	28.4 ± 1.3	27.2 ± 2.3	0.61
Kamyabi and Gholamalizad [22], 2015	Iran	Case-control	EIA	24.84	22.26	30	29	30	30	27.83 ± 25.29	31.27 ± 11.02	NR
Kumari *et al*[11][1], 2017	Indian	Case-control	EIA	24.1 ± 3.9	24.31 ± 3.19	29.53 ± 4.43	29.58 ± 4.01	120	109	68.9 ± 2.46	37.5 ± 1.84	0.85
Baig *et al*[23], 2019	Pakistan	Case-control	RIA	NR	NR	NR	NR	235	205	35.32 ± 0.9	37.11 ± 1.19	2.16
Demir *et al*[19], 2007	Turkey	PCS	RIA	25	24.5	29.3	28.9	27	30	7 ± 1	3.4 ± 1	1.17

[1]The serum leptin level in the original study was measured in pg, and converted to ng using the standard method.

BMI: Body mass index; EIA: Enzyme-linked immunosorbent assay; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; NR: Not reported; PCS: Prospective comparable controlled study; RIA: Radioimmunoassay; RCT: Randomized control trial; SD: Standard deviation; UI: Unexplained infertility.

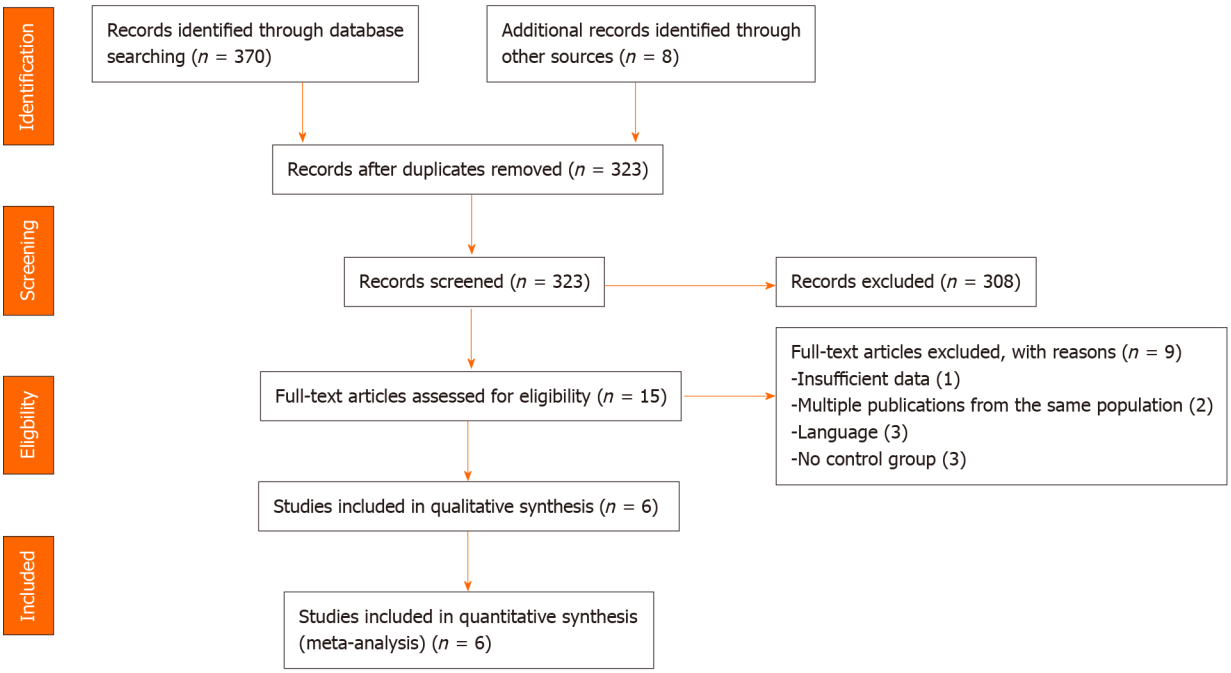

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Figure 1 Flow diagram of the studies included in this meta-analysis.

with UI", the investigators considered studies that reported serum leptin levels in their results. The result is expressed as the mean and standard deviation (SD).

Study risk of bias assessment

The inclusion criteria were appraised for all retrieved articles by using their title and abstract first, and then, the full text was screened to check the quality of each study before the final selection. The following was the quality assessment criteria for the studies in the current review: (1) The diagnosis of female UI occurred after performing all available fertility tests; (2) The sample was representative for the cases and controls; (3) The controls enrolled were taken from the same population; (4) The controls had no any past history of UI; (5) The cases and controls were matched for age or BMI or the two of them together; and (6) The methods which were used to check the serum level of leptin were the same for

cases and controls for each individual study.

A comprehensive search (electronic/database search, manual search, grey literature search, and unpublished studies search) was done to minimize the risk of bias. The risk of bias from the included studies was individually appraised by three investigators (AA, MA, and SO) using a critical appraisal tool (Joanna Briggs Institute Quality Assessment Tool)[25]. The publication bias for the included studies was checked by visual inspection of the funnel plot and checking the statistical symmetry of the funnel plot using Egger's regression test.

Effect measures

In light of the study objectives, the mean difference was used to synthesize and present the results for the analysis.

Synthesis methods

STATA software version 16 was used to synthesize and analyze the meta-analysis data. The recommendations of the I^2 statistic described by Higgins *et al*[26] (I^2 of 75/100% and above suggesting considerable heterogeneity) were used to perform this meta-analysis. The standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for each study, based on the sample size, study mean, and SD of serum leptin levels in the case and control groups.

The potential publication bias was checked using a funnel plot and Egger's regression test, and it was assumed to be significant if P values were less than 0.10. To identify the sources of heterogeneity, meta-regression was performed to evaluate the between-study heterogeneity and to assess the influence of different study features, such as sample size, test method, BMI, and LH/FSH ratio.

The studies were excluded from the final review if: (1) They had missing data; and (2) They had a high risk of bias. The study results were reported according to the PRISMA guidelines and the findings of the included studies are first presented using a narrative synthesis, followed by a meta-analysis chart.

RESULTS

Study selection

As shown in Figure 1, a total of 378 articles were identified through the major electronic and non-electronic databases, and other relevant sources. A total of 55 studies were removed due to duplication, and the remaining 323 studies were kept for further critical screening. From the 323 studies which were kept in the first phase, 308 were excluded after they went through a very careful screening according to their titles and abstracts. From the remaining 15 articles, 9 studies were excluded due to inconsistency with the study inclusion criteria. Finally, 6 studies that fulfilled the eligibility criteria, involving 515 women with UI and 437 controls, were included for the systematic review and meta-analysis.

Study characteristics

The circulating leptin levels in patients with UI *vs* controls were evaluated in all 6 studies. In 4 studies, serum leptin levels were measured by enzyme-linked immunosorbent assay and by radioimmunoassay in the remaining two studies. Two studies were done in Iran, and one in each in Pakistan, Iraq, India, and Turkey. All studies were matched using both BMI and age. However, one study did not report them, but it stated that "the study was matched using BMI and age". In all included studies, the mean range was between 21.7 and 24.8 for BMI, and between 29 and 31 years for age. In addition, some missing information in the original studies was retrieved from the corresponding authors. Table 1 shows the detailed characteristics of all included studies.

Results of synthesis

Figure 2 shows the result of this meta-analysis. The pooled estimate of the included studies showed that leptin levels were significantly higher in UI cases than in controls, with an SMD of 0.97 (95%CI: -0.49 to 2.43). The heterogeneity across studies was highly significant ($P < 0.00001$; $I^2 = 98.8\%$), hence the random effect model was employed for the analysis.

Sensitivity and meta-regression analysis

A sensitivity analysis was conducted by sequentially excluding studies from the meta-analysis to further investigate the possible sources of the heterogeneity among the studies, and the results suggested that the meta-analysis result was stable. In addition, multivariate meta-regression was performed to evaluate the influence of several factors that may modify the association between serum leptin levels and UI, including test method, BMI, sample size, and LH/FSH ratio (adjusted $P = 0.177$, 0.208, 0.997, and 0.15, respectively). However, the results showed that these confounding factors did not substantially affect the heterogeneity. For the test of publication bias, the funnel plots (Figure 3) were visually symmetric and the Egger's test for publication bias yielded a P value of 0.279, hence these results did not provide evidence of a significant effect.

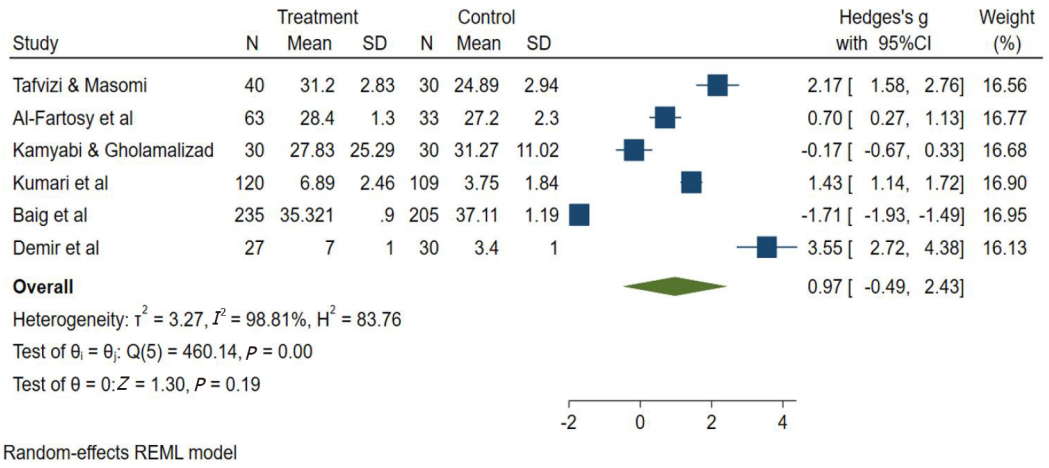

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Figure 2 Forest plot (random-effects model) for circulating leptin levels in women with unexplained infertility.

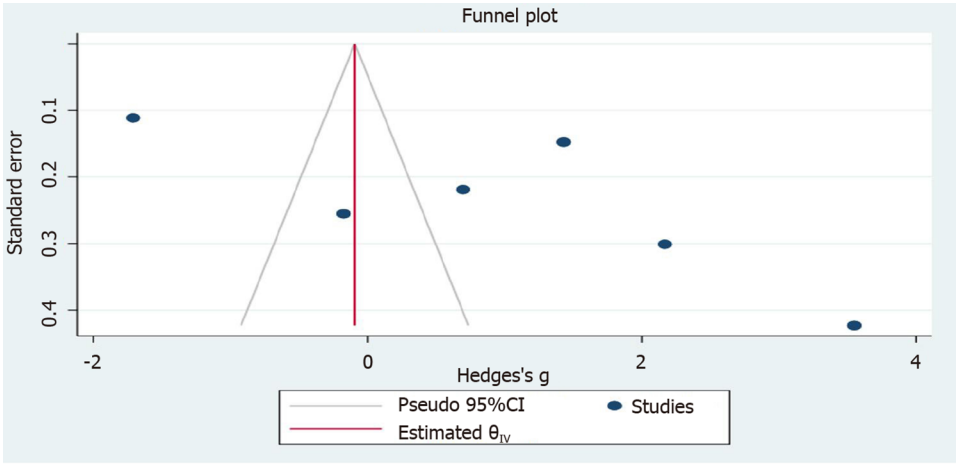

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Figure 3 Funnel plot for publication bias.

DISCUSSION

The term UI emerged due to the fact that the current knowledge on assessment and treatment of the reproductive system is still inadequate[3]. Many studies have been carried out to find the exact cause of UI and the best diagnostic biomarker. However, leptin has been found as one of the best biomarkers. Leptin displays biological activities by binding and activating specific leptin receptors, which are found in many organs including the hypothalamus-pituitary-ovarian axis (HPO axis) in females. Leptin plays a role in the function of the HPO axis by stimulating the release of gonadotrophin-releasing hormone, gonadotrophins, and aromatase enzymes from the hypothalamus, pituitary gland, and ovaries, respectively[13,15,17,27,28]. Also, the available evidence indicated that a high level of leptin has negative effects on female reproduction due to its inhibitory effect on the HPO axis, ovarian physiology, folliculogenesis, steroidogenesis, and the production and release of oxytocin and prostaglandin[29-32]. In line with available evidence, the current study showed that leptin level was significantly higher in women with UI compared with the control group. Similar results were found when leptin concentrations were pooled in endometriosis and polycystic ovary syndrome (PCOS) cases, pathological conditions with a strong correlation with infertility. In these studies, leptin levels were higher in women with endometriosis and PCOS groups compared with control groups[33,34].

Studies have suggested that factors like age and BMI have effects on leptin levels, and usually have a positive correlation with female infertility[35,36]. However, in the present study, all the included studies were matched by both age and BMI, and because of that, the effect of age and BMI on leptin level was not examined.

This is the first comprehensive quantitative meta-analysis summarizing available evidence to determine the serum leptin level in women with UI.

CONCLUSION

The results of this meta-analysis suggest the presence of elevated levels of leptin levels in women with UI compared with fertile women. Hence, leptin could be a potential biomarker for UI in women, and it may be useful for identifying women at a high risk of infertility. However, further investigations need to be carried out in order to clarify the exact association between leptin levels and UI.

ARTICLE HIGHLIGHTS

Research background

Despite many breakthroughs in the field of infertility diagnosis and treatment, there are still some infertility cases with unknown causes (unexplained infertility). To overcome this diagnostic issue, many serum biomarkers have been used as predictive markers for unexplained infertility in females.

Research motivation

Leptin is one of the most accurate biomarkers for unexplained infertility. Nevertheless, conflicting results regarding leptin levels in women with unexplained infertility have been reported.

Research objectives

The objective of this study was to conduct a systematic review and meta-analysis to find the serum leptin levels in women with unexplained infertility.

Research methods

A systematic literature search was conducted before April 30, 2021 from PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar, OpenGrey, OATD, and the infertility conferences abstract.

Research results

A total of six articles were included in this meta-analysis after 15 articles had been subjected to full-text evaluations.

Research conclusions

Leptin could be a potential biomarker for unexplained infertility in women.

Research perspectives

The effect of other adipokines should be evaluated in future studies to find their possible relation with female infertility.

FOOTNOTES

Author contributions: Abdullah AA, Ahmed M, and Oladokun A conceived and designed the review, developed the search strings, screened and selected the studies, and drafted the manuscript, and Oladokun A rigorously reviewed the manuscript; Abdullah AA is the guarantor of the review; Abdullah AA and Ahmed M extracted the data, evaluated the quality of the studies, and carried out analysis and interpretation.

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MINIREVIEWS

Is there a role for liver transplantation in the treatment of hepatocellular carcinoma in non-cirrhotic liver?

Luis Cesar Bredt, Ingryd Betina Garcia Felisberto, Doroty Eva Garcia Felisberto

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Abstract

Whether liver transplantation (LT) plays a role in the treatment of patients with hepatocellular carcinoma (HCC) in non-cirrhotic liver (NCL) is a matter of debate. The recommendations for LT in this setting are extremely fragile and less well-defined than for cirrhosis-associated HCC. All reports of LT for NCL-HCC revealed that long-term outcomes of these patients are poor, and these dismal figures are justified by the advanced tumor stage at the time of LT, suggesting the presence of systemic micrometastatic disease. The decision-making regarding LT for NCL-HCC is difficult, since specific selection criteria are scarce, and basically the potential candidates are those with unresectable only-liver tumor at admission, or unresectable intrahepatic recurrence post-resection. Besides the surgical aspects regarding the tumor resectability, other phenotypic and genetic characteristics of the tumor should be considered for the indication of LT in this scenario. The present minireview aims to discuss and analyze the last series of LT for NCL-HCC, in order to help clinicians in the decision-making process regarding the role of LT in NCL-HCC treatment.

Key Words: Liver transplantation; Non-cirrhotic liver; Liver; Cancer; Hepatocellular carcinoma; Treatment

Core Tip: The present manuscript aims to discuss and analyze the last series of liver transplantation for hepatocellular carcinoma in non-cirrhotic liver, with a special focus on the indications, prognostic factors and long-term outcomes, in order to help clinicians in the decision-making regarding the role of liver transplantation in the non-cirrhotic liver –hepatocellular carcinoma scenario on the basis of these analyses.

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INTRODUCTION

Hepatocellular carcinoma (HCC) occurs mainly in patients with liver cirrhosis, leading to chronic necroinflammation and hepatocellular regeneration. Nevertheless, HCC can arise in non-cirrhotic liver (NCL) in a proportion of cases that ranges widely from 7% to 54% across the geographic areas and according to the etiology of the liver disease[1-6]. The male predominance is less marked for HCC on NCL (75% men) than HCC on cirrhosis (85% men), and this sex ratio is equal in patients younger than 50 years[7]. These epidemiological data can be extrapolated for fibrolamellar (FL) HCC variant[8,9].

Authors have hypothesized distinct hepatocarcinogenesis in HCC with and without cirrhosis, although it would be an oversimplification to assume that NCL-HCC would occur in a totally healthy liver, because there is a wide range of parenchymal pathology without cirrhosis. In the last decades there was a progressive expansion of non-viral cases and namely of metabolic HCC in non-cirrhotic patients[10]. It has been reported that the role of alcohol intake is an independent predictor in non-cirrhotic subjects with chronic hepatitis B virus infection of HCC development[11] and an extremely variable HCC recurrence risk and survival in successfully treated hepatitis C virus-infected patients [12]. Therefore, the histological background of NCL-HCC can include liver steatosis, hepatitis, genotoxic substances, metabolic diseases, germline mutations, and liver adenomas[13].

In general, NCL-HCC is detected at an advanced stage, and the diagnosis is made when clinical symptoms and signs related to the enlarged lesion appear, such as pain and abdominal discomfort, and a palpable tumor have occurred. Whereas the clinical presentation can be aggressive, distinct from HCC that occurs in a cirrhotic background, the preserved liver function in NCL-HCC scenario allows more extensive liver resections. Despite these high rates of R0 resections, the outcomes are dismal, and may be theoretically justified by the presence of systemic micrometastatic disease[14].

Differently from the extensive experience of referral centers with liver transplantation (LT) for the treatment of HCC in cirrhotic liver, the LT criteria for the treatment of NCL-HCC is not sharply defined, and actually is basically limited to situations in which resection is not possible. Moreover, while the survival rates of the larger group of HCC patients with cirrhosis treated with LT has been extensively published, there are few retrospective series regarding the prognosis and long-term survival evaluation of NCL-HCC after this treatment.

The present minireview aims to discuss and analyze the last series of LT for NCL-HCC, with special focus on the indications, prognostic factors and long-term outcomes, in order to help clinicians for decision-making regarding the role of LT in the NCL-HCC scenario on the basis of these analyses.

TECHNICAL RESECTABILITY DETERMINATION

Despite the enlarged tumor burden, the preserved function of NCL generally offers the chance of performing extended liver resections safely, with totally acceptable perioperative mortality (0%–6%) and morbidity (8%–40%) of these patients[15-17].

One of the cornerstones for the indication of primary or rescue LT for NCL-HCC relies on the tumor's unresectability. The assessment of resectability differs from HCC in cirrhosis since the liver parenchyma is healthy or only minimally diseased. More extensive resections are feasible, therefore the resectability rates are higher. On the other hand, these tumors are often very bulky at presentation and are prone to vascular invasion of large vessels.

The surgical treatment strategy for both resection and LT should be directed towards R0 resection whenever possible, with both 'oncological' (prognostic) and 'technical' (surgical) criteria being considered. The technical unresectability does not always mean that the LT is indicated, because unfavorable prognostic criteria may preclude patients from succeeding even with LT.

Initially the first attempt would be the work-up for any evidence of extrahepatic disease, such as metastasis to lymph nodes, lung, or bone, that would be a formal contra-indication for both resection and LT. The evidence of homolateral or contralateral satellite nodules denotes widespread intra-hepatic

dissemination. It is crucial that an accurate assessment of tumor vascular relationships, the evaluation of the intersection of the hepatic veins with the inferior vena cava must be done, and an eventual tumoral thrombus in the portal vein trunk or branches may preclude the resection. Finally, the quality of the underlying liver parenchyma should be accessed with estimation of the future liver remnant, that would be insufficient despite no underlying cirrhosis[18].

LONG-TERM OUTCOMES AFTER LT FOR NCL-HCC

For all the wide indications of LT, they must have comparable outcomes. If a strict disease does not, then it must cause no undue prejudice to other recipients with a better prognosis[19]. The Milan criteria conception is the ideal example for this statement, and the current benchmark for LT for HCC in cirrhotic patients, because the overall 5-year survival rate of 65%–78% for Milan-in patients[20] is similar to 70%–82% survival for benign indications. In general, a 5-year overall survival rate of > 50% is recommended by the liver-transplant community in the face of liver grafts scarcity[21]. Thus, the indication of LT for NCL-HCC must be comprehensively analyzed.

Liver resection is currently the best upfront therapy for NCL-HCC[22-24]. However, in this section the role of LT in the setting of unresectable HCC at presentation or because of tumor recurrence following resection will be discussed. There is limited literature that reports the long-term survival of the subgroup NCL-HCC patients treated by LT, and the available series (Table 1) have limitations, mainly because of its retrospective and eventually multicenter design, and in some cases the reduced number of patients.

A systematic review that included all very early reported cases of LT for NCL- HCC from 1966 to 1998 revealed poor long-term outcome of these patients. The 5-year survival rates were 11.2% for non-FL-HCC and 39.4% for FL-HCC[24-26]. In the most recent series with 105 NCL-HCC transplant patients reported by Mergental *et al*[27] a 5-year overall survival of 49% was observed. For 62 patients, LT was the primary treatment with a 5-year overall survival of 43%, and for 43 patients, LT was a rescue treatment after resection, with a 5-year overall survival of 58%. Pathological data showed more favorable tumor characteristics in the rescue-LTs compared to primary-LTs (TNM staging, median size of largest tumor, number of patients Milan-in, and number of patients with serum alpha-fetoprotein level < 100 ng/mL). Rescue-LT within 12 mo after resection was the significant predictor for long-term survival.

A specific question must be addressed regarding FL-HCC, which historically the patients with FL-HCC appear to have a better prognosis, as shown by Houben and McCall[24]. Kakar *et al*[28] clearly showed that the outcomes of FL-HCC and NC-HCC are similar when same-stage diseases are considered and when the proliferative activities of these tumor variants (Ki-67) are similar[23,26]. Enlarging cohorts, including non-FL and FL-HCC with no distinction, would allow better predictions of the role of LT in patients with NCL-HCC. The analysis of the larger will be a major step forward to a better insight of the indication for LT in this scenario[14].

SELECTION OF CANDIDATES FOR LIVER TRANSPLANTATION

The risk factors for recurrence rate after resection could be very helpful in identifying NCL-HCC candidates for LT[14]. Authors have already hypothesized tumor characteristics that would be potential prognostic factors for recurrence after LT (Table 2). The small number of patients within these series, however, leads the conclusions from these studies to be handled with caution.

According to Mergental *et al*[29], lymph node invasion and macrovascular invasion were suggested to be the main predictors of recurrence after LT. Later, the same author also showed that a time period of less than 12 mo between the previous resection and tumor recurrence was a significant risk factor for poor survival. This short time span probably would reflect a more aggressive biology[27].

Data on 4373 non-cirrhotic HCC patients who underwent LT for NCL-HCC from a large database were analyzed using logistic regression model and life table methods. The identified factors that significantly related to survival were the total number of tumors, extrahepatic disease, nodal involvement, satellite lesions, vascular invasion, tumor grade and pre-LT treatment[30].

The identified variables for poor prognosis in the published studies are based on the pathological analysis of the explanted livers. Furthermore, the goal would be the evaluation of the predictors before the LT indication, such as tumor imaging at listing, lymph node involvement, the response to previous treatments, and the kinetics of the tumor growth. In the case of rescue-LT patients, the imaging characteristics before resection and the pathological characteristics of the resected tumor are crucial to assess candidates for LT at the time of recurrence[19].

The suggested favorable prognostic factors[19,23,27] such as alpha-fetoprotein level (< 100 ng/mL), tumor number (< 4), tumor diameter (< 5 cm) and no vascular and node involvement assessed on imaging at listing, would refine the selection of patients for LT for NCL-HCC, decreasing therefore, eventual futile procedures.

Table 1 Selected series that addressed the long-term survival of patients with non-cirrhotic liver - hepatocellular carcinoma treated with primary or rescue liver transplantation

Ref.	HCC variant	*n*	Recurrence rate (%)	5-year OS (%)
Pichlmayr *et al*[22], 1995	FL	36	38.0	49.0
Pinna *et al*[23], 1997	FL	13	69.2	36.3
Schlitt *et al*[25], 1999	FL	25	NR	27.0
El-Gazzaz *et al*[26], 2000	FL	9	44.0	50.0
Mergental *et al*[27], 2012	NS	105	48.5	53.5

HCC: Hepatocellular carcinoma; OS: Overall survival; FL: Fibrolamellar; NR: Not reported; NS: Not specified.

Table 2 Series of patients with hepatocellular carcinoma in non-cirrhotic liver treated with liver transplantation with reported risk factors for poor prognosis

Ref.	Risk factors
Pichlmayr *et al*[22], 1995	> 1 tumor; lymph node invasion
Pinna *et al*[23], 1997	Tumor stage; macrovascular invasion; lymph node invasion
El-Gazzaz *et al*[26], 2000	Tumor stage
Mergental *et al*[27], 2012	Macrovascular invasion; lymph node involvement; time interval between resection and LT < 1 yr

LT: Liver transplantation.

PROGNOSTIC GENETIC INFORMATION ON NCL-HCC

Recently, genetic information regarding NCL-HCC prognosis can ultimately aid the selection of candidates for LT. Clinical data analysis indicated that increased PKM2 expression in NCL-HCC was correlated with tumor vascular invasion and intrahepatic metastasis, and positive PKM2 expression was an independent poor prognostic factor for recurrence[31]. Some studies have found that the level of activity regulator of SIRT1 in NCL-HCC is significantly correlated with tumor size, vascular invasion, and tumor differentiation, consequently with disease-free survival rates[32].

MiRs are 18–25 nucleotide noncoding RNAs that can regulate gene expression. A high expression of hsa-mir-149 was found to be a risk factor for poor prognosis, and an increased hsa-miR-23c expression was associated with improved survival in patients with HCC-NCL[33]. Similarly, miR-21 levels are generally increased in HCC-NCL[33,34].

CONCLUSION

The recommendations for LT in this setting of NCL-HCC are fragile and less well-defined than for cirrhosis-associated HCC. The decision-making for LT is still difficult, since specific selection criteria are scarce. Resection must be the upfront therapy for these patients, and LT must be offered only for patients with recurrence after resection or with unresectable disease at presentation. However, besides technical unresectability, other phenotypic and genetic characteristics of the tumor should be considered for selecting patients for LT in the NCL-HCC scenario, avoiding futile procedures.

FOOTNOTES

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META-ANALYSIS

Different methods of acupuncture for relief of pain due to liver cancer: A network meta-analysis

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Abstract

BACKGROUND

Pain in the liver is a common symptom of liver cancer in late stages, and the pain incidence rate exceeds 50%[1]. In serious cancer pain, morphine and other major analgesics have been commonly administrated for clinical treatments, and their effects are accurate, but with a high incidence of side effects, such as nausea, vomiting, constipation, and other conditions. Acupuncture is a traditional Chinese medicine therapy. There have been many randomized controlled trials addressing the safety and usefulness of different methods of acupuncture in alleviating liver cancer pain. However, which of these methods is the most effective method is still unclear.

AIM

To compare the effectiveness of different acupuncture methods for alleviating pain due to liver cancer.

METHODS

Eligible studies were retrieved from eight databases (the Cochrane Library, PubMed, EMBASE, Medline, CNKI, CBM, Chongqing VIP, and Wan Fang Database) up to March 31, 2021 and screened based on the established inclusion and exclusion criteria. The quality of the include studies was evaluated. Stata software was applied for statistical analyses. Publication bias of the included studies was also determined. Finally, the network meta-analysis was carried out to evaluate the efficacy of acupuncture methods for relief of pain due to liver cancer.

RESULTS

A total of eight randomized controlled trials were included in the network meta-analysis. Eight trials (covering 5 treatments and 734 patients) provided data

suitable for analysis. Most trials focused on short-term effects and many were classed as being of poor quality with a high risk of bias, commonly associated with lack of blinding (which was sometimes impossible to achieve). End of treatment results showed that four interventions, including wrist-ankle acupuncture, triple puncture and remaining needle acupuncture, Tian Yuan acupuncture, and block acupuncture, produced a statistically significant reduction in pain when compared with the three-step analgesic ladder therapy. The surface under the cumulative ranking sorting results showed that triple puncture and remaining needle acupuncture had a relatively high effective rate.

CONCLUSION

The network meta-analysis results indicate that the overall effectiveness of triple puncture and remaining needle acupuncture is better than the other therapies.

Key Words: Pain; Liver cancer; Acupuncture; Network meta-analysis; Effectiveness; Three-step analgesic ladder

Core Tip: Seventy-five percent of patients with liver cancer suffer varying degrees of pain. Pain is widely perceived as the fifth vital sign in cancer patients, which seriously affects the quality of their life and threatens their survival. Acupuncture, part of traditional Chinese medicine, involves the application of needles, heat, pressure, and other treatments at specific sites of the body known as acupoints to affect the physical functions of the body. Numerous studies have concluded that acupuncture may be efficacious in relieving cancer-related pain. However, there is still no direct evidence on which method of acupuncture is more effective. The present study aimed to identify the best method of acupuncture for liver cancer-related pain.

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INTRODUCTION

According to the GLOBOCAN 2012, primary liver cancer is the fifth most common cancer and the third most common cause of cancer mortality worldwide[2]. More than 1 million individuals are diagnosed with this disease each year, and over 250000 patients die annually due to disease progression[3,4]. In China, primary liver cancer is the second most common malignancy, with 360000 incident cases and 350000 deaths a year currently reported[5]. With people's growing emphasis on health and advances in medical technology, the early screening and treatment of liver cancer have extended the lives of many patients. However, cancer pain brings physical suffering to patients and makes them anxious, desperate, and depressed. In addition, this further aggravates the cancer pain, resulting in a vicious circle. The current clinical treatment for cancer pain is mainly in accordance with the World Health Organization (WHO) recommended three-step analgesic ladder, under which 70%-90% of cancer pain can be relieved [6]. Nevertheless, anesthetic adverse effects, drug resistance, addiction, and other issues associated with the use of opioid analgesics have limited their clinical use. Thus, the identification of an effective treatment for relief of cancer pain with fewer toxic or adverse effects will radically improve quality of life and benefit most patients with cancer pain. Acupuncture analgesia is a traditional Chinese medicine therapy that has the advantages of safety, effectiveness, and no adverse effects and plays an important role in the treatment of cancer pain. Current clinical research shows that acupuncture combined with other therapies can effectively relieve the pain, reduce the adverse effects of Western medicine, and improve the quality of life of patients with primary liver cancer. By using network meta-analysis (NMA), both direct and indirect randomized data can be analyzed, and recommended rankings of different treatments can be provided[7,8]. Therefore, we conducted an NMA to analyze both direct and indirect comparisons of different methods of acupuncture for the relief of pain due to liver cancer. Based on the current evidence, we sorted and explored the advantages and disadvantages of different methods of acupuncture. Compared with traditional meta-analysis, the results of this study may provide a higher quality basis and reference for acupuncture treatment of pain due to liver cancer.

MATERIALS AND METHODS

This NMA was based on the international guidelines for conducting and reporting systematic reviews, as applied to NMA[9,10].

Search strategy

PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, Wan Fang Database, Chongqing VIP, and Chinese Biomedical Databases were searched from inception to March31, 2021. Randomized controlled trials (RCTs) associated with pain due to liver cancer and cancer were retrieved. The specific search strategy, which adopted a combination of subject words and free words, was made based on the Cochrane Handbook for Systematic Review of Interventions (version 5.1.0)[11]. (Liver Neoplasms, or Neoplasm or Liver Neoplasm or Hepatic neoplasm or Cancer of Liver or Hepatic Cancer or Liver Cancer or Hepatoma or Hepatocellular Carcinoma or HCC) and (Pain or Suffering or Ache) and (Acupuncture Therapy or Acupuncture or Acupuncture Points or Acupuncture Analgesia or Electro-acupuncture or Moxibustion or Acupotom or Electro-acupuncture or Electro-acupuncture or Needling or Acupoint) was used as the search strategy for Chinese and English databases.

Study selection

Two reviewers independently identified relevant studies based on titles and abstracts. In addition, full-text articles were scanned by these reviewers to identify eligible studies. All disagreements were resolved by consensus and adjudged by a third reviewer if necessary. In the case of duplicate citations, the most updated study was selected for data extraction.

Inclusion and exclusion criteria

The studies included in the review should met the following criteria: (1) The study design must be RCT; (2) Patients diagnosed with liver cancer irrespective of age and sex were enrolled; diagnostic criteria must be clear and inclusion and exclusion criteria were explicit; (3) All subjects had moderate to severe pain; (4) According to the cancer pain improvement standard of the WHO, the analgesic effects of the treatments were classified into four levels: Complete remission (CR; completely pain-free); partial remission (PR; substantial relief of pain and generally normal sleep); mild remission (MR; moderate relief of pain with residual pain and sleep disturbance); no remission (NR; no relief of pain). Usually, CR and NR are relatively easy to judge, whereas PR and MR are less well defined. CR and PR were considered effective; (5) Participants in the experimental group have received acupuncture treatments; and (6) English or Chinese language studies were included. The following studies were excluded: (1) Self-controlled and non-RCT studies; (2) Preclinical studies, systematic reviews, case reports, and meta-analyses; (3) Reports without sufficient or clear original data; and (4) Duplicate studies and studies reporting the same results.

Data collection and quality assessment

We used the risk of bias tool recommended by the Cochrane Handbook to evaluate the quality of included studies. The items considered were as follows: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Complete outcome data; (6) Selective reporting; and (7) Company funding. The possible answers to items 1–5 were 'yes' (representing low risk), 'no' (representing high risk), or 'unclear' (representing unclear risk). For item 6, 'yes' represented high risk, 'no' represented low risk, and 'unclear' represented unclear risk. Furthermore, grading of recommendation assessment, development, and evaluation (GRADE), which included five aspects (study limitation, indirectness, inconsistency, imprecision, and publication bias), was used to evaluate the quality of evidence contributing to each comparison and the overall ranking of treatment.

Statistical analysis

Stata16.0 software was used to create the network evidence graph that displays the basic information of interventions under each type of outcome indicators. Each node represents an intervention, the size of the node represents the sample size of the intervention, and the connection between the nodes represents the number of included studies under the intervention. As the outcome index of this study was a binary variable, the comparison results are expressed as relative risk. According to the ranking probability of each intervention, the best intervention could be identified.

RESULTS

Literature retrieval

A total of 5889 related studies were searched initially, and 2002 duplicate publications were excluded using Endnote X7 software. Three hundred and sixty-nine studies were initially screened out by

scanning the title and abstract. Thereafter, 49 studies that may have met the criteria were read in detail. Finally, eight RCTs with a total of 734 patients, including four studies on wrist–ankle acupuncture, one on triple puncture and remaining needle acupuncture, one on Tian Yuan acupuncture, and three on block acupuncture, were selected (Figure 1).

Basic characteristics and quality evaluation of the included studies

Of the eight articles selected, all provided statistical analysis of the age and gender of the patients, and five reported the visual analog scale scores. All studies mentioned the random grouping method, and there were no incomplete reporting data or selective reporting results, but the allocation hiding and blind methods were not described in detail. Therefore, the overall quality of the literature was fair (Table 1, Figure 2)

Network meta-analysis results of pain treatment in patients with liver cancer under different measures

The NMA of the response rate under different measures of treatment was tested for consistency, and the results showed that $P > 0.05$, so the consistency model analysis was used. The results of the NMA showed that the response rate to triple puncture and remaining needle acupuncture in treating pain in patients with liver cancer was higher than that to three-step analgesic ladder therapy, wrist-ankle acupuncture, and block acupuncture, and the differences were statistically significant ($P < 0.05$); the response rate to Tianyuan acupoint acupuncture in treating pain in patients with liver cancer was significantly higher than that of three-step analgesic ladder therapy and wrist-ankle acupuncture ($P < 0.05$); the other pairwise comparisons between the interventions showed no statistical significance. The result of ranking the probability that one intervention is the best treatment is as follows: Triple puncture and remaining needle acupuncture (88.8%) > Tianyuan acupoint acupuncture (84.8%) > block acupuncture (45.0%) > wrist-ankle acupuncture (17.7%) > three-step analgesic ladder therapy (14.1%), suggesting that triple puncture and remaining needle acupuncture may be the most effective measure for the treatment of pain in patients with liver cancer (Figures 3-5, Tables 2 and 3).

Nodal analysis

There were no results of nodal analysis and ring inconsistency testing as the network evidence graph does not form a closed ring.

Publication bias and small-sample effect assessment

A funnel plot of treatment response rate is drawn, and each point on the funnel plot is scattered and not completely symmetrical, suggesting that there may be a small publication bias. The funnel plot of the response rate has scatter points distributed at the bottom of the funnel, suggesting the presence of a small sample effect (Figure 6).

DISCUSSION

The aim of this study was to identify the effectiveness or different methods of acupuncture for relief of pain due to liver cancer. In this NMA, the association of each acupuncture and related therapies with relief of pain due to liver cancer was compared using the combination of direct and indirect evidence from eight RCTs with 734 patients. An NMA provides a basis for synthesizing all the available evidence in a consistent framework, obviating the need to make decisions by subjective inferences from disparate data. However, our analysis represents the use of the most practical methods currently available to compare a large number of different types of treatment, thus enabling us to compare different methods of acupuncture with each other. In this study, we found that triple puncture and remaining needle acupuncture had the highest effectiveness.

Acupuncture may be useful in controlling the pain experienced by many cancer patients. It is a complementary and conservative therapy that balances the flow of vital energy, and in turn helps to relieve pain. It is an analgesic adjunctive method for cancer patients that is worthy of additional high quality studies[12-14].

Danxixinfa holds that meridians blocked by qi stagnation and phlegm are involved in the pathogenesis of cancer pain. Xuezhenglun attaches significance to cancer pain attributed to blood stagnation. Professor Zhong-Ying Zhou, a master of traditional Chinese medicine, proposed the cancer virus theory[15], and pointed out that under the action of internal and external factors, cold and heat stagnation is produced in the body, and then produces 'poison', and over time cancer develops. Pain due to liver cancer can be divided into excess pain and deficiency pain. Excess pain means that external pathogens invade the body and compete in the body or accumulate in the liver meridians, resulting in disorder of qi movement; furthermore, impairment of blood circulation occurs, and finally blood stasis blocks meridians, and stagnation leads to pain. Deficiency pain is caused by a prolonged illness, in other words, the deep presence of pathogenic qi impairs the healthy qi, then the deficiency of qi and blood

Table 1 Main characteristics of the selected articles

Ref.	Cases (observation group/control group)	Treatment measures	Control measures	Evaluating indicator
Zeng *et al*[18], 2014	30/30	Wrist ankle acupuncture	Three step analgesic ladder therapy	Degree of pain relief
Liu *et al*[18], 2010	51/51	Block acupuncture	Three step analgesic ladder therapy	Degree of pain relief/VAS score
Liu *et al*[18], 2007	30/30	Block acupuncture	Three step analgesic ladder therapy	Degree of pain relief/VAS score
Liu *et al*[21], 2008	51/51	Block acupuncture	Three step analgesic ladder therapy	Degree of pain relief/VAS score
Sun *et al*[22], 2021	80/60	Triple puncture and remaining needle acupuncture	Three step analgesic ladder therapy	Degree of pain relief
Hu *et al*[22], 2004	36/50	Wrist ankle acupuncture	Three step analgesic ladder therapy	Degree of pain relief
Hu *et al*[22], 2005	36/40	Wrist ankle acupuncture	Three step analgesic ladder therapy	Degree of pain relief
Cai *et al*[22], 2009	54/54	Tianyuam acupuncture	Three step analgesic ladder therapy	Degree of pain relief/VAS score

Table 2 Analgesic effect of different acupuncture methods based on network meta-analysis

Three-step analgesic ladder				
0.71 (0.59, 0.85)	Triple puncture and remaining needle acupuncture			
0.72 (0.54, 0.97)	1.02 (0.72, 1.44)	Tian Yuan acupuncture		
1.00 (0.93, 1.08)	1.41 (1.16, 1.71)	1.38 (1.02, 1.87)	Wrist ankle acupuncture	
0.95 (0.90, 1.01)	1.34 (1.11, 1.62)	1.32 (0.97, 1.78)	0.95 (0.87, 1.05)	Block acupuncture

Table 3 Probability ranking of interventions in different outcome indicators (SUCRA)

Treatment	SUCRA	PrBest	MeanRank
Three-step analgesic ladder	14.1	0.0	4.4
Triple puncture and remaining needle acupuncture	88.8	55.3	1.4
Tian Yuan acupuncture	84.4	44.7	1.6
Wrist ankle acupuncture	17.7	0.0	4.3
Block acupuncture	45.0	0.0	3.2

makes meridians and viscera lose nourishment, that is, loss of nourishment leads to pain[16].

The main mechanisms of acupuncture in alleviating cancer pain are as follows. First, acupuncture has the function of regulating qi and blood as well as dredging channels and collaterals; hence, pain is relieved with improved blood circulation. Second, it can effectively adjust the body's immune function to achieve the effects of strengthening body resistance and eliminating pathogenic factors, tonifying deficiency, and purging excess[17]. Western medicine theory holds that the benign stimulation of acupuncture can act on the sympathetic and sensory nerves, and on the relevant autonomic nerve center through the segmental axon reflex of the nerve, thus effectively adjusting the visceral sensory function. In addition, the effective stimulation of acupuncture on acupoints can release endogenous opioid peptides through neurohumoral or meridian conduction, thus achieving acupuncture analgesia[18,19].

From our NMA, we found that triple puncture and remaining needle acupuncture had the highest effectiveness in treating moderate to severe liver cancer pain. Tianyuan acupoint acupuncture mainly uses the exterior and interior acupoint selection method, 12-meridian hedge acupoint selection method,

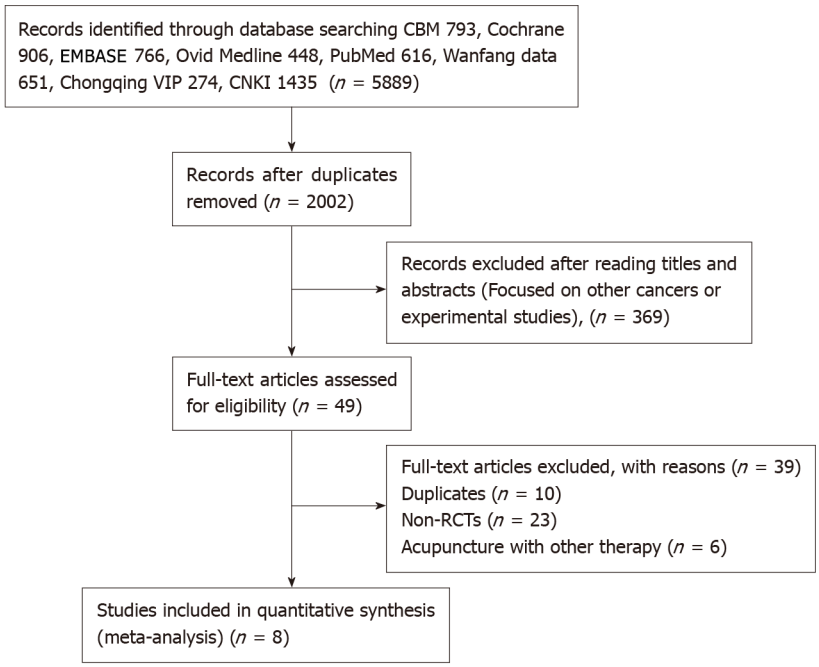

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Figure 1 Flow chart of study inclusion.

Sanyin Sanyang Guanheshu acupoint selection method, and twirling reinforcing-reducing method in the Guidelines of Acupuncture Meridians to relieve cancer pain. The exterior and interior acupoint selection method selects acupoints according to the relationship between exterior and interior deficiency of meridians, superficial acupoint is selected for interior disease, and deep acupoint is selected for exterior disease. Because liver cancer is an internal disease, the liver Beishu and Ganshu acupoints on the liver surface, as well as Ququan acupoint, were selected to tonify the liver meridian deficiency syndrome, dredge the qi and blood of the liver meridian meridians, and prevent the conduction of pathogenic factors. The 12-meridian hedge acupoint selection method is proposed according to the hedge relationship of the 12 earthly branches, that is, Zi and Wu hedge, Yin and Shen hedge, Chen and Wu hedge, *etc.* There is a corresponding relationship between the 12 meridians of the human body and the 12 earthly branches, and there is also a hedge relationship across the 12 meridians of the human body; that is, the hedge between Taiyin Lung Meridian and the Foot-Taiyang Bladder Meridian, the hedge between the Foot-Yangming Stomach Meridian and the Hand-Jueyin Pericardium Meridian, the hedge between the Hand-Shaoyin Heart Meridian and the Foot-Shaoyang Gallbladder Meridian, *etc.* According to the theory of Sanyin and Sanyang Guanheshu and the tendency of pathogenic conduction of meridians, as for the method of acupoint selection of Sanyin and Sanyang Guanshu, the Shu or He acupoint is selected for the disease at Guan acupoint, Guan or Shu is selected for the disease at He acupoint, and Guan or He is selected for the disease at Shu acupoint. The typical acupoints that can be used are Xinyuand Dazhui. Those acupoints are selected for tranquilizing, soothing the liver, relieving depression, activating blood circulation, and relieving pain. Tianyuan acupoint acupuncture uses rotational tonifying and reducing manipulation with a small amount of stimulation, while the Tianyuan acupoint selection method selects acupoints carefully, so the effect is good[20,21]. Wrist–ankle acupuncture is a method of acupuncture at specific parts of the wrist or ankle to treat systemic diseases. It is gradually formed and developed under the inspiration of the mid-dermal theory in meridian doctrine. It was officially applied in clinical practice in the early 1970s. Because of its single-acupoint selection, easy operation, and minimal damage to the body, this method is safe without needle sensation [19]. Ququan point is selected for blocking acupuncture, which is the converging point of liver meridian, where the liver meridian qi is full, and acupuncture can soothe the liver, regulate qi and meridians, and relieve pain. Dazhui is the point of the Du meridian, which is a good option for acupoint selection when treating shoulder and back pain and has the functions of activating blood circulation, dredging collaterals, and relieving pain. Liver cancer pain is caused by liver enlargement, tumor invasion of the diaphragm, and stimulation of diaphragmatic nerves into the cervical segment of the spinal cord, resulting in the right shoulder and liver pain, so acupuncture at this point can play a role in soothing the liver, activating blood circulation to relieve pain, and blocking the conduction of pathogenic factors. Acupuncture at Xinshu is used to tranquilize the mind, regulate qi and relieve depression, replenish qi and meridians, and treat cancer pain. Ganshu is the Beishu point of the liver meridian. Acupuncture can notify liver blood, and soothe liver and meridians to treat cancer pain, and the simultaneous treatment of principal and subordinate symptoms can be achieved[22]. Triple puncture and remaining needle

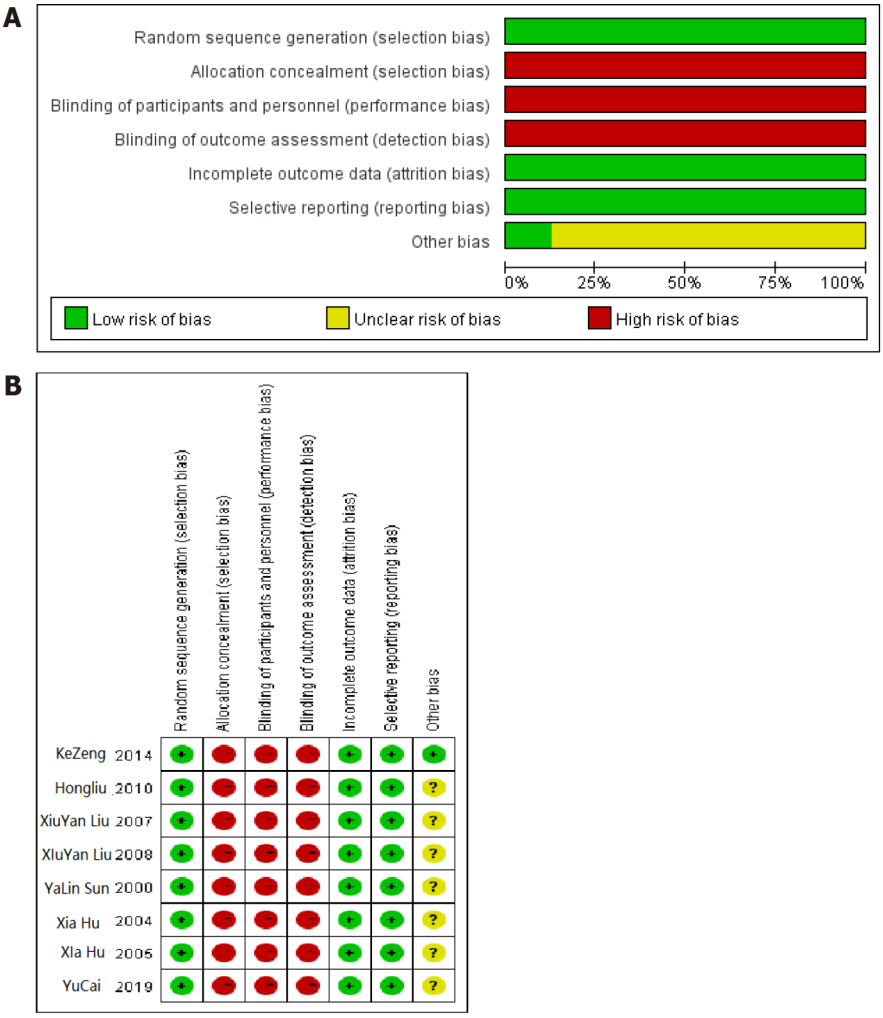

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Figure 2 Assessment of quality of the literature. A: Percentile chart of literature risk bias; B: Risk of bias assessment.

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Testing for inconsistency:
 ( 1)  [_y_E]_cons = 0

           chi2(  1) =    2.23
         Prob > chi2 =    0.1351

mvmeta command stored as F9; test command stored as F8
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Figure 3 Test for inconsistency.

acupuncture, as recorded in LingShu, is called concerted needling. Concerted needling involves insertion directly into one point and then further insertion of two more needles directly beside the first to treat cold qi and is localized but slightly deep. The method of concerted needling and needle retaining for liver cancer pain can prolong the analgesic time. From the recorded description, concerted needling selects the appropriate needle, on the selected acupoints, as follows. First, the first needle is inserted straight down the needle tip in the center of the acupoint, and then 0.5 cun (1 cun is equal to 3.3333333 cm) next to the first needle (up and down or left and right); the needle tip is aligned with the direction of the first needle, and the other two needles are straightly (obliquely) inserted; one acupoint is simultaneously inserted into by three needles, and at the same time, lifting, inserting, and twisting of the needle are performed to achieve the arrival of qi. Three needles are used together, so the name of concerted needling is given, which is mainly suitable for arthralgia with limited lesions, as well as with deep location of lesions and pathogenic factors. According to clinical research reports, the three needles of the concerted needling method not only strengthen the local irritation volume of the acupoint where

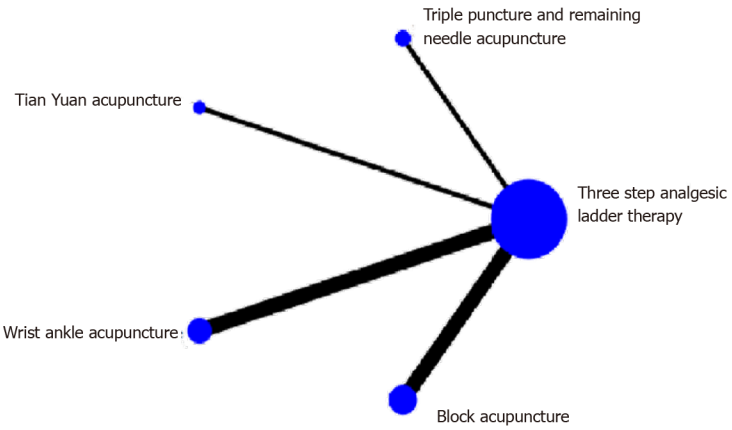

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Figure 4 Network comparing the analgesic effect of different acupuncture methods.

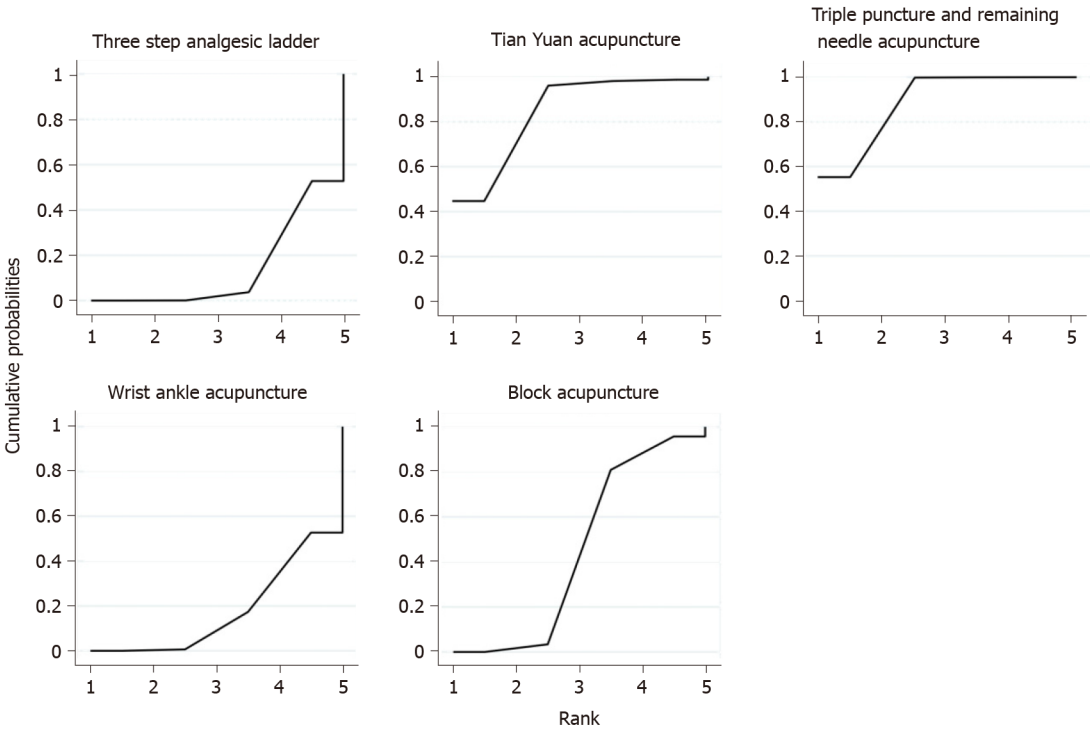

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Figure 5 Probability ranking chart of treatment efficiency.

the acupuncture is located, but also expand the scope of action of the acupoint where the acupuncture is located. This method is conducive to rapidly stimulating the conduction of meridians and qi so that the induction of acupuncture can reach the disease site directly and the needle sensation spread from shallow to deep, from near to far around the acupoint, rapidly reaching the acupuncture requirements of qi to the disease site. The method also plays a role in relieving tendons through meridians, promoting blood circulation and dredging collaterals, and removing arthralgia and relieving pain. Thus, the purpose of acupuncture treatment based on the principle of "no obstruction, no pain" is achieved[23].

This study had several limitations. First, we failed to evaluate the safety of each acupuncture therapy due to limited data in the primary studies. Future trials should report adverse events clearly to improve the quality of study design. Second, unaddressed concerns still exist regarding the long-term effects of using acupuncture and acupuncture-related therapies for pain due to liver cancer in the clinical setting. Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. Third, blinding of patients and research was not performed in the included studies that were mainly conducted in China, which may have led to publication bias. Fourth, the included studies in our NMA lacked comparisons on the effectiveness of different acupuncture therapies. Further confirmatory effectiveness trials should compare different types of acupuncture therapies. Finally,

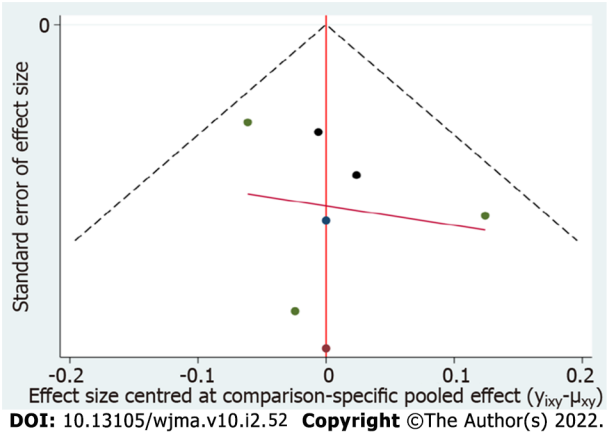

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Figure 6 Efficient funnel chart.

numerous studies that focused on other methods of acupuncture were not included in our study due to the type of design and outcome measures.

CONCLUSION

The evidence from our NMA, in which different methods of acupuncture for pain due to liver cancer were compared with each other within a coherent framework, suggests that the overall effectiveness of triple puncture and remaining needle acupuncture is better than that of other therapies. However, despite the evidence from this study, the methodological limitations associated with many of the trials indicate that high-quality trials of acupuncture treatments are still required.

ARTICLE HIGHLIGHTS

Research background

Seventy-five percent of patients with liver cancer suffer varying degrees of pain. Pain is widely perceived as the fifth vital sign in cancer patients, which seriously affects the quality of their life and threatens their survival. Acupuncture, part of traditional Chinese medicine, involves the application of needles, heat, pressure, and other treatments at specific sites of the body known as acupoints to affect the physical functions of the body. Numerous studies have concluded that acupuncture may be efficacious in relieving cancer-related pain. However, there is still no direct evidence on which method of acupuncture is more effective. The present study aimed to identify the best method of acupuncture for liver cancer-related pain. Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. The comparisons of the effectiveness of different acupuncture therapies should be conducted.

Research motivation

The aim of our study was to compare the effectiveness of different acupuncture methods for alleviating pain due to liver cancer. In this study, we found that triple puncture and remaining needle acupuncture had the highest effectiveness. The finding of our study may provide evidence for directly comparing different methods of acupuncture for liver cancer related pain.

Research objectives

The present study aimed to identify the best method of acupuncture for liver cancer-related pain. The finding of our study may provide evidence for direct comparisons of different methods of acupuncture for liver cancer related pain.

Research methods

In this network meta-analysis (NMA), the association of each acupuncture and related therapies with relief of pain due to liver cancer was compared using the combination of direct and indirect evidence from eight RCTs with 734 patients. An NMA provides a basis for synthesizing all the available evidence in a consistent framework, obviating the need to make decisions by subjective inferences from disparate data. However, our analysis represents the use of the most practical methods currently available to

compare a large number of different types of treatment, thus enabling us to compare different methods of acupuncture with each other.

Research results

We conducted an NMA to analyze both direct and indirect comparisons of different methods of acupuncture for the relief of pain due to liver cancer. Based on the current evidence, we sorted and explored the advantages and disadvantages of different methods of acupuncture. Compared with traditional meta-analysis, the results of this study may provide a higher quality basis and reference for acupuncture treatment of pain due to liver cancer.

Research conclusions

The evidence from our NMA, in which different methods of acupuncture for pain due to liver cancer were compared with each other within a coherent framework, suggests that the overall effectiveness of triple puncture and remaining needle acupuncture is better than that of other therapies. However, despite the evidence from this study, the methodological limitations associated with many of the trials indicate that high-quality trials of acupuncture treatments are still required.

Research perspectives

Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. The comparisons of the effectiveness of different acupuncture therapies should be conducted.

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FOOTNOTES

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META-ANALYSIS

Effect of auricular plaster for primary hypertension in older people: A meta-analysis

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Abstract

BACKGROUND

Hypertension is a critical public health problem globally. Antihypertensive drugs can create an extra burden on hypertension patients' self-regulation leading to an imbalance of blood supply and demand. This study aimed to evaluate the effect of auricular plaster therapy combined with western medicine to treat primary hypertension in older people.

AIM

To carry out a systematic review and meta-analysis for the effect of auricular plaster in elderly hypertension patients.

METHODS

Multiple databases like PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature on Disc, China National Knowledge Infrastructure, Wan Fang and Chinese Science and Technology Periodical Database were used to search for the relevant studies and full-text articles involved in the evaluation of auricular plaster combined with western medicine and western medicine alone for primary hypertension in older people. All included articles were quality assessed and the data analysis was conducted with the Review Manager (5.4). Forest plots, sensitivity analysis and funnel plots were also performed on the included articles.

RESULTS

In this analysis, fourteen (14) relevant studies were included. The Meta-analysis showed a significant difference in the effective ratio (OR = 3.62; 95%CI, 2.46 to 5.33; $P < 0.00001$), diastolic blood pressure change (5.68 mmHg; 95%CI, 3.49 to 7.87; $P < 0.00001$), systolic blood pressure change (MD = 8.78 mmHg; 95%CI, 5.04 to 12.53; $P < 0.00001$) and symptom score (MD = 3.20; 95%CI, 1.23 to 5.18; $P = 0.001$) between auricular plaster combined with western medicine group and

western medicine alone group. One bias was detected as selection bias and another two in reporting bias. Sensitivity analysis fulfilled the stability of the results.

CONCLUSION

Our study suggested that auricular plaster combined with western medicine improved primary hypertension better than western medicine alone. Limited by the quality of included studies, further studies should be performed to confirm our findings.

Key Words: Primary hypertension; Older people; Auricular plaster; Meta-analysis

Core Tip: Our study is different from a previous report's systematic review and meta-analysis. We focused on elderly hypertension patients and acquired relevant literature on auricular plaster in the analysis.

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INTRODUCTION

Primary hypertension, referred to as hypertension, is a syndrome with elevated blood pressure as the main clinical manifestation[1,2]. It is an important cause and risk factor for a variety of cardiovascular and cerebrovascular diseases. It affects the structure and function of essential organs such as the heart, brain and kidney and eventually leads to the failure of these organs. It is still one of the leading causes of death in patients with cardiovascular diseases[3,4]. At present, the number of people with hypertension in the world has exceeded 1 billion and 90%-95% of these are diagnosed with primary hypertension[5,6]. Hypertension has become a significant public health problem endangering human health.

Long-term high blood pressure (BP) will cause compression on the systemic blood vessels, leading to vascular blockage or rupture, stroke, heart failure, aortic dissection and other complications[7-9]. Therefore, reasonable control of blood pressure is the key to treat hypertension and reduce its complications. Patients with hypertension must take prescription medicine for life. Applying antihypertensive drugs will increase the burden of patients' self-regulation leading to the imbalance of blood supply and demand and has certain limitations[10,11]. It is of great clinical significance to explore the non-drug therapy available for hypertension[12].

In recent years, a non-drug therapy called auricular plaster has been reported to treat essential hypertension in China and the number of reports is increasing[13-15]. Auricular plaster is a common diagnosis and treatment technology of traditional Chinese medicine, also known as auricular point pressing beans or auricular point pressing seeds, which refers to sticking hard and smooth drug seeds or pills, magnetic beads and other things on the surface of the auricular points and fixing them with adhesive tape[16-18]. The human body has six meridians distributed in and around the ear and the ear is connected with organs through meridians. The auricle is the only body surface area with vagus nerve distribution. Auricular plaster can activate the vagus nerve and regulate the autonomic nervous system by stimulating auricular points with cowherb seeds to reduce blood pressure (BP)[19,20].

There are many clinical studies on auricular plaster therapy for elderly patients with primary hypertension, but the intervention methods and intervention time were quite different. Our study conducted a systematic review and meta-analysis of related randomized controlled trials (RCT) to evaluate the clinical efficacy of auricular plaster therapy combined with western medicine to treat primary hypertension in older people to provide a reference for clinical decision-making.

MATERIALS AND METHODS

Literature search strategy

We used comprehensive databases (PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature on Disc, China National Knowledge Infrastructure, Wan Fang and Chinese Science and Technology Periodical Database) to search for previous studies investigating the effects of auricular

plaster therapy for primary hypertension in the elderly. The literature search was performed from inception up to July 2021 using the following keywords: (1) Auricular plaster; (2) Primary hypertension; and (3) Western medicine. Terms were searched as text words and these three themes were combined using the Boolean operator 'or' to complete our search strategy. Our literature search was comprehensive with neither language restrictions nor publication status limitations. Two of us identified and reviewed full-text articles deemed relevant by screening the list of titles and abstracts. Disagreements were resolved through consensus between the two reviewers.

Study selection

After the primary selection, the text of the potentially relevant studies was reviewed. The studies included must meet the following inclusion criteria: (1) Comparing research patients who receive combination therapy of auricular plaster and western medicine (test group) and standard western medicine alone (control group); (2) Patients with primary hypertension [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg]; (3) Containing indicators evaluating effectiveness between test group and control group; and (4) Available in full text.

Studies were excluded based on the following pre-determined exclusion criteria: (1) Not randomized controlled trials (RCT); (2) Reviews, letters, or protocols; (3) Duplicate articles; and (4) lack of related outcomes.

Data extraction and quality assessment

Two independent reviewers performed the study selection, data extraction and quality assessment. Pre-specified data elements were extracted from each trial using a structured data abstraction form, including baseline characteristics, sample size and interventions used. The risk of bias of included RCTs was assessed using a modified version of the Cochrane Collaboration's Risk-of-Bias Tool. Two co-authors independently performed the risk-of-bias assessment on all included RCTs. When in a disagreement, the rechecking of the original article was followed by discussion and was used to reach a consensus.

Statistical analysis

Meta-analysis was performed in Review Manager (RevMan) software (version 5.4; Cochrane Collaboration) using the inverse variance method. We assumed that the studies' variability beyond subject-level sampling error was random, and consequently, we adopted a random-effect model. The Mantel-Haenszel odds ratio (OR) model was used to summarize classification data, summary estimates and a 95%CI was reported for continuous variables as the mean difference (MD). Quantifying the inconsistency and heterogeneity across studies was assessed using Cochran Q and I^2 statistics. When the heterogeneity was present, the random-effects model was used to calculate the pooled OR or MD, whereas the fixed effects model was used in its absence. We also performed a sensitivity analysis with each endpoint to determine if there was any difference between groups. Publication bias was graphically analyzed with funnel plots. We also applied Egger and Begg's statistical test. A P value of < 0.05 was considered statistically significant.

RESULTS

Results of the literature search process

An electronic search was performed to identify all potential articles published in the English language by July 2021, and initially, 932 articles were selected. After a careful review of the titles and abstracts, 126 studies were included due to immediate satisfaction with the purpose of the present meta-analysis. Further, 112 articles were excluded due to not fulfilling the inclusion criteria. The remaining 14 studies were assessed and reviewed to satisfy the inclusion criteria and were considered in our meta-analysis [21-34]. Figure 1 represents an outline of the studies' identification, inclusion and exclusion criteria, thereby summarizing the search process and the reasons for exclusion.

Study characteristics

A total of 1088 patients with primary hypertension were included in this meta-analysis study and all these studies were published from 2012 to 2021. The primary outcome contained effective ratio, DBP change, SBP change and symptom score.

The antihypertensive effect was determined according to the relevant standards in the guiding principles for clinical research of new drugs in traditional Chinese medicine[35]. (1) Strongly effective (meets one of the following conditions): Diastolic blood pressure (DBP) decreased by 10 mmHg or more, and within the normal range; DBP did not fall to the normal range but decreased by 20 mmHg or more; (2) Moderate effective (meet one of the following conditions): DBP decreased less than 10 mmHg, within the normal range; DBP decreased to 10-19 mmHg, but still higher than the normal range; Systolic blood pressure (SBP) decreased to 30 mmHg; and (3) Ineffective: Did not meet any of the above criteria. The

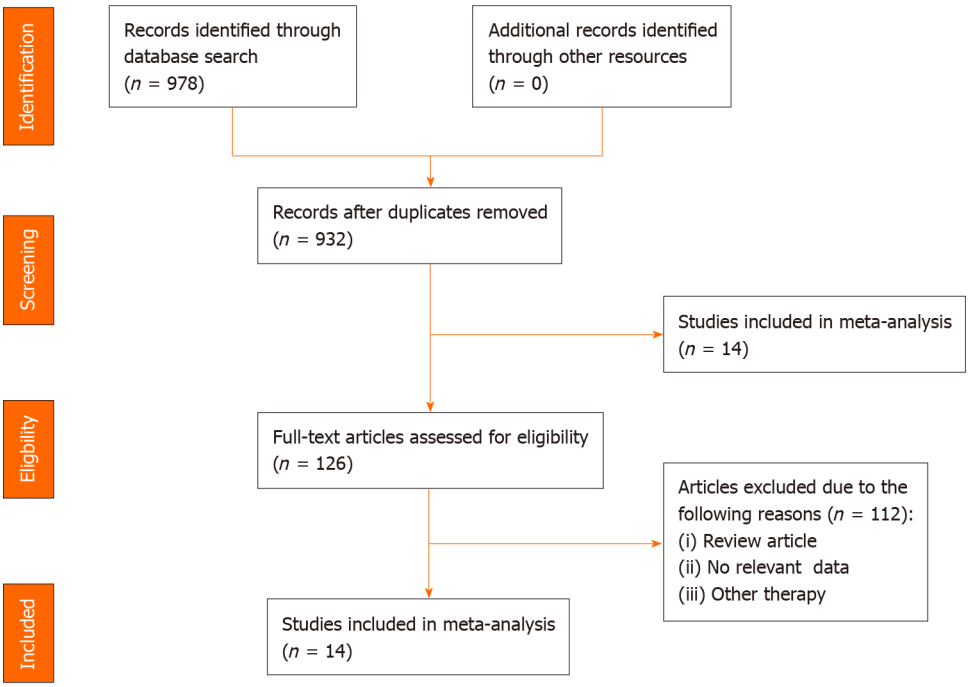

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Figure 1 Flow chart of literature search and study selection for systematic review and meta-analysis.

effective ratio in our outcome variable was the sum of strongly effective and moderate effective ratios.

Symptom score referred to the curative effect standard in the guiding principles for clinical research of new Chinese medicine in 2002[36]. Headache, vertigo and insomnia were selected to observe the symptoms and the symptoms were scored according to the degree of symptoms from mild to severe. The primary study chosen characteristics are summarized in Table 1.

Results of the quality assessment

According to the Cochrane risk of the bias assessment tool, to assess the bias risk (including selection, performance, detection, attrition and reporting bias among the included randomized trials) (Figures 2 and 3), the methodological quality of included studies was evaluated for the bias risk. There was a high risk of selection bias in one study and reporting bias in two other studies. In the summary risk of bias assessment of the 14 included studies, there is a limited selection bias, performance bias and detection bias. In general, there are only two trials with bias risk and the other six tests have no risk.

Results of heterogeneity test

The effect of auricular plaster on effective ratio was reported in 12 studies. A significant improvement in the effective ratio was identified compared with the control group (OR = 3.62; 95%CI, 2.46 to 5.33; $P < 0.00001$). There was no significant heterogeneity for effective ratio assessment ($P = 0.74$, $I^2 = 0\%$) (Figure 4).

Thirteen trials reported information about DBP change. A random-effect model was used to evaluate the heterogeneity of DBP change due to the significant heterogeneity ($P < 0.0001$, $I^2 = 89\%$). The pooled analysis showed that the test group had a better reduction of DBP than the control group (MD = 5.68 mmHg; 95%CI, 3.49 to 7.87; $P < 0.00001$) (Figure 5).

In evaluating the difference of SBP change between the test group and control group, 13 articles involved 1028 patients. Meta-analysis showed that compared to the control group, the test group had a higher reduction of SBP (MD = 8.78 mmHg; 95%CI, 5.04 to 12.53; $P < 0.00001$), with significant heterogeneity ($I^2 = 94\%$, $P < 0.00001$) (Figure 6).

Four studies reported symptom scores. A random-effect model was used to evaluate the heterogeneity among the significant heterogeneity included studies ($P < 0.00001$, $I^2 = 89\%$). The results showed that the test group improved symptom scores better than the control group (MD = 3.20; 95%CI, 1.23 to 5.18; $P = 0.001$) (Figure 7).

Results of sensitivity analysis and publication bias

The included studies will be excluded one by one for sensitivity analysis. The heterogeneity of DBP change was decreased from 89% to 87% when Wu 2013 was excluded suggesting that the meta-analysis results were robust.

Table 1 Characteristics of eligible studies

Ref.	Study design	Treatment		No. of patients		Gender (M/F)		Age		Intervention time	Primary outcome
		Test	Control	Test	Control	Test	Control	Test	Control		
Ji *et al* [23]	RCT	Auricular plaster + Nifedipine	Nifedipine	32	32	17/15	16/16	66.06 ± 4.39	66.16 ± 4.22	3 mo	2, 3
Zhou *et al*[32]	RCT	Auricular plaster + Candesartan Cilexetil	Candesartan Cilexetil	40	40	24/16	21/19	65.78 ± 9.95	66.12 ± 8.57	2 wk	1, 2, 3
Huang *et al*[28]	RCT	Auricular plaster + Levamlodipine besylate	Levamlodipine besylate	30	30	17/13	19/11	60-85	60-85	15 d	1, 2, 3
Wu *et al* [29]	RCT	Auricular plaster + Conventional drugs	Conventional drugs	41	41	23/18	21/20	60-70	60-70	6 wk	1, 2, 3
Zhou *et al*[31]	RCT	Auricular plaster + Nifedipine	Nifedipine	30	30	16/14	14/16	63.21 ± 12.25	63.55 ± 11.74	4 wk	1, 2, 3
Lin *et al* [26]	RCT	Auricular plaster + Levamlodipine besylate	Levamlodipine besylate	30	30	16/14	14/16	66.73 ± 6.81	67.6 ± 7.51	4 wk	1, 4
Zhou *et al*[33]	RCT	Auricular plaster + Conventional drugs	Conventional drugs	30	30	21/9	19/11	62-83	62-83	3 mo	1, 2, 3, 4
Zhang *et al*[21]	RCT	Auricular plaster + Amlodipine besylate	Amlodipine besylate	20	20	9/11	12/8	63.4 ± 5.2	64.8 ± 4.7	2 wk	1, 2, 3
Jiang *et al*[34]	RCT	Auricular plaster + Nifedipine	Nifedipine	54	54	30/24	31/23	65.8 ± 7.3	64.1 ± 7.2	4 wk	1, 2, 3, 4
Yu *et al* [25]	RCT	Auricular plaster + Nifedipine	Nifedipine	87	79	39/48	37/42	68.1 ± 10.7	71.1 ± 8.0	5 mo	1, 2, 3
Zhang *et al*[24]	RCT	Auricular plaster + Propranolol	Propranolol	43	43	25/18	27/16	63.02 ± 8.33	62.13 ± 7.96	15 d	2, 3
Lu *et al* [27]	RCT	Auricular plaster + Conventional drugs	Conventional drugs	50	50	26/24	27/23	60.26 ± 6.73	61.35 ± 6.56	3 wk	1, 2, 3
Zou *et al* [30]	RCT	Auricular plaster + Levamlodipine besylate	Levamlodipine besylate	20	20	12/8	14/6	62.6 ± 10.3	62.9 ± 10.5	4 wk	1, 2, 3
Yu *et al* [22]	RCT	Auricular plaster + Amlodipine besylate	Amlodipine besylate	41	41	24/17	26/15	66.4 ± 3.4	67.1 ± 3.7	8 wk	1, 2, 3, 4

1: Effective ratio; 2: DBP change; 3: SBP change; 4: Symptom score, RCT: Randomized control trail.

A funnel plot was performed to evaluate the publication bias for effective ratio qualitatively. The shape of the funnel plot showed some evidence of symmetry (Figure 8) and the Egger test was not significant (P = 0.77), which indicated no significant publication bias existed in this meta-analysis.

DISCUSSION

Hypertension is one of the most common cardiovascular diseases. In recent years, with the change of modern living habits, the incidence rate of hypertension has been increasing year by year. Hypertension has presented a trend toward younger people. How to control BP safely and reliably has become a problem that medical workers must solve today[37]. How to effectively and stably control BP and avoid large fluctuations such as a sudden fast rise or lowering of blood pressure. Maintaining a steady BP reduces the damage caused by BP fluctuations, prevents the adverse effects caused by excessive BP, reduces the damage of essential organs and effectively controls the disability rate and mortality rate which is the key to the problem[1,38,39].

At present, western medicine is the primary treatment for hypertension and the first-line antihypertensive drugs include diuretics, β Receptor blockers, calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists[40,41]. The guidelines point out that diuretics can reduce blood volume and relax peripheral blood vessels; β Receptor blockers can reduce cardiac output; Calcium antagonists can inhibit calcium influx in vascular smooth muscle and reduce myocardial contractility; Angiotensin-converting enzyme inhibitors and angiotensin receptor

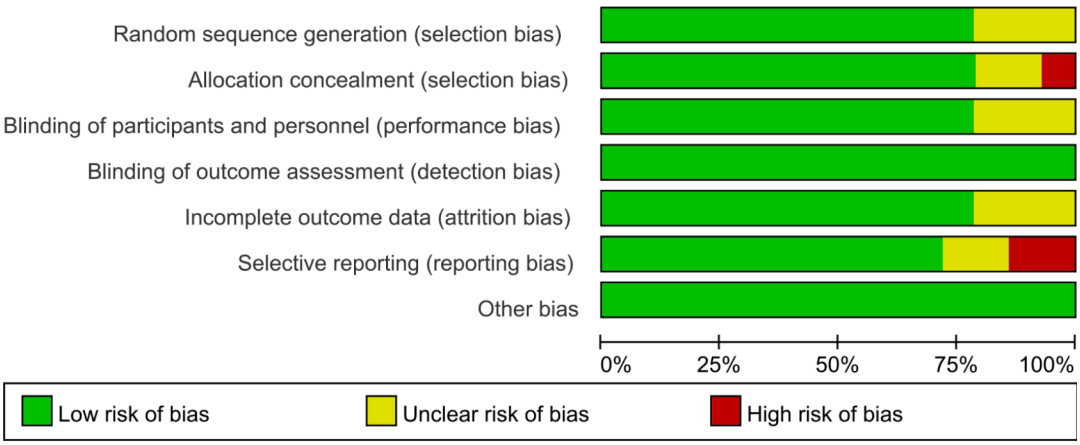

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Figure 2 Proportion of studies with low (green), high (red), or unclear (yellow) risk of bias.

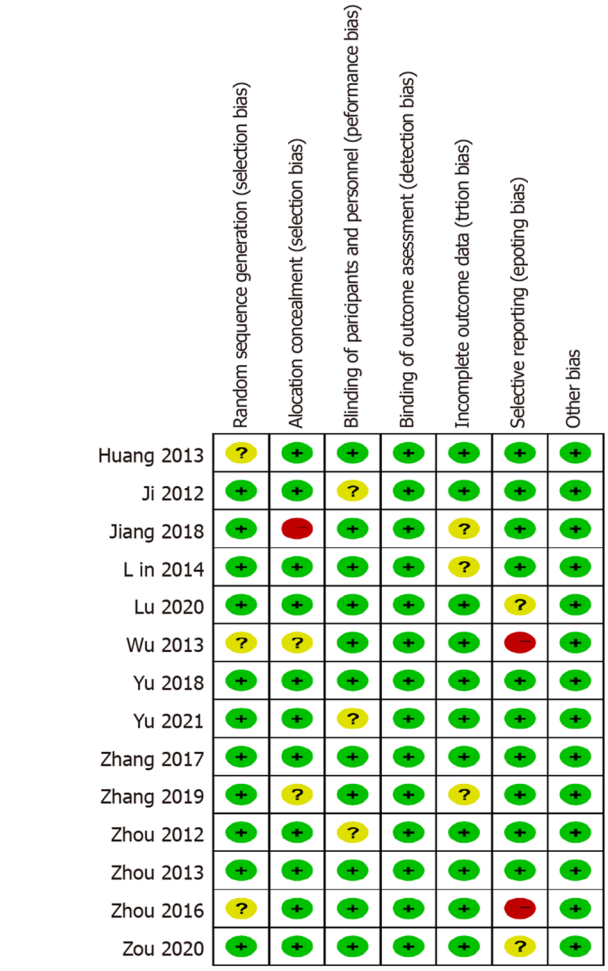

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Figure 3 Graph of the risk of bias summary.

antagonists can block the renin-angiotensin system and dilate arterioles and venules. The mechanism of action of these drugs is to improve the circulatory system from different aspects to reduce BP[42,43].

In China, auricular plaster is a diagnosis and treatment technology developed based on auricular acupuncture therapy[44]. Cowherb Seeds are complicated and can activate blood circulation and regulate BP. Auricular plaster therapy can regulate BP to a certain extent, significantly improve patients' clinical symptoms with hypertension and improve patients' satisfaction with nursing work[45,46]. Some studies have shown that auricular plaster therapy can regulate the balance of viscera and meridians,

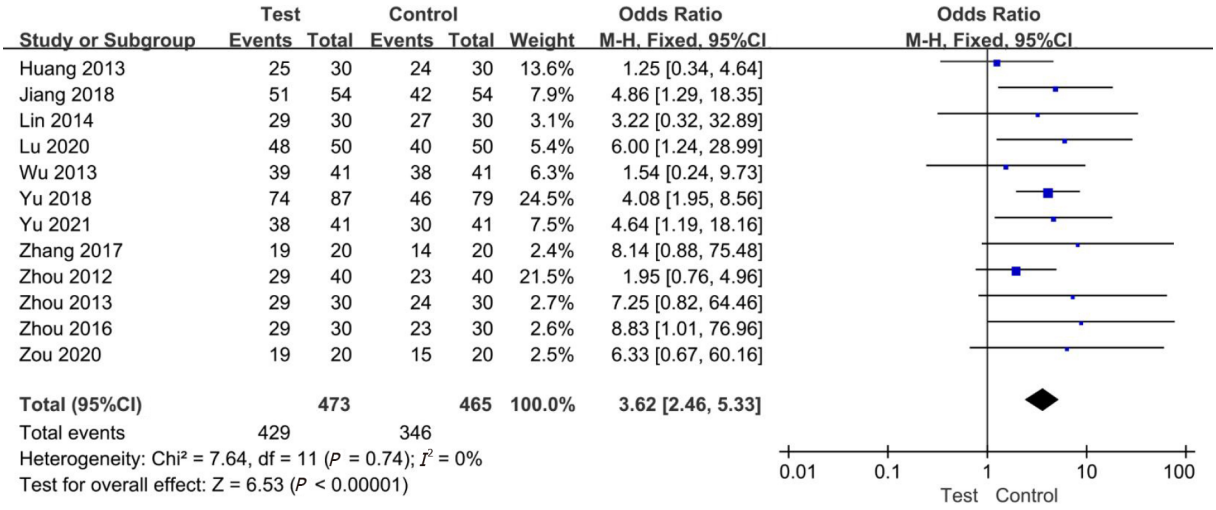

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Figure 4 Meta-analysis on the effect of auricular plaster therapy on effective ratio.

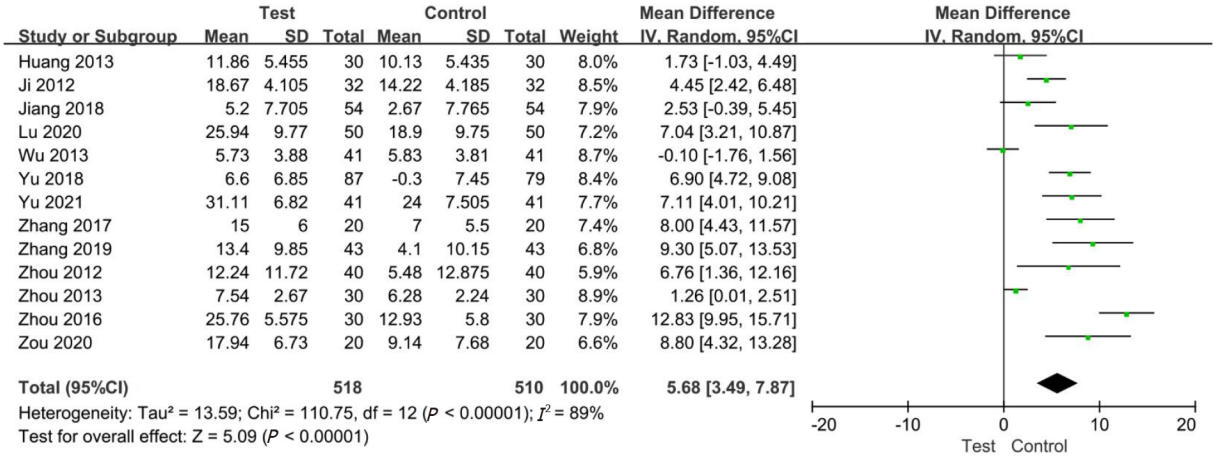

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Figure 5 Meta-analysis on the effect of auricular plaster therapy on DBP change.

promote the function of the cerebral cortex to return to normal quickly and comprehensively treat the uncoordinated nerve, body fluid and vascular function to achieve the effect of reducing BP[47,48].

Fourteen studies were included in this systematic review and meta-analysis. The meta-analysis results showed that the effective ratio of auricular plaster therapy in the treatment of hypertension based on conventional western medicine therapy was higher than that of western medicine alone therapy (OR = 3.62; $P < 0.00001$), suggesting that auricular plaster therapy had an excellent adjuvant effect on hypertension. The decrease of DBP (MD = 5.68 mmHg; $P < 0.00001$), SBP (MD = 8.78 mmHg; $P < 0.00001$) and symptom score (MD = 3.20; $P = 0.001$) were more evident than that of the control group, suggesting that the combination therapy of auricular plaster and western medicine was better than western medicine alone in improving clinical symptoms. It showed that auricular plaster therapy had significant health benefits in treating hypertension and was worthy of clinical promotion.

This study showed apparent heterogeneity in the assessment of the literature included in the improvement of SBP, DBP and symptom scores. Although sensitivity analysis showed that heterogeneity did not affect the final results, we still analyzed the source of heterogeneity. After further reading and analysis of the included studies, we found that the heterogeneity may be caused by different types of antihypertensive drugs, other antihypertensive mechanisms and different effects on SBP, DBP and clinical symptoms, which suggested that we need to conduct a subgroup analysis on different types of antihypertensive drugs.

There were some limitations in this meta-analysis. Firstly, auricular plaster therapy was a unique traditional medical method in China and the published reports were mainly in Chinese with the quality being relatively poor. Secondly, some of the included studies did not describe the implementation of random allocation and blind methods. In addition, the frequency of auricular plaster, the type and dose of western medicine was also different in the experiment which suggested that more detailed

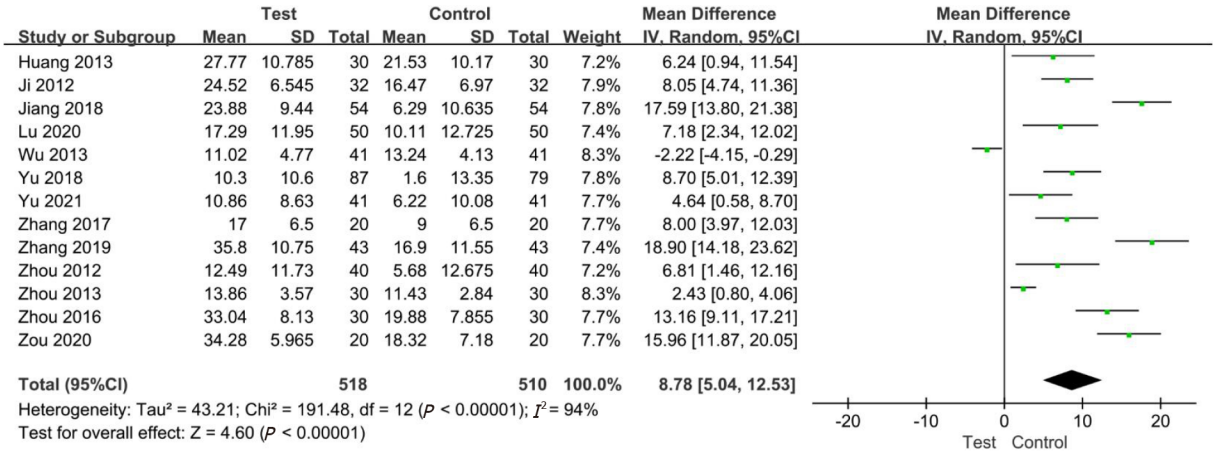

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Figure 6 Meta-analysis on the effect of auricular plaster therapy on SBP change.

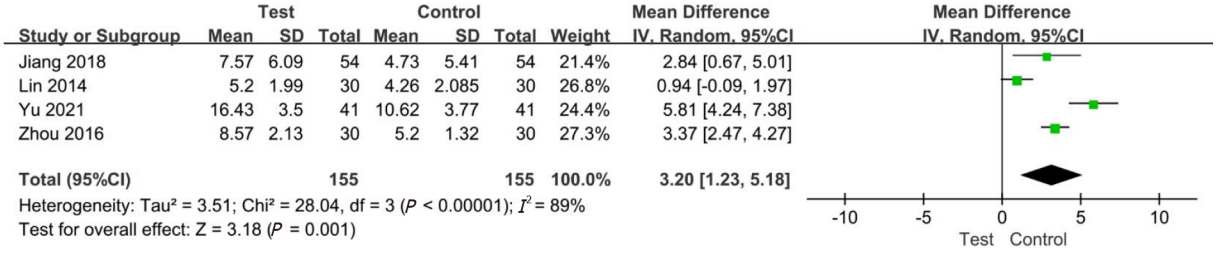

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Figure 7 Meta-analysis on the effect of auricular plaster therapy on symptom score.

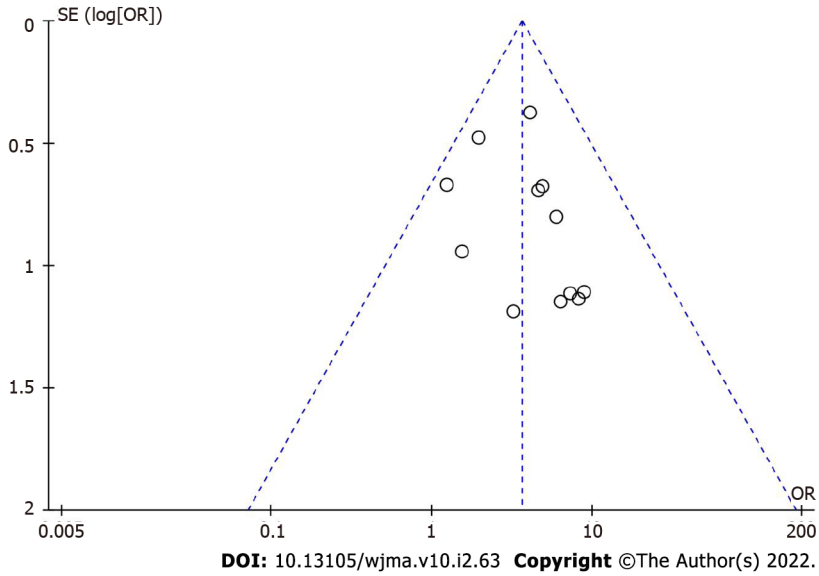

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Figure 8 Funnel plot for potential publication bias.

hierarchical or subgroup analysis can be done in the future.

CONCLUSION

In conclusion, auricular plaster combined with western medicine can improve the antihypertensive effect of primary hypertension, reduce BP and improve clinical symptoms. In view of the quality of the

included studies, the reliability of the conclusions was reduced. It is still necessary to carry out multi-center, large sample randomized controlled trials, paying attention to the implementation of the randomized method, allocation concealment method and blind method to obtain reliable research data so as to provide the evidence-based basis for clinical treatment of hypertension.

ARTICLE HIGHLIGHTS

Research background

Hypertension is a very common health problem for older people. Recently, a non-drug therapy called auricular plaster has been used to treat hypertension in China and is considered traditional Chinese medicine. There were many clinical studies which reported on auricular plaster therapy for elderly patients with hypertension but the intervention methods and intervention times were quite different.

Research motivation

We speculate about gaining a detailed insight into the effect of auricular plaster therapy on elderly patients with primary hypertension.

Research objectives

This study aimed to evaluate the effect of auricular plaster therapy combined with western medicine to treat primary hypertension in older people.

Research methods

A literature search was carried out to identify reports published through July 1, 2021. The meta-analysis was carried out for the outcomes of the significant difference in the effective ratio, diastolic blood pressure (DBP) change, systolic blood pressure (SBP) change, and symptom score between auricular plaster combined with western medicine group and western medicine alone group. Publication bias was identified by the funnel plots test.

Research results

In this analysis, fourteen (14) relevant studies were included. The Meta-analysis showed a significant difference in the clinical effective ratio (OR = 3.62; 95%CI, 2.46 to 5.33; $P < 0.00001$), DBP change (5.68 mmHg; 95%CI, 3.49 to 7.87; $P < 0.00001$), SBP change (MD = 8.78 mmHg; 95%CI, 5.04 to 12.53; $P < 0.00001$) and symptom score (MD = 3.20; 95%CI, 1.23 to 5.18; $P = 0.001$) between auricular plaster combined with western medicine group and western medicine alone group.

Research conclusions

Auricular plaster could be a potential therapy to treat hypertension in elderly patients.

Research perspectives

More prospective sample studies are needed in the future to enhance the speculation of our conclusion.

FOOTNOTES

Author contributions: Qin Y, Lou Y, and Gai Y participated in the conception and design of the study, library searches and assembling relevant literature, critical review of the paper, supervising the writing of the paper and database management; Qin Y, Shen XY, and Gai Y participated in data collection, library searches assembling relevant literature, writing the paper and critical review.

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OPINION REVIEW

Responses to disrupted operative care during the coronavirus pandemic at a Caribbean hospital

Shamir O Cawich, Gordon Narayansingh, Michael J Ramdass, Marlon Mencia, Dexter A Thomas, Shaheeba Barrow, Vijay Naraynsingh

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Abstract

The coronavirus pandemic was thrust upon all nations in the year 2020 and required swift public health responses. Resource-poor health care facilities, such as those in the Caribbean, were poorly prepared but had to respond to the threat. In this experience report we examined the response by the surgical specialty to evaluate the lessons learned and to identify positive changes that may continue post-pandemic.

Key Words: Public health; Surgery; Pandemic; Coronavirus

Core Tip: Although resource-poor nations were not prepared to deal with the pandemic, they still had to respond to the global threat. This paper discusses the surgical specialty's response in order to identify positive changes that may continue post-pandemic.

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INTRODUCTION

The coronavirus (COVID) pandemic was thrust upon all nations across the globe in the year 2020. Trinidad & Tobago, a small resource-poor Caribbean nation, recorded its first case in March, 2020. The health care system had to rapidly respond to the pandemic. In this experience report we examine the response by the surgical specialty to evaluate the lessons learned and to identify positive changes that may continue post-pandemic.

HEALTH CARE IN THE CARIBBEAN

The Anglophone Caribbean is comprised of 17 independent countries, each with their own governments, budgets and health care delivery systems. Although the cumulative population is 7.5 million persons, the region is comprised mostly of small island states, with only four countries having populations over 200000 persons[1].

Trinidad & Tobago is a small island nation in the Eastern Caribbean, covering 1980 square miles (Figure 1). There was a population of 1.3 million persons at the last national census[2]. Citizens of this nation have access to government-sponsored health care through public hospitals managed by the health mininstry[2].

The General Hospital in Port of Spain is a 400-bed tertiary referral public hospital that serves a densely populated area, with a catchment population approximately 650000 persons[3]. The hospital offers virtually all areas of subspecialty care to the population in the North-Western part of the island (Figure 1). From a surgical point of view, due to the dense population and the high prevalence of interpersonal violence, the hospital is well known as a trauma center throughout the Caribbean[3]. The hospital is also affiliated with the local University[3], provides tertiary level oncology care to the catchment population[4] and serves as a quaternary referral center for vascular, hepatobiliary and laparoscopic surgery for the nation.

Similar to other facilities across the globe, the Port of Spain General Hospital was significantly affected by the COVID pandemic[5,6]. After the first reported case in Trinidad & Tobago, there was a swift initial response to close international sea and air borders to all incoming and outgoing passengers on March 22, 2021[7]. The borders remained closed to all forms of transit until July 17, 2021. During this time, all persons had to apply to the Government for exemptions to allow emergency travel.

The Government of Trinidad & Tobago also declared a State of Emergency in an attempt to limit travel and social activity within the nation[7]. A State of Emergency is triggered when there is a existing or potential threat to the nation and/or its population[3]. While in effect, only persons deemed "essential to national function" were allowed to travel in public spaces[3].

Before this incident, a State of Emergency was declared on six prior occasions[8]. All six prior States of Emergencies were declared in response to inter-personal violence[3]. The 2021 declaration was the only one due to a natural event. As a part of this response, the government organized intensified law enforcement operations with three specific aims: curtail inter-island transit, ensure that persons who required emergency travel maintained social distancing and mask wearing and to limit social gatherings. To facilitate this, a nationwide curfew was imposed and non-compliant citizens were subject to arrest for up to 24-h.

During this State of Emergency, health workers were permitted to travel in order to ensure continued healthcare *via* the Government-funded public hospitals. The Government attempted to create a parallel health care system that attended to the needs of COVID positive patients only, preserving the regular health care system for unaffected patients. However, the underfunded and resource-poor healthcare systems were unprepared[9].

In the grand scheme of the healthcare response, surgery became an irrelevant specialty[10]. The overwhelming majority of COVID related complications affected the cardiovascular and respiratory systems. There were few, if any, surgical complications recognized. Therefore, it was understandable that surgical services in Trinidad & Tobago were curtailed. This saw surgical house officers re-allocated to COVID teams, procurement practices changed, clinics postponed, operating room lists cancelled and face-to-face multidisciplinary team meetings discontinued. These changes, while totally understandable, crippled the delivery of surgical care (Figure 2).

In the meantime, patients with surgical diseases continued to present to the hospitals for care. Surgical care was delayed in many cases, due to both patient reluctance to present to hospital[11] and prolonged transit through the healthcare delivery systems. Therefore, patients who presented for surgical care were now in advanced disease states. Surgical leaders recognized that a potential crisis was developing and responded in several ways.

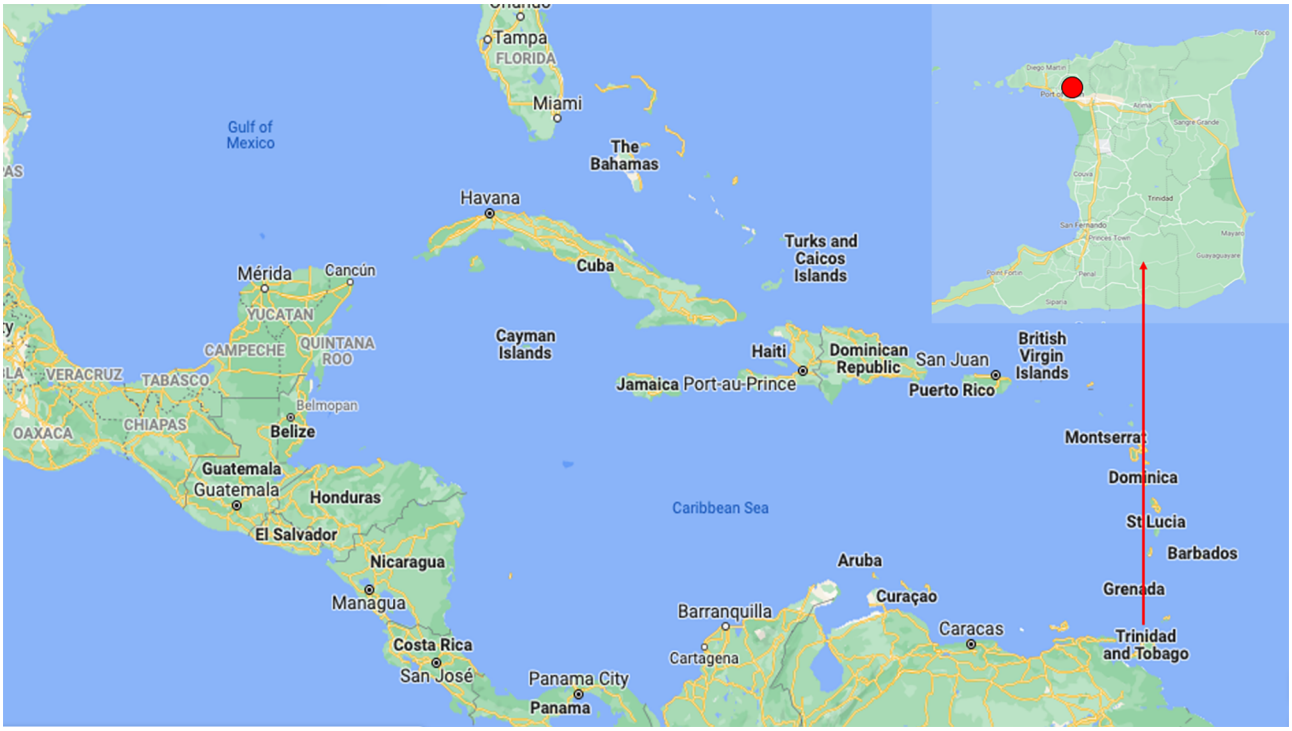

Figure 1 A Map of the Caribbean region. The island of Trinidad & Tobago (inset) is located just off the coast of South America. The Port of Spain General Hospital (red dot) is located in the North-Western part of the island in the nation's capital.

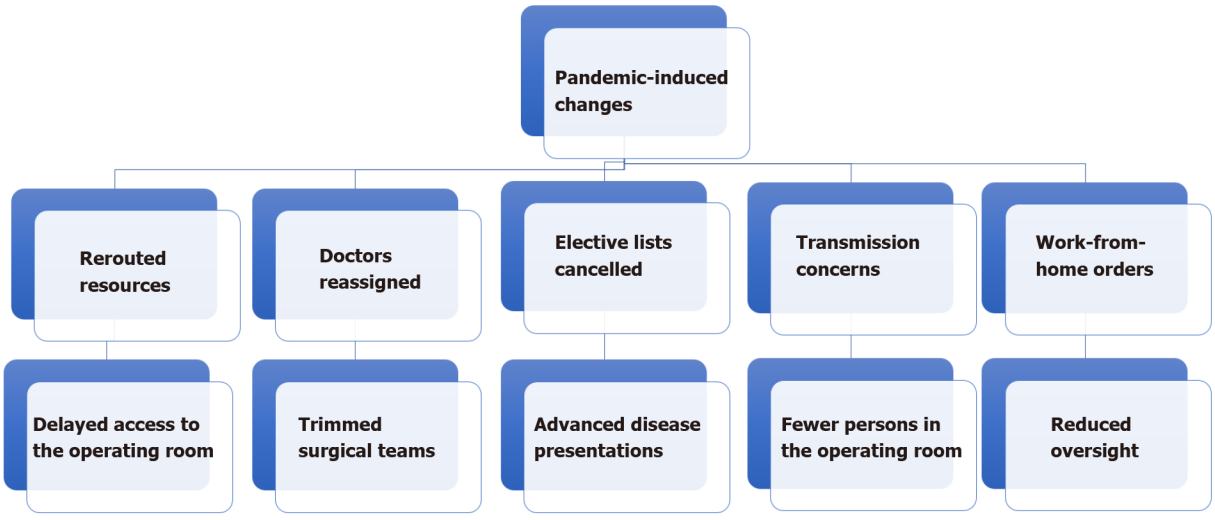

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Figure 2 A flow chart showing the variety of ways in which pandemic-induced changes affected the delivery of surgical health care in a Caribbean nation.

OUTPATIENT CARE

The Port of Spain General Hospital is a post-graduate training facility associated with a regional medical university. Surgical firms were comprised of a consultant surgeon, at least one registrar (PGY4/5) and junior residents commencing post-graduate training (PGY1/2).

Elective outpatient care required that patients attended the surgical clinic for follow-up visits. However, this could not continue as it would mean clustering of patients without effective methods to maintain social distancing. To overcome this, the surgical teams accessed a list of patients requiring elective outpatient care and contacted them by telephone for triage. Patients whose conditions allowed had their appointments postponed. For patients who required urgent consultations, the surgical teams used FaceTime (Apple Inc., Cupertino, California, United States) video conferencing applications on mobile phones to view wounds and/or carry out face-to-face consultations.

MULTIDISCIPLINARY CARE

This facility practiced a multiple disciplinary approach to health care since the year 2013[12]. Traditionally, this was achieved by healthcare workers meeting face-to-face in a dedicated meeting room to discuss cases. In this setting, there was initially poor buy-in to the MDT concept. As a result, there was little dedicated funding for MDT processes. This was overcome by members utilizing free software, such as coordination *via* WhatsApp® (WhatsApp Inc., California, United States) and Google mail® (Google Inc., Mountain View, CA 94043, United States) groups. Radiology images were accessed using free OsiriX® DICOM software (Pixmeo, Geneva, Switzerland) and shared *via* Dropbox® (Dropbox Inc, San Francisco, California). Initially, this was laborious, but when the pandemic changes were thrust upon us, we were already in a position to switch effectively to electronic meetings *via* Zoom (Zoom Video Communications, San Jose, California) – also freely available on the internet.

Interestingly, upon review of our records, we found that the attendance increased once there was no longer a need for face-to-face meetings. Also, the images were viewed directly on individual devices, allowing better visualization and participation. In the first 90 days, virtual meetings lasted for 20 min (mean) and discussed an average of 2.45 cases. After one year of virtual meetings, the process became streamlined and the workload increased, culminating in a mean meeting duration of 75 minutes and mean of 6.5 case discussions per meeting. We also recorded the attending surgeons' clinical plan pre- and post-meetings and noted that 52% of therapeutic plans had changed post-discussion.

EMERGENCY SURGICAL CARE

Patients continued to present to hospitals with surgical emergencies. Priority was given to triaging patients, channeling COVID positive patients to a parallel COVID health care facility. This ensured other patients and staff were not exposed to the virus. Since our facility had no access to any form of rapid COVID status testing, patients with suspected infections were isolated in tents until they could be formally tested, often at the expense of disease progression and poor outcomes.

Government-mandated instructions to work-from-home where possible also affected rostering of surgical teams. This affected the number of surgical nurses, doctors and support staff[9]. Redistribution of personnel to COVID units[9] further reduced the cadre of staff available for emergency surgical care. In addition, the surgical teams were ordered to further subdivide to mitigate risk of entire teams being exposed at once and to reduce utilization of scarce personal protective equipment stocks[10].

As it relates to the operating room, the usual oversight was not feasible as attending surgeons could not be present for all cases fearing the service collapsing if all members of the team became exposed/infected[13]. We turned to technology using the distance mentoring technique, described in detail in previous publications[10,14].

In summary, a PGY4/5 resident performing an operation used two smartphones to video conference with the consultant surgeon. One was fixated to the theater lights viewing the surgical field and the second was on the anesthetic machine to view the PGY4/5 residents while operating[10,14]. Occasionally, operating room staff manipulated the smart phones for closer inspection. The consultant surgeon used separate devices to virtually guide residents through surgery. We reported this experience with trauma patients[10] and since then have amassed more experience with laparoscopy[14,15], hepatobiliary surgery[14,16] and emergency operations at this facility. We were able to use this method with 96% success[10] with good outcomes. This technique may be considered in the post-pandemic operating room to maintain safety while minimizing virus transmission, once a reliable high-bandwidth network connection is present. The main concerns with this method were the inability for the attending surgeon to take over in case of a complication and the concern that it may suppress the PGY4/5 learning experience. But for the most part, our residents were encouraged by the attendings virtual presence. It is important to note that the consultant and resident surgeons had previously worked together and were well aware of the others' skill sets, capabilities and judgment.

OPERATING ROOM RESPONSE

During the pandemic, teams were truncated to one consultant and a resident with limited first-surgeon experience in major cases. While the distance mentoring technique allowed continuation of care where the PGY4/5 residents were able to safely complete 96% of emergency laparotomies[10], this would have little impact on attending surgeons. The reduction of surgical staff in the operating room remained a problem.

Robotic surgery would have been a good solution, since it had enjoyed good success across the globe [17], but it had not been used in the Caribbean before. One reason for this is that most Caribbean nations are in middle-income or low-income brackets[1,4] and could not afford to acquire commercially available surgical robots[13]. In addition, distributors were generally reluctant to supply robotic equipment to the Caribbean because most were low-income countries, including some of the poorest in

the Western Hemisphere[1,4]. From an economic standpoint, distributors may have been reluctant because they thought that these poor nations would not be able afford the hardware and necessary consumables.

Surgical leaders recognized the need to accelerate the search for affordable technology in the face of the 2020 pandemic. We were able to identify a suitable and relatively inexpensive robotic arm and then engage a distributor to supply the equipment in the Caribbean. The FreeHand® robotic arm (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) is a single robotic arm designed to control the laparoscope *via* infrared signals from the surgeon. This alleviates the need for an assistant surgeon and allows the operating room to function with skeleton staff. Via a private-public partnership, a FreeHand® robotic arm (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) was first used at this facility during the pandemic[18]. To date, the robot has been used to perform a variety of FreeHand® robot-assisted operations including liver resections, pancreatic resections, ventral hernia repairs, inguinal hernia repairs, fundoplications, colectomies, gastrectomies, prostatectomies and hysterectomies.

In our experience, this provided a good balance with a lower procurement cost than other commercially available surgical robots, but provides some advantages over traditional laparoscopy. First, the surgeon is in full control over the robot that handles the laparoscope, thereby eliminating human error by a camera person. The head movements to control the robot easy to learn as they are similar to the surgeons' actions to move their heads to view the operative field. While training is obviously necessary before embarking on the use of FreeHand, the training is fairly simple for attending surgeons who are already adept at laparoscopy.

WAY FORWARD

As this paper was being written, Trinidad & Tobago was at the peak of its third wave of the COVID pandemic and the existing responses remained in place. It is clear that humankind will have to learn to live with the pandemic induced changes. Therefore, we acknowledge that the situation is fluid and that these changes will need to be versatile. In order to overcome this, we must consolidate and have.

Leadership

Surgical leaders must recognize that the pandemic has forced us to make significant changes. Of course, some surgeons will resist the deviation from "cultural norms" in the Caribbean. We have to address this early by seeking stakeholder buy-in and by providing training for technology, which at first may seem daunting to many persons. We also believe that surgical leaders must continue to step up and advocate for policy to ensure that surgical services to function appropriately in the face of the pandemic[19,20].

Critical assessment of the healthcare environment

It is clear that the healthcare environment in the Caribbean differ significantly from those in developed countries. We work in low-resource systems with many limitations, including high dependency bed shortages, understocked blood banks, consumable shortages and limited operating time. We have found ways to overcome these challenges that may not be suitable to large, developing countries. We advocate, therefore, that surgeons must critically appraise their local hospitals and understand the pitfalls in their environment in order to introduce policy that would maintain quality service delivery that suits the local healthcare environment.

LIMITATIONS

Admittedly, these changes were largely driven by the need to continue patient care during the pandemic. We also acknowledge that technical capability has outpaced the medico-legal aspect of patient care during the pandemic. This should serve as a stimulus for policy makers to have guidelines in place for telemedicine.

CONCLUSION

The COVID pandemic has proved to be resilient and expected to continue for years to come. In the face of this, surgical leaders should continue to adapt and lead the charge for policy that will allow their hospital to continue functioning. In our environment, virtual multidisciplinary meetings, FaceTime® consultations, remote mentoring and robot-assist laparoscopy have been invaluable adjuncts that allow our service to continue functioning effectively. COVID may have acted as a catalyst increasing our use of basic digital technology. This is unlikely to return to pre-pandemic behavior, further improving our practice.

FOOTNOTES

Author contributions: Cawich SO, Narayansingh G, Mencia M, Thomas D, Barrow S, and Naraynsingh V designed and coordinated the study; Cawich SO, Narayansingh G, Mencia M and Thomas D acquired and analyzed data; Cawich SO, Narayansingh G, Mencia M, Thomas D, Barrow S, and Naraynsingh V interpreted the data; Cawich SO, Narayansingh G, Mencia M, Thomas D, Barrow S, and Naraynsingh V wrote the manuscript; all authors approved the final version of the article.

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REVIEW

Mechanism for development of malnutrition in primary biliary cholangitis

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that is associated with impaired biliary excretion processes. Along with the development of cholestasis, there is a deficient flow of bile acids into the intestinal lumen causing malnutrition (MN) that is manifested in deficiencies of both macro- and micronutrients. The mechanism for development of trophological insufficiency is multifactorial. However, the trigger of MN in PBC is impaired enterohepatic circulation of bile acids. The ingress of bile acids with a detergent effect into the general bloodstream, followed by elimination *via* the kidneys and skin, triggers a cascade of metabolic disturbances, which leads to the gradual development and progression of calorie MN. The latter gradually transforms into protein-calorie MN (PCM) (as marasmus) due to the insufficient entry of bile acids into the duodenum, which is accompanied by a decrease in the emulsification, hydrolysis, and absorption of fats and fat-soluble vitamins, as well as disturbance of intestinal motility and bacterial overgrowth. Fat-soluble vitamin deficiencies complement P CM with vitamin and mineral MN. The development of hepatocellular failure enhances the progression of PCM due to the impaired protein synthetic function of hepatocytes in the advanced stage of PBC, which results in deficiency of not only the somatic but also the visceral pool of proteins. A mixed PCM form of marasmus and kwashiorkor develops. Early recognition of energy, protein, micronutrient, and macronutrient deficiencies is of great importance because timely nutritional support can improve liver function and quality of life in patients with PBC. In this case, it is important to know what type (energy, protein-calorie, vitamin, and vitamin-mineral) and form (marasmus, marasmus-kwashiorkor) of MN is present in the patient and how it is associated with the stage of the disease. Therefore, it is recommended to screen all patients with PBC for MN, from the early asymptomatic stage of the disease in order to identify and avoid preventable complications, such as fatigue, malaise, performance decrement, sarcopenia, osteoporosis, and hepatic encephalopathy, which will be

able to provide appropriate nutritional support for correction of the trophological status.

Key Words: Primary biliary cholangitis; Malnutrition; Calorie; Protein-calorie; Vitamin-mineral malnutrition; Marasmus and marasmus-kwashiorkor malnutrition

Core Tip: The review discusses the development of malnutrition in primary biliary cholangitis. It presents the factors contributing to the gradual progression of signs of malnutrition in these patients in different stages of the disease and considers the pathogenesis of energy, protein-calorie (marasmus), and protein (kwashiorkor) malnutrition as the disease progresses. By taking into account the mechanisms of different malnutrition signs and forms, the authors present the principles of diet therapy for primary biliary cholangitis.

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INTRODUCTION

Malnutrition (MN) is common in patients with primary biliary cholangitis (PBC). MN accompanying this disease worsens its course, prognosis, and quality of life in a patient, negatively affects the outcome of the disease, and is most often recognized only in its later stages[1]. The etiology and pathophysiology of MN are multifactorial in PBC[2]. Impaired biliary excretion processes in PBC, which are accompanied by cholestasis and decreased hepatocyte function, affect the metabolism of both macronutrients and micronutrients and depends on the stage of the disease. For the timely diagnosis and correction of the abnormal trophological status, it is important to understand when, at what stage of the disease, and by what mechanisms, calorie, protein, vitamin, and mineral MN develop in PBC patients. To improve treatment results in patients with PBC, it is necessary to pay attention to the development of MN in them and to its prevention and treatment even in the early stages of the disease. The advanced, end-stages of PBC are accompanied by an imbalance between catabolism and anabolism, with the predominance of the former over the latter. The goals of nutritional therapy for patients with cholestatic liver disease are improvement of anabolic processes for valuable liver regeneration, prevention, and correction of malnutrition as well as to avoid and/or treat related complications of liver disease. It is very important to focus not only on the specific signs of the disease but also on the assessment of the nutritional status in patients during their initial examination. At the same time, the features and mechanisms of metabolic disorders should be taken into account in different stages of PBC in order to timely recognize MN and its correction during basic treatment, taking into account currently known scientific data.

DEFINITION OF MALNUTRITION

The Russian literature lacks the generally accepted term to define the nutritional status[3]. MN (synonyms: Protein-calorie, nutritional insufficiency, trophological insufficiency, malnutrition) is a pathological condition caused by a discrepancy between the intake and consumption (imbalance) of organic nutrients, calories, macronutrients, and micronutrients, leading to weight loss, a measurable negative change in the component composition of the body, which is accompanied by its dysfunction and a poorer clinical outcome[4,5]. MN is defined by the World Health Organization as the result of insufficient intake or absorption of nutrients needed to support growth and to prevent chronic or acute diseases and is often characterized by growth retardation, wasting, being underweight, and micronutrient deficiencies[6]. MN is accompanied by weight loss, lower physical performance, and worse health and causes serious metabolic disorders, immunosuppression, and endocrine dysfunctions[7,8].

PREVALENCE OF MALNUTRITION IN PATIENTS WITH LIVER DISEASE

It is very difficult to estimate the true prevalence of MN for the following reasons[5]: Physicians' extremely low attention to the trophological status; difficulties in assessing MN; and the masking of muscle tissue loss in the presence of excess fat mass and fluid retention.

About 2 billion people in the world experience various types of MN[9]. Secondary (endogenous) MN is noted in patients with various diseases. Studies indicate that MN is observed in 20%-80% of patients with liver disease, according to the clinical stage of the disease[10]. Almost any chronic illness can cause progressive weight loss. A study by Carvalho and Parise[11] has shown that as many as 75% of patients with chronic liver disease have varying degrees of MN. Hyponutrition and sarcopenia are common in patients with chronic liver disease and are associated with an increased risk for decompensation and infections as well as are frequently an independent risk factor for death in these patients and worse treatment outcomes after liver transplantation[2,12]. It is important to note that the incidence of trophological insufficiency increases in these patients as the disease progresses. In the 1990s studies[13,14], evaluation of the nutritional status in patients with different etiologies of liver cirrhosis and with various degrees of liver failure came to the consensus that MN was recognized in all types of cirrhosis [15] and, according to various authors, it ranged from 40% to 100%[16-19]. There is a high prevalence of MN in individuals with decompensated liver cirrhosis. The prevalence of MN is 46% in patients classified as Child-Pugh A cirrhosis and 84% and 95% in those classified as Child-Pugh B and C, respectively[11]. MN cases can be as much as 100% in patients on the waiting list for liver transplantation[20,21].

PBC AND MALNUTRITION

MN develops in PBC patients with and without established cirrhosis[22,23]. According to Wicks *et al* [22], MN is detected in 33% of patients with different stages of PBC. Primary biliary cholangitis (PBC; ICD-10 K.74.3; ICD-11 (beta draft) DB37.2) is a disease, formerly (until 2015) known as primary biliary cirrhosis (PBC)[24], is the chronic, progressive autoimmune cholestatic liver disease proceeding with epithelial destruction, necrosis, and apoptosis, mainly affecting the intralobular and septal bile ducts, which eventually leads to liver cirrhosis[25,26]. PBC is characterized by T-cell-mediated destruction of epithelial cells that line the small intrahepatic bile ducts[27]. This leads to ductulopenia and persistent cholestasis to develop end-stage cirrhosis with hepatocellular failure[26].

Early-stage disease may be asymptomatic or have nonspecific symptoms, such as weakness, fatigue, reduced performance, anorexia/hyporexia, and malaise, which can be easily confused with other conditions. During this period, MN caused by the disease itself is generally invisible since there are no significant damage to the liver cells involved in metabolic processes. In early-stage PBC, there is a slight decrease in energy consumption, which does not lead to clinically pronounced protein-calorie MN, but there is already a potentially modifiable MN during this period[28-30].

As cholestasis progresses, excess bile acids have a chronic (continuous) aggressive effect on the liver parenchyma, which is manifested by the development of gradually progressing hepatocellular failure. The trophological status of patients with PBC also decreases as the disease progresses, which is partly due to a significant decrease in energy consumption[22]. Patients with advanced PBC develop liver cirrhosis that may be accompanied by ascites, portal hypertension, esophageal/gastric variceal hemorrhage, and hepatic encephalopathy[31]. Portal hypertension can develop in patients with cholestatic liver disease before cirrhosis is established[32,33]. There is almost a direct relationship between the severity of liver disease and the degree of MN[30]. In this case, the state of nutrition is disturbed secondarily to the symptoms of the disease[33]. Severe protein-calorie MN more frequently develops and is observed in advanced and end stages of PBC, generally in patients who have been suffering from this disease for more than one decade[29] and when there is a 25% or less decline in the total number of functioning hepatocytes[34]. Trophological insufficiency becomes more easily detectable when the patients with PBC develop severe cirrhosis with ascites.

THE PATHOGENESIS OF MALNUTRITION IN PBC

The causes and mechanisms leading to MN and weight loss in patients with PBC are multifactorial and can be divided into three groups: insufficient intake of nutrients; abnormalities in digestion and absorption (maldigestion and malabsorption syndromes); and increased metabolic rate (accelerated catabolism).

Insufficient intake of nutrients in patients with PBC

In early-stage PBC, the trophological changes are associated with elevated plasma bile acid levels in these patients, which gives rise to an early and, most commonly, the only for several months or even

years pathognomonic symptom of the disease, such as local or diffuse (extension), moderate or pronounced (degree), and persistent or transient (duration) skin itching[26,35]. The cause of skin itching is the epidermal deposition of bile acids that are abundant in the blood of patients with PBC even in the asymptomatic and early stages of the disease, long before developing jaundice. In this case, all fractions of conjugated bile acids increase in the blood.

In response to excess plasma bile acids in PBC patients, whose body tries to remove toxic bile acids having detergent properties from the general circulation through the kidneys and skin. In this case, 50%-85% of bile acids that are unconjugated with glycine or taurine are detected in the skin, and less than 20% of bile acids are found as sulfoesters[25,26,36]. Itching is more marked at night and frequently enhanced in contact with tissues as well as in warmth. Itching is not relieved by symptomatic (antihistamine, sedative) medications; it often causes excruciating insomnia, emotional changes, anxiety, and depression[24]. All this leads to decreased appetite and insufficient intake of food ingredients, which is accompanied by an increase in glycogenolysis and by a reduction in glycogenogenesis.

Glycogenolysis, a biochemical process of breaking down glycogen into glucose, occurs primarily in the liver and muscles. The main purpose of glycogenolysis is to keep blood glucose levels stable to provide the body with energy. Due to its glycogen stores and glycogenolysis processes, the liver provides up to 75% of the body's need for glucose as the primary substrate quickly used to replenish energy.

Glycogenogenesis is a metabolic pathway that synthesizes glycogen from glucose. This process takes place in all tissues; however, it occurs mainly in the liver and muscles. The starting point for glycogenogenesis is glucose-6-phosphate that can be obtained from glucose in the reaction catalyzed by glucokinase in the liver and by hexokinase in the muscles. Liver glycogen is known to be used as an energy material by all tissues and organs. At the same time, glycogen in muscles is employed by them as an energy material exclusively for their own needs.

Green *et al*[37] indicated that even in the early stages of PBC, glycogen stores gradually reduce in the liver, which is associated with an increase in glycogenolysis and a decrease in glycogenogenesis. The authors have convincingly shown that glucokinase activity in PBC patients reduces significantly (down to zero), which suggests that liver glycogen production decreases[37]. At the same time, hexokinase (performs phosphorylation of hexoses) that is responsible for glycogen synthesis mainly in the muscles significantly increases during this period in PBC patients *vs* healthy individuals[37]. At the same time, hexokinase (that produces phosphorylation of hexoses), which is responsible for glycogen synthesis mainly in the muscles, significantly increases during this period in PBC patients *vs* healthy individuals [37].

Excruciating insomnia, emotional changes, anxiety, and depression, which develop even in the early stages of the disease, contribute to a decline in glycogen stores and to gradually progressing energy deficiency (a reduction in the level of glucose used as an energy substrate) with the clinical manifestations of obvious weakness, rapid fatigue, and decreases in performance, functional status, and quality of life in PBC patients[24,33,35,38-40]. Moreover, the asthenic syndrome in patients with PBC is more pronounced than in those with other chronic liver diseases[24]. There is evidence that an important role in the mechanism of fatigue development is played by aromatic amino acids, such as tyrosine, phenylalanine, and tryptophan, which are abundant in the blood of patients with PBC[39,41,42].

And so, in early-stage PBC, an imperceptible trophological change occurs as calorie MN that manifests itself only as general weakness and/or reduced working capacity for a fairly long time[40,43, 44].

The developing impairment of biliary excretion processes (accumulation of blood bile acid) in patients with PBC even in the asymptomatic and early stages of the disease contributes to the development of calorie MN, which requires that higher-calorie foods be included in the diet of these patients.

Even slight nutrient deficiencies accompanied by a gradual increase in glycogenolysis and a decrease in glycogenogenesis leads to the inclusion of compensation mechanisms. The latter are intended to protect higher energy-consuming vital organs (the brain, myocardium, erythrocytes, *etc*.) from energy deficiency by redistributing plastic and energy resources[5]. This brings about the mobilization of energy resources of adipose tissue and the consumption of fatty acids as an energy material. Fatty acids become important substrates for energy production. Due to the acceleration of fatty acid β-oxidation processes, there is a progressive decline in fat stores in patients with PBC[45,46]. The activation of these processes occurs as cholestasis progresses.

Along with this, patients with PBC are observed to have elevated levels of palmitic and oleic fatty acids[37]. The latter are the main components of biliary phospholipids (Figure 1) that are involved in the formation of micellar and lamellar structures consisting of phospholipids, cholesterol, and bile acids [47]. In patients with PBC, the plasma levels of palmitic and oleic acids as well as phospholipids and cholesterol increase even in the early stages of the disease and are aimed at neutralizing the detergent effect of excess bile acids entering the general circulation as cholestasis progresses[26,32]. In PBC patients, cholesterol, phospholipids, and palmitic and oleic acids can enter the general circulation due to an increase in their synthesis in the liver and to the entry of bile components into the blood as a consequence of progressive cholestasis.

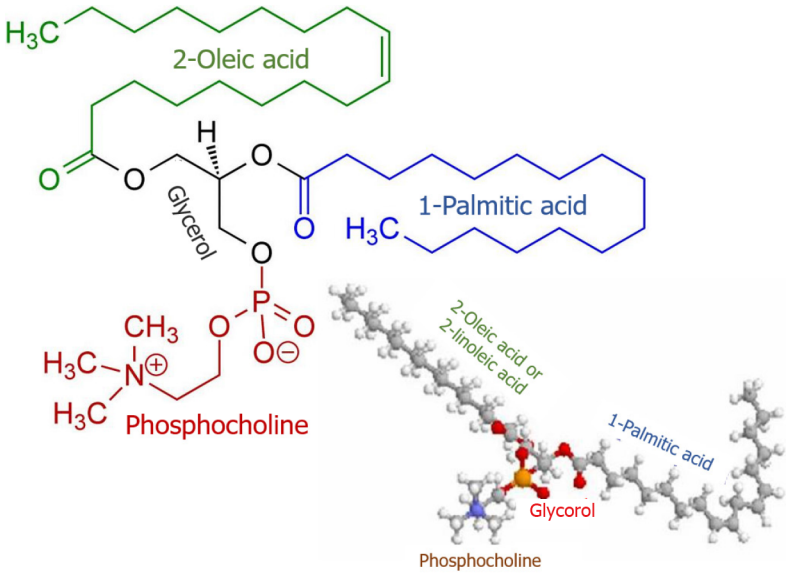

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Figure 1 Chemical structure of phosphatidylcholine containing palmitic and oleic fatty acids.

The higher synthesis of phospholipids requires an increased amount of not only palmitic and oleic fatty acids but also orthophosphate. In this connection, even in the early stages of the disease, the plasma of patients with PBC displays the moderately enhanced activity of the hepatic fraction of alkaline phosphatase and 5′-nucleotidase, which indicates changes in phosphorus metabolism[26]. These enzymes are involved in the hydrolysis of phosphomonoesters to yield orthophosphate that is essential as the main component for the biosynthesis of phospholipids that in turn are required to neutralize the increased content of plasma bile acid levels in patients with PBC.

In patients with PBC, the long-term elevated plasma levels of cholesterol in response to the increase in its synthesis in the liver can give rise to xanthelasmas, single or multiple, pale-yellow formations that are slightly raised above the skin. In these patients, the increased levels of cholesterol as well as those of phospholipids are aimed at neutralizing the detergent effect of bile acids entering the general circulation. At the same time, despite the increase in their total plasma cholesterol, the patients with PBC were found to have mild hepatic steatosis and a low risk for atherosclerosis and cardiovascular events[48].

The developing impairment of biliary excretion processes (accumulation of blood bile acids) in patients with PBC even in its early stages causes fat metabolic changes that are aimed at compensating for energy deficit (accelerated fatty acid β-oxidation) and at neutralizing the detergent effect of excess bile acids (the increased synthesis of phospholipids and cholesterol). Therefore, standard foods are generally well tolerated by PBC patients who do not require a low-cholesterol diet in the early stages of the disease. Their diets can include foods that are high in phosphorus to maintain sufficient synthesis of phospholipids. Low-fat diets to reduce xanthelasmas have been recognized to be unsuccessful and even harmful[49].

Abnormalities in digestion and absorption (maldigestion and malabsorption syndromes)

Intrahepatic cholestasis in PBC is a multifactorial process that is associated with damage to subcellular structures in the epithelial cells of the intrahepatic bile ducts and with changes in bile acid metabolism due to impaired bile excretion. Insufficient entry of bile acids into the intestinal lumen in patients with PBC tends to decrease the rate of fat hydrolysis processes and to inadequately absorb fats and fat-soluble vitamins (A, D, E, and K) in the small intestine. This contributes to the progression of MN due to steatorrhea (fecal excretion of more than 7 g of fat per day) and to the gradual development of vitamin and mineral deficiencies[25,26]. The severity of steatorrhea correlates with lower bile acid production and concentrations ($r = 0.82$; $P < 0.0001$), elevated serum bilirubin levels ($r = 0.88$; $P < 0.001$), and late histological stages of PBC ($P < 0.005$)[50]. All patients with serum total bilirubin levels greater than 4.5 mg/dL have severe steatorrhea (the fecal fat excretion is greater than 25 g/d)[26,50].

The mechanism of steatorrhea development is associated with insufficient fat emulsification owing to the reduced ingress of bile acids into the intestinal lumen[51]. In this case, the processes of fat hydrolysis by pancreatic lipases are not disrupted. The results obtained by Ros *et al*[52] showed that pancreatic function was generally preserved and does not cause steatorrhea in PBC. In patients with PBC, the serum activity of alkaline phosphatase does not correlate with the severity of steatorrhea, and the pancreatic amylase is in the normal range[52]. Fat emulsification is required to increase the area of contact of the substrate with lipase enzymes. A decrease in the processes of fat emulsification leads to

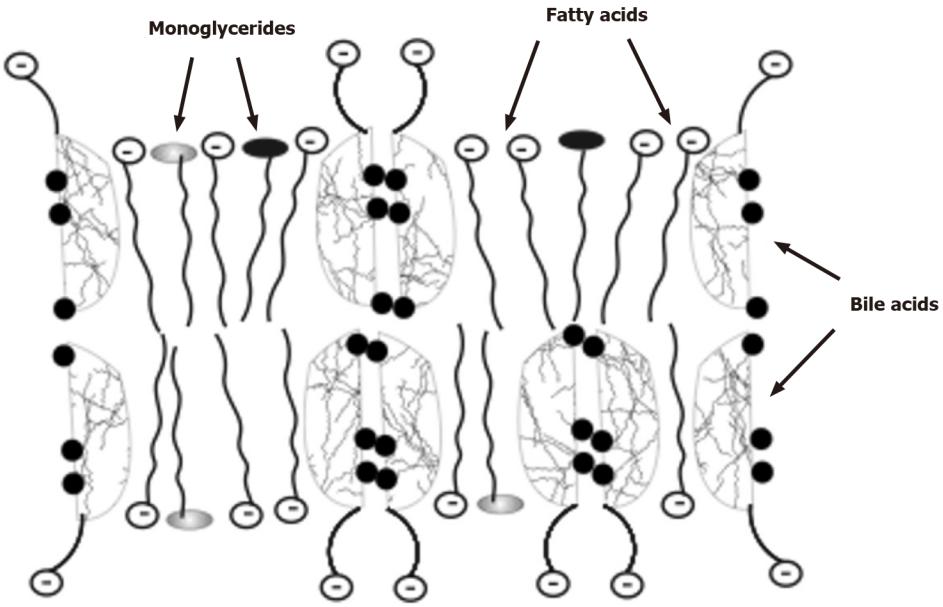

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Figure 2 Schematic diagram of the composition of lipoid-bile acids complexes formed in the small bowel.

the lower rate of hydrolysis of fats, which results in their incomplete digestion, when moving along the intestine, and contributes to the gradual development of steatorrhea.

In addition to the emulsification of fats, bile acids are involved in the absorption of hydrolyzed fats and fat-soluble vitamins. Fatty acids and monoglycerides, which are formed from neutral fats and phospholipids, with the participation of bile acids and under the action of lipases are absorbed by enterocytes as an emulsion of lipoid-bile acid complexes in the upper small intestine (Figure 2). Being potent detergents, bile acids form micellar or lamellar structures with fatty acids and monoglycerides for absorption by enterocytes[25,26]. The complexes disintegrate inside the enterocytes. Fatty acids with monoglycerides remain in the enterocytes (used by a cell as a building, energetic material or packed into chylomicrons), while bile acids come back into the intestinal lumen and take part in the emulsification of fats and in the formation of new lipoid-bile acids complexes for delivery of fatty acids, monoglycerides, and fat-soluble vitamins to the enterocytes. While moving through the small intestine, bile acids are able to participate 4-6 times in the delivery of fatty acids and monoglycerides into the enterocytes [53]. Thus, insufficient amounts of bile acids in PBC interfere with the absorption of fats and fat-soluble vitamins.

Intestinal bile acid deficiency not only impairs fat emulsification and the decreased absorption of fatty acids, monoglycerides, and fat-soluble vitamins, in patients with PBC[52] but also leads to intestinal microbiome dysbiosis[54]. DiBaise *et al*[55] suggested that dysbiosis also plays a significant role in the development of steatorrhea in patients with PBC and that bacterial overgrowth should be obligatorily assessed in these patients.

Since the insufficient entry of bile acids into the intestine is one of the first signs of the disease, even in its early stages, patients with PBC can be found to have fecal matter of incompletely digested fats, one of the signs of steatorrhea. As the disease progresses and steatorrhea develops, most patients have semi-liquid stools up to diarrhea of varying severity. With this, some patients with PBC are observed to have constipation. The latter can be attributed to a certain change in the gut microbiome and an insufficient effect of a small amount of bile acids on intestinal motility.

Steatorrhea in the presence of gradually and imperceptibly developing calorie MN leads to the development of slowly progressive weight loss in patients with PBC. Mid-arm circumference, triceps skinfold thickness, and dual energy X-ray absorptiometry-estimated % fat decreased significantly with disease progression ($P < 0.001$) and especially when liver cirrhosis with ascites is established[22].

The development of slowly progressive weight loss can be facilitated by the use of certain drugs. Thus, cholestyramine used to relieve itching can cause abdominal distention, constipation, or diarrhea, which suppresses, restricts, and disrupts food intake, resulting in inadequate intake of food ingredients and in higher energy deficiency[32].

The developing impairment of biliary excretion processes (insufficient flow of bile acids into the duodenum) in patients with PBC even in its early stages contributes to the development of slowly progressive weight loss, which requires the prescription of ursodeoxycholic acid preparations and the incorporation of high-calorie foods for their diets. Since these patients eat less during meals due to early satiety, it is possible to recommend smaller, more frequent higher-calorie meals[28,29]. At the same time, fats should not be restricted in their eating patterns. Edible fats should be restricted only if the

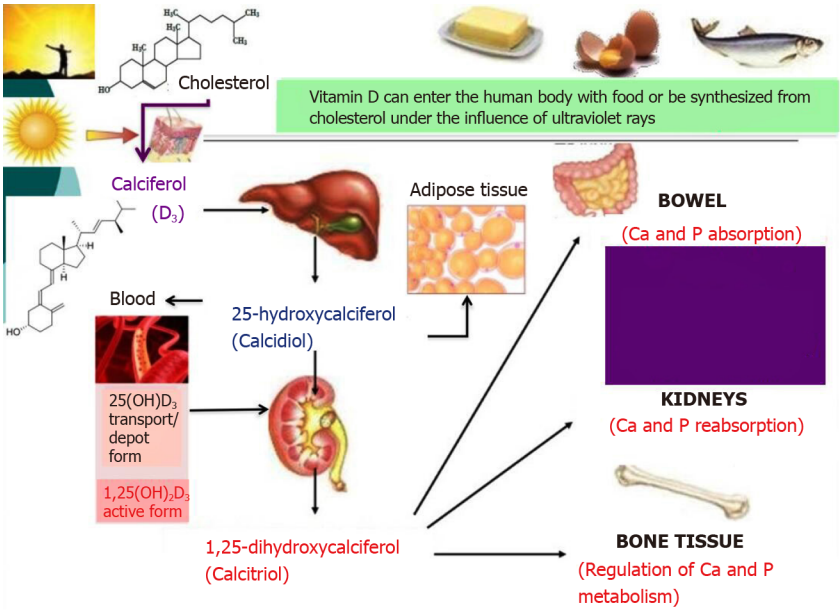

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Figure 3 Metabolism of vitamin D and its involvement in the metabolism of phosphorus and calcium.

patients have obvious steatorrhea or severe nausea or symptoms of indigestion when consuming fats. However, it should be borne in mind that foods that have no or low fat and/or triglycerides containing the average fatty acid chain length are generally better tolerated. Therefore, it is important to individually assess the patients' tolerances to different fats and to make appropriate recommendations.

Vitamin and mineral deficiencies: Bile acids play an important role in absorbing the fat-soluble vitamins A, D, E, and K from the intestines. Bile acids can include fat-soluble vitamins in the lipoid-bile acid complexes and thus transport them into the enterocyte. Insufficient entry of bile acids in the intestine in PBC leads to a decrease in the absorption of fat-soluble vitamins and to the development of vitamin deficiencies[56]. Deficiency of vitamins A, D, E, and K was identified in 33.5%, 13.2%, 1.9%, and 7.8% of PBC patients, respectively[56].

Despite the fact that insufficient ingress of bile acids in PBC occurs even in its early stages, fat-soluble vitamin deficiencies are more frequently manifested at the stage of frank cholestasis with pronounced signs of the disease or in the stage of cirrhosis development. The ability of fat-soluble vitamins to accumulate in significant quantities and to be stored in the liver and adipocytes as well as that of some of them to be synthesized in the body cause fat-soluble vitamin deficiencies to generally not develop in early-stage PBC. Thus, vitamin D is synthesized in the skin from cholesterol upon exposure to ultraviolet rays, whereas vitamin K is synthesized by the intestinal microflora. But as the disease progresses and hepatocellular failure develops, there is deficiency of these fat-soluble vitamins since they are metabolized in the liver.

Vitamin D takes an active part in phosphorus and calcium metabolism. Dietary (edible) vitamin D and vitamin D_3 (calciferol) that is newly synthesized by ultraviolet radiation from cholesterol are inactive forms of this vitamin. In the liver, it is hydroxylated to 25-hydroxycalciferol (calcidiol) that can accumulate and be stored in the liver and adipose tissue. The serum concentration of 25-hydroxycalciferol is considered the most reliable indicator of the total metabolism of vitamin D; therefore, this indicator can be used to determine the body's supply of this vitamin[25,26]. When blood calcium decreases, there is an increase in the synthesis of parathyroid hormone that stimulates the renal hydroxylation of calcidiol to 1,25-dihydroxycalciferol (calcitriol), the active form of vitamin D, which is also involved in the regulation of metabolism of calcium and phosphorus: it increases their absorption in the intestine, their reabsorption in the renal tubules, and regulates the exchange of calcium and phosphorus in the bones (Figure 3).

In PBC, as hepatocellular failure develops, there is a gradually progressive deficiency of calcidiol, precursor of the active vitamin D, leading to osteodystrophy accompanied by osteopenia. The latter is a recognized complication of cholestatic liver disease with a prevalence of 10% to 56% depending on the stage of the disease[57]. PBC is a condition that causes osteopenia more often than other chronic liver diseases[58-61], as clinically manifested by the development of signs of osteoporosis[62].

Osteoporosis: Osteoporosis is a systemic skeletal disease characterized by low bone mass and bone tissue microarchitectural deterioration, thus resulting in increased bone fragility and a higher risk for unmotivated fractures[63-65]. The prevalence of osteoporosis among patients with PBC ranges from

20% to 37% or more, which is higher than that in the general population (10%-11%)[59-61,66]. According to Lindor *et al*[32], the incidence of osteoporosis in PBC is 30%. Osteoporosis increases with liver disease progression[67].

The molecular mechanisms of osteoporosis in patients with PBC are associated with the impaired enterohepatic bile acid circulation, followed by the decreased concentration of bile acids in the small bowel and by malabsorption of fat-soluble vitamin D[68]. In PBC patients with severe cholestasis along with developed intestinal malabsorption of dietary vitamin D, calciferol is slowly converted to calcidiol in the liver as hepatic cell failure progresses[69] and due to those monooxygenases are competitively inhibited[70]. In these patients, the lower amount of calcidiol causes a decrease in the renal production of the active form of vitamin D, calcitriol. This results in an impairment of phosphorus and calcium metabolism, which gives rise to osteodystrophy[58,71,72] that can manifest itself as bone pain even in the early stages of PBC. The development of bone densitometry could estimate bone mass and assess the risk of fractures[58], which correlated with bone mineral density[64]. In this case, laboratory tests yield important information about the metabolic status of the bone. The serum level of calcium and phosphorus is usually slightly reduced in patients with PBC[58]. In Sherlock's[51] opinion, impaired phosphorus and calcium metabolism in PBC patients is facilitated by steatorrhea; increased intestinal fat content can form insoluble soaps with calcium, preventing its further absorption by enterocytes. Reduced calcium absorption correlates well with increased fecal fat excretion and to a lesser extent with the severity of jaundice[73]. Genetic factors also play a role in the development of osteoporosis[74-76]. Bone X-ray and densitometry and morphological examination of a bone tissue biopsy specimen from a patient with PBC most commonly reveal the signs of osteoporosis[58]. In the later stages of the disease, there are pathological fractures of the vertebrae and ribs, less frequently those of pelvic bones and long bones[66].

In patients with PBC, long-term steroid therapy that accelerates and aggravates the development of osteoporosis can lead to clinically significant bone loss with a more than 2-fold increase in the risk of fractures[77]. Atraumatic fractures are especially dangerous in PBC patients who have undergone orthotopic liver transplantation and are treated with high-dose corticosteroids[62].

Glucocorticosteroids decrease the intestinal absorption of calcium by lowering the production of calcitriol (1,25-dihydroxyvitamin D_3), by suppressing the tubular reabsorption of calcium in the kidneys, and by increasing its urinary excretion. A decrease in blood calcium levels leads to a compensatory increase in parathyroid hormone production and bone resorption. In addition, glucocorticosteroids directly increase the release of parathyroid hormone and suppress the function of osteoblasts by enhancing the activity of osteoclasts and indirectly inhibiting the formation of bone tissue, by suppressing the synthesis of testosterone in the gonads, and by reducing the generation of growth hormone, insulin-like growth factor 1 that is synthesized by the liver and stimulates bone collagen type 1 synthesis and osteoblastic function[58,78,79].

Thus, the pathogenesis of osteoporosis in patients with PBC is complex and multifactorial[58,62,80] and involves impaired vitamin D and K absorption and metabolism[81], magnesium ion deficiency, decreased intestinal absorption of calcium and its reabsorption in the renal tubules, increased bone resorption[82,83], elevated levels of bilirubin that inhibits osteoblast function[58,66,84], genetic predisposition[85], and adverse reactions of drugs, such as corticosteroids and cholestyramine, which are used to treat patients with PBC[86]. The development of osteoporosis is associated with the severity of the disease rather than its duration. Osteoporosis can affect quality of life and the course of the disease[58]. Deficiency of the active form of vitamin D (calcitriol) is a risk factor for osteosarcopenia[66,87].

Vitamin K: Vitamin K is required for the synthesis of coagulation factors VII, IX, and X and prothrombin in the liver[88-90]. During the early stages of PBC, vitamin K deficiency is generally absent. As malabsorption and impaired liver protein synthesis progress in late-stage PBC, there is a threat of reduced clotting factor synthesis[91]. Patients with PBC show lower plasma vitamin K levels in 23% of cases, which is usually accompanied by an increase in prothrombin time[92]. In patients with PBC in its end stage, portal hypertension, esophageal/gastric varices, and vitamin K deficiency increases the likelihood of massive bleeding that is difficult to stop.

Vitamin A: Vitamin A absorption requires an intact enterohepatic circulation of bile acids and formation of lipid-bile acid micellar and lamellar structures in the intestine. Significant malabsorption progression in patients with PBC, especially in those with severe cholestasis, can cause decreased intestinal vitamin A absorption accompanied by a reduction in serum retinol levels. In hepatocellular failure, the synthesis of hepatic retinol-binding protein is impaired, which also contributes to lower serum vitamin A concentrations[29]. Clinically, vitamin A deficiency is uncommon in patients with PBC. Just the same, patients with severe PBC sometimes develop insufficient dark adaptation (nyctalopia, night blindness, hemeralopia)[29]. There may be other potential manifestations of vitamin A deficiency, such as dry skin, elastosis, dermatological disorders, and impaired humoral and cell-mediated immunity[29].

The developing impairment of biliary excretion processes (insufficient flow of bile acids into the duodenum) in patients with PBC in the stage of obvious cholestasis and hepatocellular failure contributes to the gradual development of fat-soluble vitamin deficiencies, which requires the use of

ursodeoxycholic acid preparations, the control of plasma fat-soluble vitamin levels, and the dietary intake of foods fortified with appropriate vitamins if the latter are low. If there is deficiency of vitamin D, its active form (calcitriol) is given in combination with calcium supplements and bisphosphonates.

Changes in copper metabolism: The liver is known to play an important role in the metabolism of copper due to the hepatocyte production of ceruloplasmin-copper complexes and its excretion in bile. In health, about 80% of the copper entering the body is excreted in bile and feces.

In late-stage PBC, in which hepatocellular failure develops, copper accumulates in the liver, sometimes up to a level of 25 mg per 100 g of dry weight of liver tissue (the normal value of up to 6 mg per 100 g)[93]. At the same time, due to binding to ceruloplasmin, there are no clinical signs of copper that is toxic to humans nor is the Kayser-Fleischer ring detected.

The accumulation of copper in the body of patients with PBC leads to the activation of the copper-containing enzyme tyrosinase. As a result, the production of melanin increases, which causes skin hyperpigmentation in these patients. With this, the body tries to excrete excess copper not only through the kidneys but also through the skin. This results in copper deposition in the epidermis.

The developing impairment of biliary excretion processes (accumulation of bile acids in hepatocytes) in patients with PBC in the stage of obvious hepatocellular failure is accompanied by abnormal copper metabolism, which requires that foods containing more than 0.5 mg of copper per 100 g of the product should be carefully incorporated into a diet, and copper utensils should not be used for cooking and storing food.

Increased metabolic rate (accelerated catabolism)

As calorie malnutrition and steatorrhea develop in PBC patients, their adaptive response leads to an increased demand of the internal organs for oxygen, which is accompanied by activation of catabolic processes, by mobilization of energy resources of adipose tissue, and by consumption of muscle protein as an energy material along with the active use of carbohydrates[54].

As glycogen stores are depleted in patients with PBC, the requirements by glucose-dependent tissues for glucose are compensated by the activation of gluconeogenesis. The latter serves as an important source for maintaining the normal glucose levels in the body and is a metabolic pathway that results in the generation of glucose from noncarbohydrate compounds. The process takes place mainly in the liver and less intensively in the renal cortex as well as in the intestinal mucosa[94]. The important precursors of glucose in gluconeogenesis are three-carbon compounds, such as lactate, pyruvate, and glycerol, which are generated by fat hydrolysis in adipocytes as well as amino acids hydrolysis of somatic (muscle) proteins. The metabolism of aromatic amino acids is known to occur predominantly in the liver, while that of branched-chain amino acids happens mainly in the muscles[43]. Patients with PBC display decreased serum concentrations of branched-chain amino acids and the increased serum level of aromatic amino acids[95-97]. In PBC patients, the increase in plasma aromatic amino acids correlates with the progression of hepatocellular failure and serves as one of its degree markers.

Unlike carbohydrates and fats, proteins and amino acids have a limited ability to be stored in the human body[94]. Amino acids are generally either used by the body as a plastic material or undergo metabolic degradation[94]. The nitrogen contained in amino acids during their degradation is converted into urea and creatinine and is excreted by the kidneys, whereas the carbon skeleton can be used for the biosynthesis of glucose (gluconeogenesis) or fatty acids or be oxidized to carbon dioxide and water to produce energy, inter alia, as ATP.

Muscles play an important role in the metabolism of amino acids, including through gluconeogenesis. Amino acids present in muscle proteins are an important source of glucose formation and metabolic energy production[94]. Glycogen and glucose deficiencies in patients with PBC enhances the catabolism of muscle (somatic) proteins to release free amino acids, many of which (primarily branched-chain amino acids) are immediately converted into pyruvate or first into oxaloacetate and then into pyruvate. The latter is converted to alanine, acquiring an amino group from other amino acids. Alanine from muscles is transported by blood to the liver, where it can be converted back into pyruvate that is used as an energy substrate or is involved in gluconeogenesis[94]. In patients with PBC, increased gluconeogenesis gradually leads to the massive breakdown and deficiency of muscle protein.

The balance between somatic protein synthesis and degradation is disturbed, which leads to the development of muscle atrophy (sarcopenia). Sarcopenia is characterized by loss of skeletal muscle mass and strength, and it is classified as secondary sarcopenia in PBC[66]. Fülster *et al*[98] showed that skeletal muscle atrophy that develops in chronic diseases is also associated with low exercise tolerance. The exact mechanism contributing to sarcopenia in PBC is not clearly defined. Increased branched-chain amino acid breakdown, muscle autophagy, corticosteroids, hyperammonemia, myostatin, and physical inactivity are considered as potential contributors to sarcopenia[99,100]. The lack of amino acids and energy activates autophagy, a process in which the cell components are degraded by lysosomal enzymes. In PBC, hepatic glycogen loss, followed by accelerated gluconeogenesis, increased branched-chain amino acid catabolism, and glucocorticoid intake can result in muscle autophagy and represent an important mechanism of muscle wasting in these patients[101]. Secondary sarcopenia caused by PBC worsens quality of life and prognosis in these patients[102-104].

Osteoporosis and sarcopenia are closely related to each other and frequently coexist in patients with chronic liver diseases[105,106]. The new term "osteosarcopenia" that implies the coexistence of sarcopenia and osteoporosis has appeared[106]. Saeki *et al*[66] showed that the prevalence of osteosarcopenia in patients with PBC was 15.4%. Osteosarcopenia is a hazardous duet because it causes both ease of falling (due to sarcopenia) and bone vulnerability (due to osteoporosis)[106]. Osteoporosis and sarcopenia are especially problematic in postmenopausal women with PBC[66].

Protein-calorie MN and imperceptibly progressive sarcopenia gradually develop in the presence of energy deficiency, occurring in early-stage PBC in patients with clinical manifestations of cholestasis [19]. When cirrhosis develops in PBC patients, the rate of amino acid-driven gluconeogenesis significantly increases[94]. Despite the increased somatic protein degradation associated with calorie MN, the visceral pool of the protein that is synthesized in hepatocytes in PBC remains within normal limits (with minor deviations) until hepatocellular failure develops. The blood level of albumin and globulin in patients with PBC in its early stages and in the presence of severe cholestasis is within the normal range[25,26]. At the same time, the patient's serum even in the asymptomatic stage of the disease is found to have antimitochondrial antibodies with a diagnostic titer of 1:40 and higher. As cholestasis progresses, there is an increase in the level of γ-globulins[25,26].

The developing impairment of biliary excretion processes (accumulation of bile acids in plasma and hepatocytes) in patients with PBC in the stage of obvious cholestasis results in the gradual development of protein-calorie MN following the pattern of marasmus and sarcopenia. This requires a higher protein diet (predominantly that containing branched-chain amino acids).

As PBC progresses, the resting metabolic rate and systemic thermogenesis increase due to enhanced catabolic processes[37,54]. There is a metabolic situation of resource redistribution, which is amplified as cholestasis and hepatocellular failure progress. The development of hepatocellular failure in end-stage PBC is accompanied by protein synthesizing dysfunction in hepatocytes[54]. In addition to protein-calorie MN in PBC patients during decompensated hepatocellular failure, the synthesis of urea and serum proteins decreases in the liver and the breakdown of visceral proteins increases, which causes a drastic reduction in the plasma level of circulating albumin, and there is higher urinary nitrogen excretion[107]. The continuing enhanced catabolism of somatic proteins is accompanied by the development of visceral protein deficiency, followed by edema and ascites[29]. The clinical manifestations of the impaired trophologic status in patients with end-stage PBC acquire an intermediate form of protein-calorie MN, such as marasmus-kwashiorkor. The development of PCM is facilitated by a decrease in the intestinal absorption of proteins. Portal hypertension resulting in circulatory hypoxia of the intestinal mucosa and in its increased permeability also causes a higher loss of proteins.

The developing impairment of biliary excretion processes (accumulation of bile acids in hepatocytes and plasma) in patients with PBC in the stage of obvious hepatocellular failure (a loss of 75% or more of the functioning liver cells) is accompanied by hepatocyte protein-synthetic dysfunction, which leads to visceral protein deficiency and as a consequence to the development of edema and ascites. There is a transition of the clinical form of PCM as marasmus to mixed marasmus and kwashiorkor MN. This requires a reduction in salt and fluid intake and if there are no signs of hepatic encephalopathy a higher protein diet. Nutritional support during this period should include protein modules with a predominant content of branched-chain amino acids as well as different amounts and ratios of nonessential and essential amino acids[94]. To prevent protein catabolism and to maintain nitrogen balance, it is advisable to have a meal that contains 50 g of carbohydrates before bedtime[108,109].

There is a marked improvement in the nutritional status of PBC patients at the stage of development of cirrhosis and resistant ascites after successful treatment of the latter, which emphasizes the importance of nutritional support in these patients[110].

Hepatic encephalopathy: In end-stage PBC, progressive hepatocellular failure, portal hypertension, and portosystemic shunting lead to hepatic encephalopathy (HE)[111,112]. HE is considered to mean potentially reversible neuropsychiatric disorders, the development of which is based on detoxifying dysfunction of liver and portal blood shunting, developing in the presence of severe liver injuries[111, 113]. HE is a classic symptom of advanced hepatocellular failure[111,112]. In prognostic terms, the encephalopathy associated with progressive hepatocyte death becomes a formidable and almost always fatal complication of PBC. The prevalence of minimal HE among patients with liver cirrhosis ranges from 30% to 84%[114].

There is a metabolic theory of HE, which is based on the reversibility of its main symptoms in very extensive cerebral disorders[115]. In PBC, one can identify two factors that determine the relationship between the liver and the nervous system and play a role in the pathogenesis of HE[113]: The ability of the liver to detoxify neurotoxic poisons (ammonia, mercaptan, skatole, indole, phenols, *etc*) produced in the intestine by the digestion of food ingredients and as a result of vital microbial activity[116,117].

Cerebral metabolism strongly depends on the maintenance of the normal glycemic level that is appreciably determined by the storage of glycogen in the liver and the rate of glycolysis between meals. As mentioned above, the glycogen stores are depleted in PBC. A decrease in the intensity of oxygen and glucose metabolism in PBC is accompanied by reductions in energy production and neuronal activity, which contributes to the development of signs of HE[115]. Positron emission tomography shows that in HE there is a strong correlation between the reduction in cerebral blood flow (in the frontal and parietal

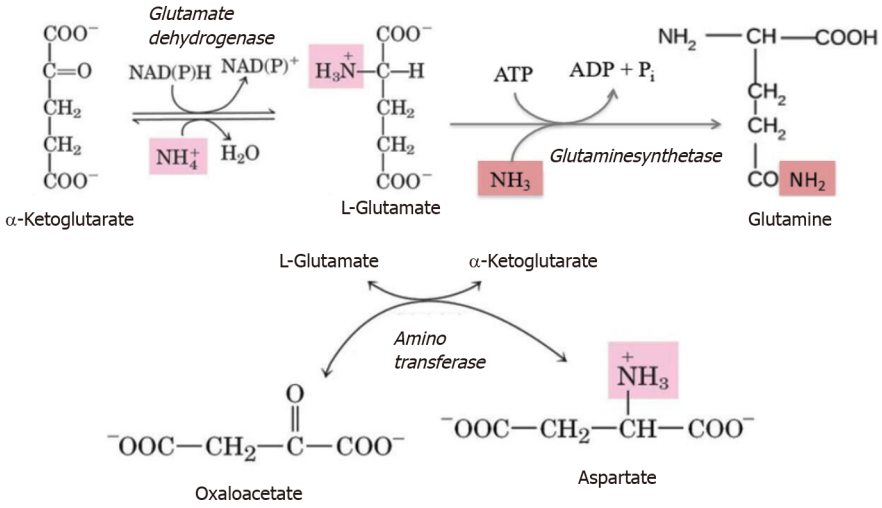

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Figure 4 Use of α-ketoglutarate, glutamate, oxaloacetate, and aspartate to detoxify ammonia.

lobes of the cerebral cortex), which is accompanied by decreased glucose metabolism and the results of neuropsychological tests[113].

The basis for the pathogenesis of HE is hepatocellular failure, accompanied by a decrease in the hepatic clearance of neurotoxic poisons produced in the intestine by the digestion of food ingredients and as a result of vital microbial activity, portosystemic shunting, and amino acid metabolic disturbance that gives rise to false neurotransmitters[115].

Protein and amino acid degradation results in the formation of amine nitrogen that, unlike the hydrocarbon portion of amino acids, is unsuitable for energy production[94]. Therefore, the amino groups that cannot be reused, for example, in transamination reactions, are converted to ammonia. The latter in the cells is produced by the deamination of amino acids, nucleotides, and biogenic amines. Ammonia is a toxic substance and its blood concentration in health does not exceed 50 μmol/L. In health, about 7% of the ammonia formed in the body passes through the tissue of the brain without causing any changes in its functions[111]. The fundamental reaction of ammonia neutralization, which takes place in all tissues, is the binding of NH_3 to glutamate to form glutamine (Figure 4). Its major tissue suppliers of glutamine are muscles, brain, and liver.

In addition to ammonia formed in tissues, significant amounts of NH_3 are generated in the intestine by the bacterial microflora and as a result of food protein hydrolysis. The intestinal absorption of ammonia can cause its significant supply to the liver. This occurs with intake of higher protein foods, incomplete bowel evacuation, alkalization of intestinal contents, overgrowth of opportunistic pathogens, and bleeding esophageal/gastric varices with the development of portal hypertension[112]. The concentration of toxic products, primarily ammonia, as well as skatole, indole, and phenols, thereof may increase in the intestine. In health, these substances enter the portal venous system and undergo the ornithine cycle in the liver. Through deamination, transamination, and decarboxylation reactions, they are converted to urea, a product that is relatively harmless for the body[94]. Urea is the major end product of nitrogen metabolism (85% of all nitrogen is excreted from the body with urea). Urea in the human body is synthesized only in the liver[91].

Neuronal dysfunction results from elevated neurotoxic ammonia levels in the blood in hyperammonemia[110]. The latter is observed in patients with PBC in the cirrhosis developmental stage and is caused by the increased intestinal absorption of ammonia, its impaired hepatocyte detoxification (reduced urea cycle enzyme activity), and lower ammonia binding in hypotrophic skeletal muscles (decreased glutamine synthetase activity)[112,118]. The disturbed hepatic blood flow is of great importance in the development of HE. The development of cirrhosis in end-stage PBC causes blood to shunt either inside the liver itself (portal hepatic venous anastomoses that function as intrahepatic shunts form around the lobules) or blood to flow from the portal vein into the general circulation, bypassing the liver through natural collaterals[115]. Portosystemic shunting and collateral blood flow pathways cause blood flowing from the intestine to enter the general circulation, bypassing the liver. The toxic substances and primarily ammonia, which are contained in the blood portal system, enter the general bloodstream non-neutralized.

Hyperammonemia in patients with PBC triggers compensatory mechanisms of the metabolism and clearance of ammonia, by activating the processes of its neutralization in skeletal muscles and neurons [119]. The elevated blood level of ammonia results in its increased penetration through the blood-brain barrier into the brain, which has an adverse effect on astrocytes. Ammonia detoxification in the astrocytes is affected by glutamate synthetase, leading to the binding of ammonia to glutamate to yield glutamine (Figure 4)[120].

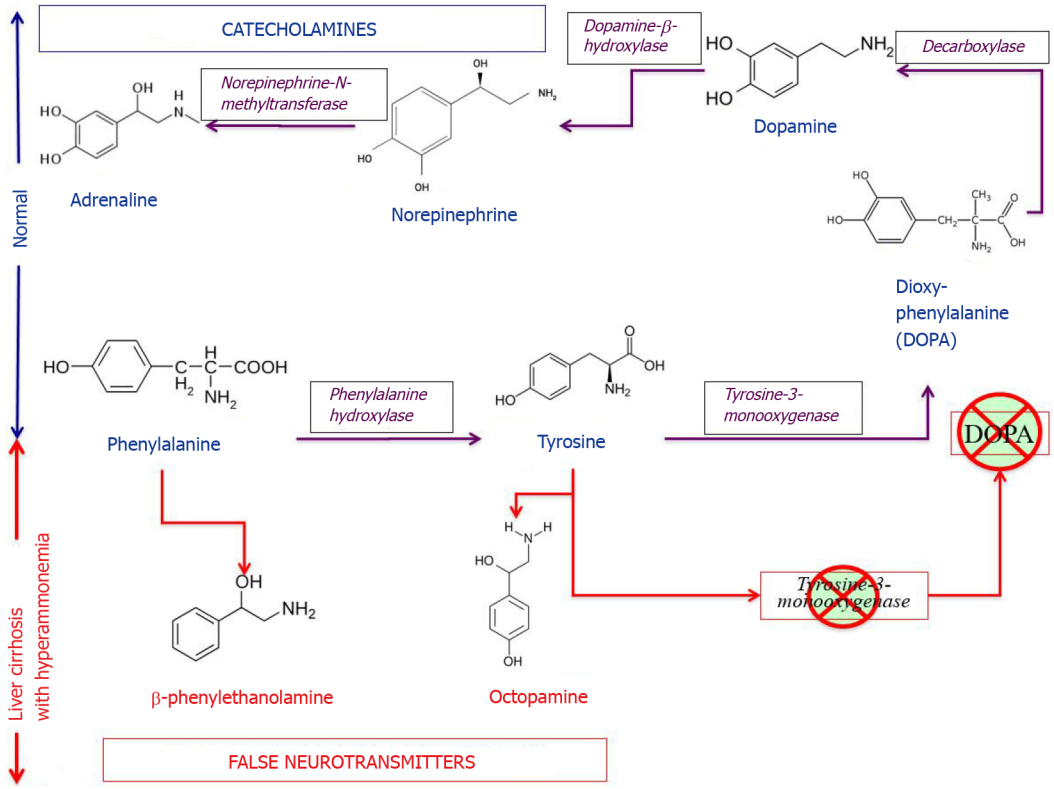

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Figure 5 Synthesis of false neurotransmitters in hyperammonemia.

Excess ammonia in the muscle tissues can also be inactivated due to its interaction with both glutamate and aspartate to synthesize glutamine (Figure 4)[113,121]. When ammonia is excessive, there is a depletion of glutamate and aspartate stores (with simultaneous accumulation of glutamine). The larger amount of glutamine produced is released into the bloodstream in exchange for branched-chain amino acids[122].

In PBC, hyperammonemia thus requires increased production of glutamate and aspartate from α-ketoglutarate and oxaloacetate. This causes a portion of α-ketoglutarate and oxaloacetate to leak away from the tricarboxylic acid cycle, which is accompanied by decreased ATP synthesis. Since the neurons are especially sensitive to decreased energy production, this fact plays a role in the mechanism for the development of clinical signs of HE and causes enhanced energy deficiency in patients with PBC.

The muscles are also sensitive to decreased ATP energy production. Thus, to increase the levels of α-ketoglutarate and oxaloacetate in muscles, which are needed for the Krebs cycle, and to maintain a sufficient glutamate level, accelerated branched-chain amino acid catabolism occurs in PBC patients with hyperammonemia. This results in the insufficient synthesis of muscle proteins and their depletion [123,124]. Hyperammonemia is associated with HE, enhanced branched-chain amino acid catabolism, and sarcopenia[125]. Sarcopenia exacerbates HE, which in turn aggravates a decline in food intake and the development of MN. There is a vicious circle that is difficult to break.

There is evidence that hyperammonemia affects the saturation center in the hypothalamus and suppresses appetite, which can also increase protein-calorie MN in patients with PBC[111,113].

Along with hyperammonemia, a disturbance in the synthesis and metabolism of the major neurotransmitters derived from the aromatic amino acids tyrosine and phenylalanine plays an important role in the pathogenesis of HE in patients with PBC at the stage of development of hepatocellular failure and portosystemic shunting[115]. ter Borg *et al*[39] found elevated concentrations of the aromatic amino acids, tyrosine and phenylalanine, and decreased blood concentrations of the branched-chain amino acids, valine, isoleucine, and leucine, in patients with PBC both at the stage of development of cirrhosis and without cirrhosis[39]. Increased entry of aromatic amino acids into the blood (due to their impaired catabolism in the liver) inhibits the enzyme systems involved in the conversion of aromatic amino acids to catecholamines, which reduces the biosynthesis of dopamine and norepinephrine and increases the synthesis of serotonin from tryptophan. Entering the brain *via* the blood-brain barrier, tyrosine and phenylalanine are involved in the synthesis of false neurotransmitters, such as β-phenylethanolamine and octopamine (Figure 5).

Tyramine is formed from the amino acid tyrosine under the action of bacterial decarboxylases in the intestine. The former is a physiologically active and toxic substance. It easily enters the general circulation and penetrating the blood-brain barrier affects excitatory and inhibitor processes in the

nervous system when patients with PBC undergo portosystemic shunting. Along with hyperammonemia, false neurotransmitters (tyramine) inhibit neuronal function and enhance HE progression [39]. Cognitive impairment, forgetfulness, feeling sleepy during meals and snacks, and having difficulties in cooking food when HE develops in late-stage PBC are significant challenges faced by patients in this group[126]. Subsequently, MN itself becomes an independent predictor of mortality in patients with PBC.

The developing impairment of biliary excretion processes (accumulation of bile acids in hepatocytes) in patients with PBC causes obvious hepatocellular failure, which is accompanied by hepatocyte detoxifying dysfunction, hyperammonemia, and the formation of false neurotransmitters with the development of HE. This requires a strict dietary protein restriction, branched-chain amino acid diets (containing a minimum amount of aromatic amino acids), the prescription of antibiotics (the effect of which is based on their effect on microorganisms that produce nitrogenous compounds in the gastrointestinal tract), aimed at a change in the ratio of neurotransmitters, a decrease in the formation and absorption of ammonia and other toxins formed in the intestine, and an increase in the elimination of ammonia. Strict vegetarian diets (vegetable protein up to 120 g/d) and dairy proteins are generally well tolerated (presumably due to the low aromatic amino acid levels). During this period, patients with PBC usually need to be placed on a waiting list to undergo liver transplant surgery. The European Society for Clinical Nutrition and Metabolism guidelines are used in clinical practice to meet the energy and protein requirements of patients with MN and weight loss in surgical or intensive care units.

Poor nutritional status has serious implications for postoperative complications among candidates for liver transplantation, as it is an important predictor of mortality and postoperative complications in patients with PBC.

CONCLUSION

PBC is a chronic, slowly progressive disease of the liver and biliary tract, which results in a change in the trophological status of these patients. The causes of MN in PBC are complex and multifactorial since the liver is involved in many metabolic processes of the body. But the leading role in the development of MN in patients with PBC is played by a disturbance in biliary excretion processes, and as a consequence there are changes in the metabolism of macronutrients and micronutrients. Trophological insufficiency develops gradually and imperceptibly as cholestasis progresses with the insufficient entry of bile acids in the duodenum with their simultaneous deposition in hepatocytes and entrance into the general circulation. It is precisely these changes that trigger the development of calorie (energy) MN, even in the asymptomatic and early stages of the disease. Compensatory mechanisms for obtaining energy from fatty acids and amino acids of somatic proteins are turned on with time, which is accompanied by protein-calorie (as marasmus) MN with a slowly progressive weight loss. Lipid metabolism disorders also develop. There is an increased synthesis of cholesterol and phospholipids to neutralize the detergent effect of excess plasma bile acids. Insufficient intestinal entry of bile acids contributes to the development of steatorrhea and fat-soluble vitamin deficiencies in these patients. Hence, an increase in PCM occurs and vitamin and mineral deficiencies gradually progress. The latter gives rise to osteoporosis and osteosarcopenia. Prolonged exposure of hepatocytes to excessive bile acid concentrations leads to liver fibrosis and cirrhosis, portal hypertension, and portosystemic shunting to impair protein synthesizing and detoxifying functions of the liver. Occurring visceral protein deficiency results in edema, ascites, and increased PCM with a transition to the mixed form of marasmus and kwashiorkor. Developing hyperammonemia and resulting false neurotransmitters lead to changes in the central nervous system, and HE develops. MN progresses as the severity of the disease progresses. All this makes the correction of MN especially difficult in patients with PBC. Thus, assessment of nutritional status and control of MN are of great importance for improving treatment outcomes in these patients. The presented mechanisms of trophological changes in PBC should assist in timely recognition of MN and in correctly selecting a nutrition support regimen for these patients at different stages of disease development along with symptomatic therapy.

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REVIEW

Viral hepatitis: A narrative review of hepatitis A–E

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Abstract

Viral hepatitis continues to be a major health concern leading to hepatic decompensation ranging from acute hepatitis to cirrhosis and hepatocellular carcinoma. The hepatic and extrahepatic manifestations are not only debilitating but also associated with a significant economic burden. Over the last two decades, the field of virology has made significant breakthroughs leading to a better understanding of the pathophysiology of viral hepatitis, which in turn has led to new therapeutic options. The advent of direct-acting antiviral agents changed the landscape of hepatitis C virus (HCV) therapy, and new drugs are in the pipeline for chronic hepatitis B virus (HBV) treatment. There has also been a significant emphasis on screening and surveillance programs, widespread availability of vaccines, and linkage of care. Despite these efforts, significant gaps persist in care, and there is a pressing need for increased collaboration and teamwork across the globe to achieve a reduction of disease burden and elimination of HBV and HCV.

Key Words: Viral hepatitis; Recent advances; Novel therapies; Barriers to cure; Future direction

Core tip: Viral hepatitis is an important etiology for acute and chronic hepatic dysfunction with significant mortality and morbidity. This review aims to summarize the recent advances in the field and to focus on new novel therapeutic approaches as well as highlighting the barriers to achieving a complete cure. We also focus on preventive measures and strategies to optimize care.

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INTRODUCTION

Hepatitis A

Epidemiology: Hepatitis A virus (HAV) belongs to the Picornaviridae family and is a single-stranded RNA virus that affects around 1.5 million people annually[1]. HAV is a resilient virus and is able to survive in most environments for months despite freezing temperatures, acidic environments, and exposure to chemical agents, thus making it an ideal agent for infection through exposure to contaminated water and food supplies[2]. Since the advent of the HAV vaccine in 1996, there has been a significant decline in HAV incidence rate worldwide[3]. Incidence and prevalence depend on socioeconomic status and geography of the population. Seroprevalence rates are inversely proportional to general hygiene and sanitary conditions and socioeconomic status[4,5].

Prevalence of viral hepatitis in pediatric population: The prevalence in children of HAV varies based on region from where the data are reported, with higher exposure rates in Africa and South East Asia compared to Europe and the USA[6]. Global estimates for HBV prevalence are significantly lower among children, estimated at 1.3% in children under 5 years. There are limited data on hepatitis D prevalence in children[7]. Estimates show that HCV infection in the pediatric population to be approximately 5 million children and adolescents globally. Studies show that the prevalence rates are rising, ranging from 0.05%–0.36% in the USA and Europe to 1.8%–5.8% in developing countries, including Mexico[8-10]. A systematic review of hepatitis E infection in pediatric population projected a worldwide, seroprevalence of 10% with rising prevalence with age[11].

Disease phases: The incubation period of HAV is usually 14–28 d, and patients are contagious for 2 wk prior to, and up to 1–2 wk after symptom onset[6]. Most patients recover spontaneously without chronic consequences[12]. Clinical presentation is variable where children can be completely asymptomatic, while adults can present with jaundice, changes in stool and urine color. Relapsing hepatitis A is characterized by the reappearance of clinical features and laboratory abnormalities consistent with acute hepatitis A after initial resolution of symptoms. Relapse can occur during 6 mo after initial illness. The duration of clinical relapse is generally < 3 wk, however biochemical relapse can last as long as 12 mo. A minority of patients can progress and develop acute liver failure and may need a liver transplant[13,14]. Hepatitis A infection resolves completely in the majority (> 99%) of the cases[15]. HAV infection, unlike some other viruses, does not cause chronic liver disease[16].

Hepatitis A vaccine and future directions: The current recommendations by The Advisory Committee on Immunization Practices are two shots of HAV vaccine, 6 mo apart[17]. There has been a decline in HAV infection from 11.7 to 0.4 cases per 100 000 population, a reduction by 96.6% because of aggressive screening and vaccination protocols[18]. Despite intense public health measures, sporadic hepatitis A cases continue to occur, highlighting the need for ongoing efforts for screening, surveillance, immunization, and education programs.

Hepatitis B

Epidemiology: Hepatitis B has emerged as a global health problem with estimated 350 million cases worldwide of chronic hepatitis B infection[19]. WHO Western Pacific Region and the WHO African Region are estimated to have the highest burden of chronic hepatitis B infection. Countries with high prevalence include Ghana, Gabon, Somalia, China, Cambodia and Mongolia[20]. In the USA, 2.2 million have chronic hepatitis B (CHB) with a higher prevalence (3.45%) among first-generation immigrants [21]. Patients with CHB carry a 15%–40% lifetime risk of developing serious sequelae of infection with an increased risk of death from complications such as cirrhosis and[22] hepatocellular carcinoma (HCC) [23].

Disease transmission and phases: The route of hepatitis B virus spread is *via* contact of blood or bodily fluids of an infected person. The route of HBV transmission varies depending on the prevalence and

geographic area. Vertical transmission at birth and close household contact among children are among the more common modes in Asia and Sub-Saharan Africa where HBV is endemic[24]. In areas with low prevalence, especially developed nations, transmission of HBV among adults usually occurs *via* sexual transmission, percutaneous inoculation through contaminated needles, blood transfusions, or healthcare-associated risk factors such as hemodialysis[24-29]. In the USA and Europe, prevalence rates are higher in areas with a larger ratio of immigrant population, who likely contracted HBV in their country of origin[30,31].

The natural history of HBV depends on the age of the patient at which infection is acquired. For example, in adults, it usually presents as an acute, self-resolving infection where patients who are immunocompetent develop hepatitis B surface antibody to hepatitis B surface antigen (HBsAg), while only 1%–5% progress to developing chronic infection[32]. In contrast, the majority of patients infected by vertical transmission or horizontal infection during early childhood are likely to develop CHB, with the risk of developing CHB rising to 90% if the infection was acquired at birth and 16%–30% if infected during childhood[33,34].

Chronic hepatitis B can be divided into five phases based on the patient's viral load, elevation in liver enzymes, and hepatitis B serologies[35]. The early high replicative phase or immune tolerant phase is characterized by positive hepatitis B e antigen (HBeAg), high levels of HBV DNA and normal serum alanine transaminase (ALT). The next stage's hallmark is immune activation, where HBeAg remains positive along with high levels of HBV DNA and elevated serum ALT with associated hepatic necroinflammation. Based on the immune activation, the disease may progress to loss of HBeAg and development of hepatitis B e antibody (anti-HBe). This stage is characterized by moderate to high levels of DNA with risk of progression to hepatic fibrosis and cirrhosis. In the nonreplicative phase (previously known as inactive carrier phase), in which HBV DNA is usually low or undetectable, HBeAg is absent and patients have normal serum ALT. Lastly, the HBsAg loss/occult phase is defined by loss of HBsAg but detectable HBV DNA in the liver and measurable HBV DNA in serum[36].

Extrahepatic manifestations: Both acute and chronic hepatitis B have extrahepatic manifestations. Polyarteritis nodosa is vasculitis of small and medium-sized vessels and manifests as a serious systemic complication of hepatitis B[37]. HBV-associated glomerulonephritis is commonly seen in children and is self-limited. In adults however HBV glomerulonephritis can slowly progress to renal failure[38]. Approximately one-third of the patients with hepatitis B can have the serum-sickness-like arthritis-dermatitis prodrome[39]. Many cutaneous disorders typically related to immune complex deposition are associated with hepatitis B. These include bullous pemphigoid, lichen planus and Gianotti–Crosti syndrome (papular acrodermatitis of childhood). Neurological manifestations include Guillain Barré syndrome, anxiety/depression and psychosis[40].

Definition of cure: Spontaneous seroconversion is the spontaneous loss of HBeAg and development of anti-HBe. This state is associated with low HBV-DNA levels and clinical remission of liver disease in many patients[41,42]. There is improvement in liver fibrosis when patients have HBeAg seroconversion [43]. Overall 0.5% and 0.8% of chronically infected patients will clear HBsAg per year[44]. This clearance of HbsAg is referred to as the recovery phase of hepatitis B.

Resolved CHB is characterized by sustained loss of HBsAg in a patient who was previously HBsAg positive, along with undetectable HBV-DNA levels and no clinical or histological evidence of active viral infection[45].

Functional cure is defined as loss of HbsAg with gain of anti-HbS. True cure is defined as elimination of HBsAg and closed covalent circular DNA (cccDNA)[45].

BARRIERS TO CURE

Clearance of hepatitis B and host immune response

HBV is a DNA virus with a complex structure and categorized into 10 different genotypes (A–J) based on global distribution, and the severity of the disease, risk of HCC, and response to certain treatments [46]. HBV enters the hepatocytes as a consequence of an interaction between the surface antigen and the sodium taurocholate cotransporting polypeptide[47]. After entry into the hepatocyte, the cccDNA develops when the relaxed circular DNA integrates with host cell nucleus, and at the time of HBV replication, cccDNA can generate pregenomic RNA to function as the template for the fully double-stranded DNA[48]. Figure 1 shows the lifecycle of HBV virus.

A few copies of cccDNA can initiate a full-blown infection after active replication, especially when the host is immunosuppressed[49]. Persistent cccDNA has been detected in hepatocytes of patients with resolved HBV infections, and hence the ultimate goal of HBV eradication should aim to clear any remnant cccDNA[42-46]. Another important reason to aim for clearance of cccDNA is the risk of progression to cirrhosis and HCC in patients with low to no HBV DNA in serum, highlighting the important of the role of ccc DNA[50,51].

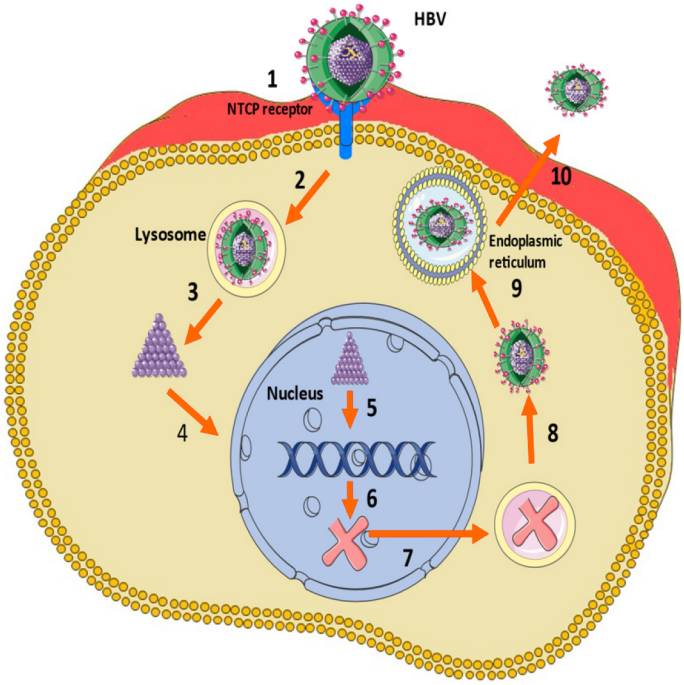

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Figure 1 Lifecycle of hepatitis B virus (HBV). 1: Attachment of the virion to the sodium taurocholate cotransporting peptide (NTCP); 2: Endocytosis; 3: Capsid release; 4: relaxed circular DNA entry into the nucleus; 5: closed covalent circular DNA synthesis; 6: Transcription; 7: mRNA transfer to the cytoplasm and encapsidation; 9: DNA synthesis and budding of virions into the endoplasmic reticulum lumen; 10: Virus release through multivesicular body transfer to hepatocyte surface.

HBV is unique when compared to other hepatotropic viruses as there is a lack of innate response during HBV infection[52,53]. Chronic HBV affects the immune system by interfering with the function of T cells and in the synthesis of neutralizing antibodies, which are essential in mounting an appropriate immune response to the virus[54,55]. HBV exposure *in utero* induces a state of trained immunity against HBV[56], and HBV exposed neonates have variable levels of IL-10 and proinflammatory cytokines, and new pharmacotherapeutics exploring this pathway needs further research[56,57]. The goals of therapy have been to control viral replication so that inflammation, development of fibrosis and cirrhosis, and risk of HCC can be reduced, hence lowering the risk of decompensated liver disease and its sequelae and need for a liver transplant.

HBV vaccine and linkage of care

HBV vaccine, although available since 1982, was not widely available because of its high cost. The Global Alliance for Vaccines and Immunization was able to increase vaccine coverage in the early 2000s [58]. There still are major discrepancies in the availability and utilization of the vaccine, especially with regard to universal birth dose administration[59]. Different regions of the world have variable vaccine administration rates. In 2016, the rate of universal HBV single dose vaccine administration was 93% in the Western Pacific followed by 73% in Southeast Asia, 49% in America and Europe and only 19% in the African Region[60]. WHO recommends HBV vaccine at birth, followed by two or three doses at least 4 wk apart. Hepatitis B vaccine within 12 h is recommended for newborns born to mothers whose HBsAg status is unknown[61]. Adults who were not vaccinated as children can also receive HBV vaccine with first dose as soon as possible followed by 2 doses at 1 and 6 mo after the first dose[61]. Currently approved vaccines in the USA include single antigen hepatitis B vaccine and combined hepatitis A and hepatitis B vaccines. In adults aged 19–59 years they can either receive two doses 4 wk apart of single antigen hepatitis B vaccine or a three-dose series for the combination vaccine.

Multiple factors account for variation in vaccination and linkage of care for HBV across the globe. In China, the major limitation to access and care is secondary to the large population, high prevalence and the low coverage of diagnosis and treatment programs[62]. In resource-rich nations like Australia and New Zealand, despite subsidized screening, specialist management, and treatment for HBV, the barriers include lack of awareness about the implications of HBV infection in healthcare workers, and absence of consistent clinical guidelines regarding diagnosis and referral to a specialist[63,64]. In the USA, a recent systematic review highlighted the obstacles to care, which include access to medical care and lack of education and awareness amongst the patients, along with fear of stigma regarding the diagnosis as barriers to testing and care[65]. Implementation of effective vaccination policies worldwide, along with strategies to prevent vertical transmission and widely available testing and treatment, would be

necessary to attain a reduction in HBV infections worldwide[66].

Current therapies and limitations: Current treatment options for CHB include interferons (IFNs) and nucleoside analogs but they suppress the viral replication and do not eliminate the virus, and aid in achieving a functional cure[67]. In $HBeAg^+$ patients, the loss of serum HBeAg and appearance of HBeAb and loss of circulating HBV DNA is the major goal[22]. Current therapies lead to HBeAg seroconversion in only 20%–30% of treated patients and a mortality reduction by 50% over a 10-year period[22,68,69]. Table 1 summarizes the current antiviral therapies for adults and children.

Goal of new therapies: Eradication of cccDNA is the ultimate goal of ongoing research for novel HBV treatments. Hurdles to measurement of cccDNA include lack of sophisticated assays and challenges to biopsy. There is a need for surrogate markers for loss of cccDNA, HBV DNA, HBeAg[70]. Table 2 summarizes the newer therapies.

Gene editing – future direction: The major hurdle to eradication of HBV is that current antiviral therapies do not eradicate latently integrated or nonreplicating episomal viral genomes. Furthermore, HBV infection disseminates extensively beyond the liver and broad range of cell lines, including neurons, endothelial cells, macrophages, polymorphic nuclear leukocytes, peripheral blood mononuclear cells, and are permissive for HBV replication.

Gene editing provides the ability to alter an organism's DNA. Targeted endonucleases are highly specific enzymes designed to introduce DNA double-strand breaks into desired target sequences .The major classes of DNA-cleaving enzymes include zinc finger nucleases, Tal-effector nucleases, RNA-guided engineered nucleases such as CRISPR/Cas9 and mega nucleases/homing endonucleases[71].

The features that make HBV amenable are small viral genome (3.2 kb) with four proteins (envelope, nucleocapsid, polymerase, and X protein). HBV also has low to intermediate mutability rate and the polymerase mutation rate rages from 1.4×10^{-5}–3.2×10^{-5} mutations/site/year. These factors make it a good target for cleavage enzyme. CRISPR/Cas9 inhibits HBV replication and can be used to target HBV [72,73]. Recently, when Cas9 and guide RNAs were delivered using plasmids into mouse liver, cccDNA could be cleaved, disrupted and cleared[74]. Animal studies after gene editing of CRISPR-Cas9 gene showed improved survival with entacavir with reduced HBV DNA and cccDNA levels[75]. Recent findings of removal of full-length 3175-bp integrated HBV DNA fragment using CRISPR-Cas9 demonstrated that CRISP-Cas9 system may emerge as powerful tool capable of promoting a radical or "sterile" HBV cure[76,77].

HEPATITIS C

Epidemiology

Globally, hepatitis C virus (HCV) infection prevalence is 1%, and there are about 2.3 million cases in the USA[78]. The highest prevalence is in the Eastern Mediterranean and European Regions, followed by South East Asian and Western Pacific Regions. Countries with high prevalence are Russia, Gabon, Egypt and Syria[78,79]. HCV is an RNA virus, and similar to HBV, it is transmitted *via* contacting blood or body fluids of infected individuals, with most common routes of transmission being intravenous drug use, blood product transfusion, solid organ transplantation, or unintentional cross-contamination in hospitals and other medical facilities[80]. Intranasal cocaine use and tattoos administered in unclean parlors are other risk factors[81,82]. Perinatal transmission, though very rare, has been reported in 2%–8% of infected mothers[83].

Hepatitis C in pediatric populations: The estimated prevalence of HCV in 2018 in the pediatric population aged 0–18 years was 0.13% corresponding to 3.26 million children[84]. Direct-acting antivirals (DAAs) are the treatment option for HCV infection in children and adolescents aged ≥ 3 years. Presence of extrahepatic manifestations like rash, advanced fibrosis, cryoglobulinemia, and glomerulonephritis is an indication for early antiviral therapy. Table 3 summarizes the treatment options in pediatric populations.

Extrahepatic manifestations: Chronic HCV, which is untreated can cause chronic inflammation, followed by progressive liver fibrosis leading to the development of cirrhosis and HCC[85,86]. Various extrahepatic manifestations are reported in chronic HCV infection like mixed cryoglobulinemia, vasculitis, glomerulonephritis, and B-cell non-Hodgkin's lymphoma, along with increased rates of insulin resistance, diabetes, atherosclerosis, and cognitive impairment[87-89]. A meta-analysis of 102 studies looking at prevalence, quality of life, and economic burden of extrahepatic manifestations of HCV showed diabetes (15%) and depression (25%) were the most common extrahepatic manifestations [90].

Barriers to elimination: The goal of WHO has been to develop and work on strategies to reduce new infections while treating patients who are infected with HCV[91].

Table 1 Approved antivirals for adults and children for chronic hepatitis B

Drug	Adult dosing	Pediatric dosing	Potential side effects	Pregnancy category
Peg-IFN-a-2a (adult) IFN-a-2b (children)	180 mcg wkly	> 1 yr dose: 6 million IU/m^2 three times wkly	Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders in adults, anorexia, and weight loss in children	C
Entecavir	0.5 mg daily	> 2 yr dose: weight-based to 10-30 kg; above 30 kg: 0.5 mg daily	Lactic acidosis (decompensated cirrhosis only)	C
Tenofovir dipovoxil fumarate	300 daily	> 12 yr	Fanconi syndrome, osteomalacia, lactic acidosis	B
Tenofovir alafenamide	25 mg daily	-	Lactic acidosis	There are insufficient human data on use during pregnancy to inform a drug-associated risk of birth defects and miscarriage
Lamivudine	100 mg daily	2 yr dose: 3 mg/kg daily to max 100 mg	Pancreatitis lactic acidosis	C
Adefovir	10 mg daily	12 yr	Acute renal failure Fanconi syndrome lactic acidosis	C
Telbivudine	600 mg daily	-	Creatine kinase elevation and myopathy peripheral neuropathy lactic acidosis	B

Since the advent of oral DAAs in 2014, there has been a dramatic change in the landscape of HCV therapy[92,93]. DAA therapies are not only well-tolerated and safe but offer cure rates of > 95%[94,95]. In comparison to IFNs, treatment with DAAs is short term[96]. With the new agents and multiple options, treatment can be tailored based on presence and absence of cirrhosis, decompensated disease, coinfection with human immunodeficiency virus (HIV) and renal function and need for dialysis. Table 4 summarizes the available DAAs, their target population, and genotype coverage. DAAs are promising and have changed the landscape of chronic hepatitis C infection, but there are several barriers to care and cure and below mentioned are a few.

Awareness and screening programs

There remains a general misunderstanding and also lack of awareness regarding HCV in the general population worldwide, as evident by a 2017 WHO Global Hepatitis Report, where only 20% of 71 million people with HCV worldwide, were aware of the infection at the time of confirmation[91]. A large population-based study in the USA from 2001 to 2008 showed only 49.7% of patients with HCV infection were aware of their status[97]. Another National Health and Nutrition Examination Survey study showed that cirrhosis was equally common in patients who were unaware of their diagnosis compared to those who knew about their infection[98]. At a patient level, fear of the stigma associated with the diagnosis and at the provider level, lack of time, knowledge, and discomfort in asking about high-risk behaviors are barriers to screening, testing, and cure[99]. The provider perceptions have changed over the years and now most providers believe that they play an active role in their patient's treatment and their decisions to start treatment are not influenced by high risk behaviors amongst patients[100].

In developing countries, the absence of screening programs and limited resources have resulted in the vast majority of patients being undiagnosed[101-103]. A systematic review and meta-analysis of studies published after 1995 showed that in Africa, only 19% of blood transfusions are screened for HCV due to cost constraints[104].

The screening strategies have to be tailored according to the population and the country to make these cost effective[105]. As shown in a systematic review of 67 screening programs, in low HCV-prevalence populations, prescreening can increase efficiency, whereas in high prevalence countries widespread screening programs are cost effective[106-108].

High risk groups: Intravenous drug users (IVDUs) are a well-known high-risk population and the global burden of HCV in injecting drug users is approximately 67%[109]. In Europe the prevalence of HCV is estimated to be 50 times higher in individuals who inject drugs compared with the general population[110]. In the past, this subset of HCV patients was not regarded as eligible for treatment due to concern for poor adherence, reinfection and psychiatric ailments[111]. Current guidelines recommend that people who inject drugs (PWIDs) should not be excluded from HCV treatment[112] and multiple recent studies have shown that there is direct relationship between influences of IV drugs on the efficacy of DAA therapy among adherent patients[113-115], and the SIMPLIFY trial demonstrated that PWIDs should be offered HCV treatment regardless of ongoing drug use[116]. In this high-risk group testing,

Table 2 Drugs in pipeline for hepatitis B virus

drug class	Drug	Company	Phase
Core protein inhibitors	AB-506	Arbutus Biopharma	1
	ABI-H0731	Assembly Biosciences	1,2
	ABI-H2158	Assembly Biosciences	1
	EDP-514	Enanta Pharmaceuticals	1
	JNJ-6379	Johnson & Johnson	1,2
	JNJ-0440	Johnson & Johnson	1
	RO7049389	Roche	1
siRNA, antisense RNA	AB-729	Arbutus Biopharma	1
	DCR-HBVS	Dicerna Pharmaceuticals	1
	GSK/IONIS-HBV-L_{Rx}	Ionis/GlaxoSmithKline	1,2
	IONIS-HBV_{Rx}	Ionis/GlaxoSmithKline	1,2
	JNJ-3989 (ARO-HBV)	Johnson & Johnson	1,2
	RO7062931	Roche	1
	Vir-2218 (ALN-HBV02)	Vir Biotechnology/Alnylam	1
pol/RT inhibitor	Tenofovir exalidex	ContraVir Pharmaceuticals	1,2
HBsAg secretion inhibitors	REP-2139	Replicor	1,2
	REP-2165	Replicor	1,2
HBV entry inhibitor	Bulevirtide	Hepatera Ltd	1,2
TLR-7 agonists	AL-034	Johnson & Johnson/Alios	1
	RG-7854	Roche	1
	RO7020531	Roche	1
TLR-8 agonist	GS-9688	Gilead Sciences	1,2
Therapeutic vaccines	AIC-649	AiCuris	1
	INO-1800	Inovio Pharmaceuticals	1
	TG1050	Transgene	1
RIG-I and NOD2 agonist	Inarigivir	Spring Bank	1,2
Apoptosis inducer	APG-1387	Ascentage Pharma	1
FXR agonist	EYP-001	Enyo Pharma	1,2

HBV: hepatitis B virus; HBsAg: Hepatitis B surface antigen; TLR: Toll-like receptor.

access to care, prescription of DAA therapy, along with the elimination of stigma associated with the infection have been proposed as effective strategies for this specific population[117-119].

Prevention of HBV/HCV infection: Both HBV and HCV can be transmitted perinatally, *via* needle stick injury and *via* household contacts. Perinatal transmission for HBV can be prevented by providing hepatitis B immunoglobulins and vaccines within 12 h of birth to infants of HbsAg-positive mothers [120]. Unfortunately for HCV infection, there are no interventions or prophylactic measures that have been proven to prevent perinatal transmission. Management of needle stick injury for HBV depends on the vaccination status of exposed individual and HBV status of patient. For individuals who suffer needle stick injury and are unvaccinated, vaccination series should be initiated. For vaccinated individuals with documented vaccine response no treatment is required. If the vaccination status is unknown, then its recommended to check anti-Hbs titers and if negative, initiating vaccine series is recommended[121]. Recommendations for prevention of HCV after needle stick injury include testing for HCV RNA, HCV antibodies and ALT immediately after the event, repeat laboratory analysis in 2–8 wk, and referral to specialist if infection occurs[122]. Household contacts should be extensively counselled and education includes measures to avoid sharing razors or toothbrushes etc. that

Table 3 DAA therapy in pediatric population

Regimen	Patient population	Duration (wk)
Genotype 1		
Ledipasvir/sofosbuvir	Prior exposure to DAA and IFN (± ribavirin) , no cirrhosis	12
	Prior exposure to DAA and IFN (± ribavirin) , compensated cirrhosis	24
Glecaprevir/pibrentasvi	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure, no cirrhosis, compensated cirrhosis	16
	Age ≥ 12 yr or weighing ≥ 45 kg with prior exposure to NS3/4A protease inhibitors but no NS5A inhibitor exposure, no cirrhosis, compensated cirrhosis	12
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis	12
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis	8
Genotype 2		
Glecaprevir /pibrentasvir	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis	8
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, compensated cirrhosis	12
Genotype 3		
Glecaprevir/pibrentasvir	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, no cirrhosis or compensated cirrhosis	16
Genotype 4		
Glecaprevir/pibrentasvir	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, compensated cirrhosis	12
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, no cirrhosis	8
Ledipasvir/sofosbuvir	Age ≥ 3 yr with prior exposure to an IFN (± ribavirin) plus an HCV protease inhibitor regimen, no cirrhosis or compensated cirrhosis	12
Genotype 5		
Ledipasvir/sofosbuvir	Age ≥ 3 yr with prior exposure to an IFN (± ribavirin) plus an HCV protease inhibitor regimen, no cirrhosis or compensated cirrhosis	12
Glecaprevir/pibrentasvir	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, no cirrhosis	8
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis	12
Genotype 6		
Glecaprevir/pibrentasvir	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, no cirrhosis	8
	Age ≥ 12 yr or weight ≥ 45 kg with prior exposure to an IFN-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis	12
Ledipasvir/sofosbuvir	Age ≥ 3 yr with prior exposure to an IFN (± ribavirin) plus an HCV protease inhibitor regimen, no cirrhosis, compensated cirrhosis	12

DAA: Direct-acting antiviral; IFN: Interferon; HCV: Hepatitis C virus.

predisposes one to contact with body fluids, HCV/HBV positive individuals should refrain from donating blood, organ and tissue[123].

HBV/HCV coinfection: The worldwide incidence of HBV/HCV coinfection is reported to range from 5% to 15%[124,125]. The incidence varies significantly depending on geographic location, with higher incidence in endemic areas[126]. HBV/HCV coinfection leads to higher rate of cirrhosis, HCC and decompensated liver disease compared to monoinfection[124,127]. Four serological profiles are seen in coinfection–codominant, HCV dominant, HBV dominant, and neither replicative, and these can evolve

Table 4 DAA therapy for chronic hepatitis C virus

Regimen	Patient population	Duration (wk)
Genotype 1		
Daclatasvir + sofosbuvir	Decompensated cirrhosis regardless of subtype	12
	HIV/HCV coinfection when antiretroviral regimen cannot be made to accommodate recommended regimens	12
Elbasvir/grazoprevir	Treatment naive or Peg/RBV experienced regardless of cirrhosis	12
	Severe renal impairment (CKD stage 4/5)	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Glecaprevir/pibrentasvir	Treatment naive or Peg/RBV experienced without cirrhosis	8
	Treatment naive or Peg/RBV experienced with cirrhosis, and non-NS5A failures (including NS3) regardless of cirrhosis	12
	Post liver transplant without cirrhosis	12
	Severe renal impairment (CKD stage 4 or 5)	8–12
	Post kidney transplant regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Ledipasvir/sofosbuvir	Treatment naive regardless of cirrhosis	12
	Treatment naive, no cirrhosis, non-black, HIV negative, and HCV RNA <106 IU/mL	8
	Peg/RBV (± NS3 protease inhibitor) experienced without cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/RBV (± NS3 protease inhibitor) experienced	12
	Decompensated cirrhosis, prior sofosbuvir failure only	24
	Post liver transplant regardless of cirrhosis or decompensation	12
	Post kidney transplant regardless of cirrhosis	12
Sofosbuvir/velpatasvir	Treatment naive or Peg/RBV ± NS3 protease inhibitor experienced regardless of cirrhosis	12
	GT1b, non-NS5A DAA experienced regardless of cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/RBV (± NS3 protease inhibitor) experienced	12
	Decompensated cirrhosis, DAA failure (including NS5A)b	24
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitor) regardless of cirrhosis	12
	GT1a, non-NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Genotype 2		
Daclatasvir + sofosbuvir	Decompensated cirrhosis	12
	Post liver transplant regardless of cirrhosis or decompensation	12
Glecaprevir/pibrentasvir	Treatment naive or Peg/RBV experienced without cirrhosis	8
	Treatment naive or Peg/RBV experienced with cirrhosis, and sofosbuvir failures regardless of cirrhosis	12
	Post liver transplant without cirrhosis	12
	Severe renal impairment (CKD stage 4 or 5)	8–12
	Post kidney transplant regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Sofosbuvir/velpatasvir	Treatment naive, or Peg/RBV or non-NS5A experienced regardless of cirrhosis	12

	Decompensated cirrhosis, treatment naive or Peg/RBV or non-NS5A experienced	12
	Decompensated cirrhosis, DAA failure (including sofosbuvir ± NS5A)b	24
	Post liver transplant with decompensated cirrhosis	12
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Genotype 3		
Daclatasvir + sofosbuvir	Decompensated cirrhosis	12
	Post liver transplant regardless of cirrhosis or decompensation	12
Glecaprevir/pibrentasvir	Treatment naive without cirrhosis	8
	Treatment naive with compensated cirrhosis	12
	Post liver transplant without cirrhosis	12
	Severe renal impairment (CKD stage 4 or 5)	8–12
	Post kidney transplant regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Sofosbuvir + elbasvir/grazoprevir	Peg/RBV experienced with compensated cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Sofosbuvir/velpatasvir	Treatment naive without cirrhosis	12
	Treatment naive with cirrhosis or Peg/RBV experienced without cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/ RBV experienced	12
	Decompensated cirrhosis, previously exposed to DAA (including sofosbuvir ± NS5A)b	24
	Post liver transplant with decompensated cirrhosis	12
Sofosbuvir/velpatasvir/voxilaprevir	Peg/RBV experienced with cirrhosis, or DAA failure (including NS5A inhibitors) regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Genotype 4		
Daclatasvir + sofosbuvir	Decompensated cirrhosis	12
	HIV/HCV coinfection when antiretroviral regimen cannot be made to accommodate recommended regimens	12
Elbasvir/grazoprevir	Treatment naive or Peg/RBV experienced with prior relapse, regardless of cirrhosis	12
	Severe renal impairment (CKD stage 4/5)	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Glecaprevir/pibrentasvir	Treatment naive or Peg/RBV experienced without cirrhosis	8
	Treatment naive or Peg/RBV experienced with cirrhosis	12
	Post liver transplant without cirrhosis	12
	Severe renal impairment (CKD stage 4 or 5)	8–12
	Post kidney transplant regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
	Treatment naive regardless of cirrhosis or Peg/RBV experienced without cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/ RBV experienced	12
	Decompensated cirrhosis, sofosbuvir failure	24
	Post liver transplant regardless of cirrhosis or decompensation	12

	Post kidney transplant regardless of cirrhosis	12
Sofosbuvir/velpatasvir	Treatment naive or Peg/RBV experienced regardless of cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/ RBV (± NS3 protease inhibitor) experienced	12
	Decompensated cirrhosis, DAA failure (including NS5A)	24
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Sofusbuvir/ledipasvir	Treatment naive, compensated cirrhosis – not for decompensated cirrhosis	12
Genotype 5 or 6		
Glecaprevir/pibrentasvir	Treatment naive or Peg/RBV experienced without cirrhosis	8
	Treatment naive or Peg/RBV experienced with cirrhosis	12
	Post liver transplant without cirrhosis	12
	Severe renal impairment (CKD stage 4 or 5)	8–12
	Post kidney transplant regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	
Ledipasvir/sofosbuvir	Treatment naive or Peg/RBV experienced regardless of cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/ RBV experienced	12
	Decompensated cirrhosis, sofosbuvir failure	24
	Post liver transplant regardless of cirrhosis or decompensation	12
Sofosbuvir/velpatasvir	Treatment naive or Peg/RBV experienced regardless of cirrhosis	12
	Decompensated cirrhosis, treatment naive or Peg/RBV (± NS3 protease inhibitor) experienced	12
	Decompensated cirrhosis, DAA failure (including NS5A)	24
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12
	Not for decompensated cirrhosis or post liver transplant with cirrhosis	

Adapted from American Association for the Study of Liver Diseases/IDSA guidelines (https://www.hcvguidelines.org/). CKD: Chronic kidney disease; DAA: Direct-acting antiviral; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; RBV: Ribavirin; Peg: Pegylated interferon.

over period of time[128]. The aim in these scenarios would be to identify and eradicate the dominant virus and then monitor for reactivation of the other virus. Close monitoring of HBV DNA and HCV RNA is essential before determining viral dominance[129]. HBV monoinfection is treated with a nucleo(s)tide analog (*e.g.*, entacavir or tenofovir, lamivudine) and/or pegylated IFN (Peg-IFN). Currently, DAAs are the mainstay of treatment for HCV monoinfection although Peg-IFN plus ribavirin is effective, but is rarely used[126].

HBV/HCV infection after liver transplantation: HBV recurrence after liver transplantation is a major causes of graft failure, graft cirrhosis and allograft dysfunction. Patients can be categorized into high and low risk for recurrent HBV based on pretransplant viral load, HbeAg positivity and history of antiviral drug resistance[130]. Combination of potent nucleos(t)ide analog and hepatitis B immunoglobulin (HBIG) is recommended after liver transplantation for the prevention of HBV recurrence in patients with CHB. Recent data suggest that patients with low risk of recurrence need to be on continued monoprophylaxis with nucleos(t)ide analogs; however, HBIG can be discontinued[77]. HCV recurrence after liver transplantation is universal in patients with HCV viremia at the time of transplantation. The viral levels are shown to rebound and reach pretransplant level with 72 h and DAA therapy should be started within this timeframe to prevent graft reinfection and loss[131].

HEPATITIS D

Epidemiology

Hepatitis delta virus (HDV) is a defective virus that encodes its own genome but needs HBsAg and hence HBV for replication, propagation and transmission[132]. The two high-risk groups at risk of infection include IVDUs and patients with high-risk sexual behaviors[133]. In the USA, HDV infection was considered to be a rare, but data over the last decade estimating seroprevalence of HDV have shown higher rates, especially in Asians and immigrants[45].

Transmission: HDV is transmitted parenterally and sexually, while vertical transmission is thought to be rare[134,135]. In low-endemicity regions and developed nations, IVD use is the main route of transmission[133].

Clinical presentation: HDV infection is always associated with HBV infection as HBV is integral to the assembly of the hepatitis D virion and release. Two major patterns of infection can occur: superinfection and coinfection.

Coinfection is concurrent infection with both HDV and HBV. Clinically, the presentation is difficult to differentiate from other causes of hepatitis and especially acute HBV[136]. Patients who are coinfected can present with symptoms that can be mild to severe fulminant hepatitis[137]. Coinfection is usually self-limited, but it is important to highlight the fact that coinfection can cause severe fulminant hepatitis compared to superinfection[137].

Superinfection occurs when HDV infects an individual with CHB, in whom pre-existing HBsAg provides an ideal environment for HDV expression. Patients progress from acute hepatitis to chronic infection in up to 90% of cases, whereas the rest either resolve or progress to fulminant disease[136]. Chronic HDV infection, in comparison to HBV monoinfection, is more severe and, up to 70% percent of patients rapidly progress to cirrhosis within 5–10 years[138].

Diagnosis and management: In patients suspected to have HDV, the first-line screening test is ELISA for anti-HDV. The acute phase of HDV infection is characterized by positive IgM anti-HDV in serum. IgG anti-HDV antibodies are representative of chronic HDV infection or past exposure[139]. HDV screening for all HBV-infected individuals is recommended by the European guidelines whereas in the USA screening is limited to patients with high-risk factors such as HIV or HCV infections and patients with low or undetectable HBV DNA presenting with elevated aminotransferases[45]. Screening of all HBsAg-positive patients should be considered given concerns regarding underestimation of prevalence of HDV[140,141]. This approach would lead to more accurate determination of HDV prevalence and would also lead to earlier intervention and treatment[142].

The current treatment option for chronic HDV infection is Peg-IFN-α for 12 mo based on guidelines from the American Association for the Study of Liver Diseases, Asian Pacific Association for the Study of the Liver, and the European Association for the Study of the Liver[45,77,143]. Overall, the response rate to therapy is low with only a 10%–20% rate of sustained HDV clearance and 10% rate of HbsAg clearance with 1 year of standard IFN-α[144,145]. Studies revealed that 1 year of therapy with Peg-IFN proved to have a better response rate than standard IFN therapy however it hardly exceeded 25% of sustained HDV clearance[146,147].

Combination therapy involving standard IFN-α with ribavirin[148] or lamivudine[149,150] is not more efficacious than monotherapy with IFN for chronic hepatitis D. Similar results are obtained when Peg-IFN-α is used in combination with ribavirin[151] or adefovir[147].

Novel therapeutics: Given the low overall virological response rate and high rate of relapse, there is an increasing need for therapeutic strategies aimed at improving efficacy and offering it to patients for whom IFN is contraindicated due to advanced liver disease. Currently, three new medications that affect HDV life cycle are being studied in clinical trials, with varying mechanism of actions: hepatocyte entry inhibitors, farnesyltransferase inhibitors, and nucleic acid polymers. Table 5 summarizes these novel therapies with the associated adverse effects. Figure 2 highlights the different targeted approaches for treatment of chronic hepatitis D.

Additional approaches: siRNAs have shown early promise in this field. In a phase IIa clinical trial that showed that a single injection of siRNA ARC-520d decreased HbsAg levels in HbeAg negative CHB patients in a dose-dependent fashion[152]. A multi-dose extension study of up to 12 doses, with once monthly dosing, demonstrated an increased decline of HbAg level, especially in HbeAg-positive rather than HbeAg-negative patients[153]. The study was stopped because of adverse effects of the carrier molecule but demonstrated the effect and highlighted the scope of siRNA as a potential treatment option.

Currently, for the management of HDV, new approaches such as DNA vaccines[154], anti-HB immune complexes[155]https://www-ncbi-nlm-nih-gov.ezproxy3.lhl.uab.edu/pmc/articles/PMC5580405/-ref-75, and immunologically active adjuvants such as β-glucosylceramide are being explored. Targeting the HBV and immune system interaction is another area that has garnered significant interest. Preclinical studies have shown that the Toll-like receptors (TLRs) play a key role in

Table 5 Novel drug treatments for chronic hepatitis D virus

Drug	Mode of action	Administration route	Phase of study	Adverse effect
Myrcludex B	Interferes with hepatitis D virus entry into hepatocyte	Subcutaneous, daily for 6 mo	Ib, IIa	Lipase and amylase elevation in phase I but not in phase II study
	Through sodium taurocholate cotransporting	± pegylated interferon (Peg-IFN)		Elevation of taurine- and glycine-conjugated bile acids without apparent clinical consequences
	polypeptide inhibition			Thrombocytopenia, neutropenia, lymphopenia, and eosinophilia: Generally mild, transient
Lonafarnib	Farnesyltransferase inhibitor, inhibits virion assembly	Oral, 2 to 12 mo, ± ritonavir	II	Gastrointestinal toxicity (anorexia, nausea with or without vomiting, diarrhea, weight loss): Dose dependent and in lower dose cohorts generally mild and well tolerated
		± peg-IFN		
Rep-2139-Ca	Nucleic acid polymer, binds with high affinity to	Intravenous infusion, once wkly	II	Hair loss, dysphagia, anorexia, dysgeusia, in hepatitis B study: Related to heavy metal exposure at the trial site
	Amphipathic proteins, which are required at various	for 4-6 mo ± peg-IFN		Administration route-related side effects: peripheral grade 1 hyperemia, fever, chills, and headache
	Stages of the viral life cycle			

IFN: Interferon.

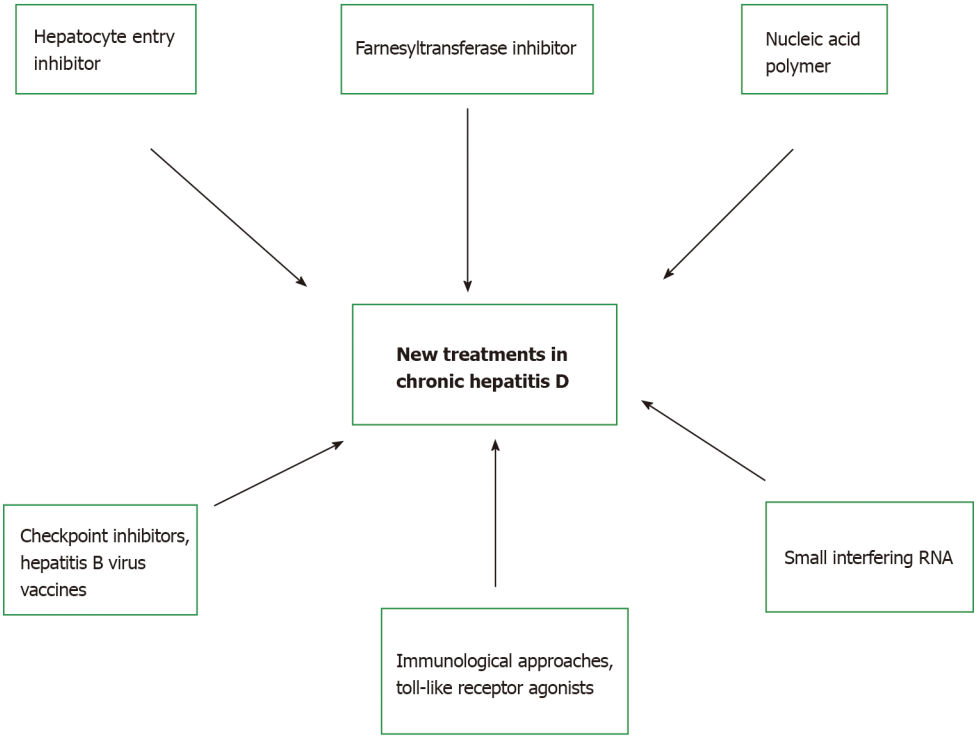

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Figure 2 New treatments in chronic hepatitis D, with specific targets.

sensing pathogen-associated molecule patterns and activating intracellular antiviral pathways as well as the production of proinflammatory cytokines and antiviral effectors like IFN[156]. In a study assessing the safety, pharmacokinetics, and pharmacodynamics of oral TLR-7 agonist, GS-920 led to induction of peripheral mRNA expression of IFN-stimulated gene 15 production in CHB patients; however, there was no effect on HBV DNA[157]. Immune checkpoint inhibitors have also been studies in chronic viral hepatitis, and a phase Ib clinical study of nivolumab in CHB patients highlighted its tolerance and association with significant decline in HbsAg after a single dose over a 24-wk period[158].

HEPATITIS E

Epidemiology

HEV is a small, nonenveloped virus and belongs to the Hepeviridae family and is further classified into genotypes 1–4 and 7[159]. Globally an estimated 2.2 billion people are infected by HEV with 70 000 deaths attributed to HEV annually[160,161].

HEV is mainly transmitted *via* contaminated water and consumption of undercooked pork or wild boar and other foods, while reports of blood transfusion related transmission has been recently recognized[162,163]. Outbreaks of HEV1 and HEV2 genotypes are documented in areas with inadequate sanitary conditions and lack of access to clean water[164]. The prevalence of anti-HEV IgG in Africa ranges from 4.6% to 10.7%, and 34% to 94% in Asia[165-169]. HEV prevalence is probably underestimated as seen in a large German cohort study, as the majority of practitioners do not regularly test for HEV in the presence of acute hepatitis symptoms; in part, due to lack of high clinical suspicion but also absence of standardized testing, leading to increased morbidity and mortality among susceptible individuals[170].

The diagnosis of HEV infection is often challenging given lack of standardized testing and need for HEV PCR for definitive diagnosis[171-173]. Paradoxically, in immunocompromised hosts who do not mount an adequate antibody response, PCR testing should be the cornerstone of diagnosis[174,175]. There is no US FDA-approved diagnostic test and available serological assays have variable sensitivities and specificities making accurate diagnosis often challenging[176-178].

Clinical presentation: Clinical presentation in HEV is variable, ranging from asymptomatic carriers to fulminant hepatitis. In acute HEV, the incubation period is typically 3–8 wk. followed by a short prodrome leading to a symptomatic phase that can last for several days to weeks (mean 4–6 wk)[179]. HEV can also infect patients with chronic liver disease and can cause decompensation, and lead to high mortality[180-182]. Extrahepatic manifestations of HEV include rash, arthralgias, Guillain–Barré syndrome palsies, and pseudotumor cerebri[183].

Based on the patients' immune response to acute HEV, some may progress to chronic HEV infection, which is defined by persistent elevated aminotransferase levels for at least 3 mo combined with positive serum HEV RNA and consistent histological findings on liver biopsy[182]. Chronic HEV primarily occurs in immunosuppressed patients such as organ transplantation recipients or those with HIV infection, and hemodialysis[184-189].

Infection with HEV, specifically genotype 1, during pregnancy leads to increased risk of adverse outcomes to the fetus such as spontaneous abortion, *in utero* fetal demise, and premature delivery, while placing the mother at risk of severe hepatitis and complications[190]. HEV in pregnancy is associated with eclampsia, hemorrhage, and acute liver failure, and carries a high mortality rate of 15%–25%, especially in the third trimester[182,191].

Treatment: Acute HEV in immunocompetent hosts is self-limiting illness followed by spontaneous clearance and usually does not require treatment[192]. Monotherapy with ribavirin is the current treatment of choice for patients with chronic HEV infection[193]. Three months of ribavirin monotherapy for chronic HEV has been associated with around 78% sustained virological response [194]. No established treatment for HEV is available for pregnant women as ribavirin is contraindicated in pregnancy, hence supportive care is recommended[195,196]. Peg-IFN, as an alternative to ribavirin has shown limited success[197,198]. There is a need for direct-acting novel therapies as HEV remains a serious public health concern particularly among pregnant women and immunocompromised patients. The current efforts for these drug developments are focusing either on the inhibition and manipulation of host components or developing DAA therapies that can target viral enzymes without affecting host components[199].

Hepatitis E vaccine and surveillance programs: The need for hepatitis E vaccine was recognized secondary to its worldwide prevalence and severe complications in high risk populations. Early studies of recombinant vaccines in healthy adults have shown promising results, but study populations have unfortunately not included the high-risk groups who are most susceptible to severe and chronic HEV. A Nepalese randomized, placebo controlled, double blinded , phase 2 clinical trial of a recombinant HEV vaccine given at 0, 1 and 6 mo to 898 patients (*vs* 896 placebo) revealed vaccine efficacy of 88.5% in intention to treat analysis[200]. In a different phase 3 clinical trial, Hecolin (Xiamen Innovax Biotech, China) had 112 604 participants, of which 56302 in the study arm and 56 302 in the placebo arm, received three doses of rHEV and hepatitis B vaccine at 0, 1 and 6 mo respectively. The vaccine efficacy of 95.5%was reported in an intention to treat analysis[201]. This vaccine is only approved and commercially available in China[202].

An HEV vaccine that is available worldwide would reduce the incidence of the infection in endemic areas and also confer protection to travelers[203]. Areas and countries with high prevalence should also focus on improved sanitation, access to clean water with a specific focus on high-risk groups, especially pregnant women and patients with chronic medical conditions[167,204].

CONCLUSION

With the recent advancements in the area of molecular virology, the landscape for the management of viral hepatitis has evolved dramatically. We have a better understanding of the molecular structure of these pathogens and their interplay with our immune system, which has paved the way for novel drugs and therapeutics. While the success of the decade is focused on DAAs as the cure for HCV, the burden of chronic HBV and HDV infections persists as research is ongoing for both a cure for HBV and treatment options for HDV. Drugs that hold promise regarding complete eradication of HBV cccDNA from hepatocytes are under investigation and may be pivotal in complete eradication of the infection in the future. Despite the advancement in the field of serological and PCR testing for HBV, HCV, and HDV, there is a continued need for improvements in screening protocols for these infections. Standardized testing along with options for treatment and vaccination remain areas of interest for HEV. Work continues on implementation of universal vaccination for HAV and HBV, while clinical trials are ongoing for HEV vaccination. There remains a pressing need for increased collaborative efforts to help combat these illnesses, as we continue to learn about the viral hepatitis to fill the gaps in our knowledge.

FOOTNOTES

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MINIREVIEWS

Rare post-endoscopic retrograde cholangiopancreatography complications: Can we avoid them?

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Abstract

Regarded as a minimally invasive procedure, endoscopic retrograde cholangiopancreatography (ERCP) is commonly used to manage various pancreaticobiliary disorders. The rate of complications is low and starts from 4% for diagnostic interventions. The group of most frequent negative outcomes is commonly known and includes pancreatitis, cholecystitis, and hemorrhage. Rare adverse effects occur occasionally but carry a significant risk of unexpected and potentially dangerous results. In some cases, including splenic injury, the knowledge of pre-existing conditions might be helpful in avoiding the unwanted outcome, while in others, the risk factors are not clearly defined. Such situations demand increased caution in the post-ERCP period. The appearance of abdominal pain, peritoneal symptoms, or instability of the patient's hemodynamic condition should alert the physician and lead to further investigation of the possible causes. The diagnostic process usually involves imaging tests. The implementation of the appropriate treatment should be immediate, as many of the rare complications carry the risk of dangerous, even potentially lethal, results.

Key Words: Endoscopic retrograde cholangiopancreatography; Pancreaticobiliary disorders; Rare complications; Risk factors; Prevention

Core Tip: Endoscopic retrograde cholangiopancreatography is a common procedure used to manage pancreaticobiliary disorders. The group of most frequent complications is well described and includes pancreatitis, cholecystitis, and hemorrhage. Rare adverse effects occur occasionally but carry a significant risk of unexpected and potentially dangerous results. In some cases, the knowledge of pre-existing conditions might be helpful in avoiding the unwanted outcome, while in others, the risk factors are not clearly defined. Such situations demand increased caution in the post-procedure period. Physicians should be alerted by symptoms of abdominal pain or instability of patient's condition, investigate further for possible causes, and be ready to implement the appropriate treatment immediately.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is nowadays a common procedure used to manage various pancreaticobiliary disorders, including bile duct stones, malignant obstructions, and strictures. Regarded as a minimally invasive procedure, diagnostic ERCP is a technique with a low complication rate starting from 4%, though significantly rising up in cases of a therapeutic procedure[1,2]. The most common complications include pancreatitis (1.7%-4.9%), hemorrhage (1.2%-4.5%), and cholangitis (0.6%-2.3%)[3,4]. A history of previous pancreatitis and cholecystitis has been a well-documented risk factor for post-ERCP pancreatitis (PEP) and post-ERCP cholecystitis (PEC)[5,6], while pre-cut sphincterotomy increases the risk of post-ERCP hemorrhage[7].

The group of less common post-ERCP adverse effects is diverse and heterogeneous, which makes it much more difficult to predict and, therefore, manage. Unexpected complications might be a result of the introduction of the endoscope itself or of its accessories (*i.e.*, a variety of splenic and hepatic injuries, impaction of the stone retrieval basket or stent migration, and colonic or small bowel perforation), might be due to the air leakage (localized or systemic embolism and pneumothorax), might be caused by an allergic reaction to the contrast, or might as well be the consequence of existing comorbid diseases (*i.e.* cardiopulmonary events and sedation-related adverse effects). The uncommon post-ERCP complications occur significantly less often than PEP or PEC. The Italian systematic review presents a rate of 1.3%, with a mortality rate of 0.07% (12973 patients with a total of 173 rare adverse effects and 9 deaths)[8]. While the occurrence of miscellaneous complications seems low and insignificant, it tends to extend the length of the patient's hospitalization, might result in surgical interventions and, possibly – in rare cases – causes death. Therefore, the awareness of its existence is crucial in order to recognize the problem, manage it properly, and avoid the possible negative outcomes.

Commonly known adverse effects, such as PEP, had been already analyzed thoroughly from multiple points of view. This review focuses on the rare post-ERCP complications, mostly those directly connected to the technical aspects of the procedure, especially the ones requiring a surgical intervention. We take a closer look at some of the possibly severe final outcomes and discuss potential strategies of prevention and management. In order to present the subject in a clear manner, the various post-ERCP complications have been divided into minor groups.

SPLENIC INJURY

While splenic injuries as a result of colonoscopy are well documented, cases of post-ERCP splenic injuries remain rare. The severity of possible negative outcomes varies, but even though they are not common, they can potentially be lethal[9]. Possible risk factors for this uncommon complication include chronic pancreatitis, as the calcified ligaments stiffen and decrease the mobility of the organs[10]. Another presumed mechanism of the complication might be the bowing of the endoscope with torsion of the greater curvature while cannulating the papilla[11]. Postoperative adhesions due to prior surgical abdominal interventions might also lead to splenic injury, as they decrease the mobility between the spleen and other organs[12].

According to the American Association for the Surgery of Trauma, splenic injury can be graded depending on the severity of the damage. Table 1 shows the American Association for the Surgery of Trauma: Splenic injury grading scale[13].

Post-ERCP splenic injury was first reported in 1989 by Trondsen *et al*[14]. The case considered a 46-year-old female patient who underwent ERCP with sphincterotomy which resulted, 15 h later, in splenectomy due to the decapsulated spleen. Although most of the post-ERCP splenic injuries require a

Table 1 American Association for the Surgery of Trauma: Splenic injury grading scale[13]

GRADE I	Laceration < 1 cm; Subcapsular hematoma < 10% of the surface area
GRADE II	Laceration 1-3 cm; Subcapsular hematoma 10%-50% of the surface area
GRADE III	Laceration > 3 cm; Subcapsular hematoma > 50% of the surface area; Ruptured subcapsular or parenchymal hematoma
GRADE IV	Segmental or hilar vascular injury; Devascularization > 25% of the spleen
GRADE V	Hilar injury; Shattered spleen

surgical procedure, in less severe cases, such as subcapsular hematomas[15], peri-splenic hematomas [11], or splenic abscess[16], the management might be conservative.

One of the latest reports on the subject presents a non-surgical approach to the post-ERCP spleen injury. Bajwa *et al*[17] reported the case of an 83-year-old woman who underwent ERCP procedure with sphincterotomy which resulted in forming a grade 3 splenic laceration with intraparenchymal and subcapsular hematoma and moderate peritoneal free fluid. As the patient was hemodynamically stable with no signs of peritoneal symptoms, the management remained conservative. Splenectomy becomes a procedure of choice in more severe cases including a rupture of the spleen[18] or an avulsion of the short gastric vessels[12]. The decision should consider the dynamics of the patient's condition as they do not always present with acute abdomen and the onset of the symptoms might often be delayed. As the pain in the upper left abdomen is not always accompanied by signs of peritoneal irritation or significant decrease of hemoglobin levels, it should itself be considered a strong premise to diagnose the possible causes. All the reports on the subject acknowledge that a fast response in those cases is crucial for properly managing the issue.

HEPATIC INJURY

Subcapsular hepatic hematoma is an incidental but potentially dangerous complication. The pathological mechanism of this unique event might be explained by accidental puncture and laceration of small parenchymal vessels by an endoscopic guide wire[19] (Figure 1).

Subcapsular hepatic hematoma as a post-ERCP complication was first presented in 2000 by Ortega *et al*[20]. ERCP was performed on an 81-year-old man due to choledocholithiasis. Following the procedure, the patient presented abdominal pain and a computed tomography (CT) scan revealed a hepatic hematoma. Drainage was the management chosen in this case, with a catheter left for 3 wk after the puncture. According to Pivetta *et al*[21], a total of 61 cases were reported worldwide as for the year 2020.

The latest case, not included in the Pivetta report, presented by Petrucci *et al*[22], considers a 43-year-old woman who underwent ERCP for stent removal. The abdominal pain in the right upper quadrant appeared the following day and a CT scan revealed a subcapsular hepatic hematoma affecting most of the right lobe. The management was conservative at first, but as the pain reappeared accompanied by fever, the patient underwent series of procedures, including interventional radiology guided drainage, laparoscopic washout, and laparotomy with necrosectomy of the liver capsule.

Subcapsular hepatic hematoma should be considered in case of post-ERCP clinical symptoms such as persistent abdominal pain, peritoneal symptoms, and hypotension. Although significant, the laboratory test results should not be considered as main indicators of this complication, except for a decrease of haematocrit and haemoglobin levels. Imaging, such as computed tomography and ultrasound, is a helpful tool to confirm the diagnosis and evaluate the necessity of a surgical intervention[23]. With various possibilities of action, a decision must be made based on the clinical and hemodynamic status of the patient. In most cases concerning hemodynamically stable patients, a conservative management is the treatment of choice. This includes the use of prophylactic antibiotics due to the risk of an infection of the hematoma, and continuing the monitoring of the patient's hemodynamic status[24]. In the event of instability of the patient's status, a more invasive treatment should be introduced. Procedures such as selective embolization of a branch of the hepatic artery or percutaneous drainage of the hematoma might be helpful in cases of active bleeding and decrease of haemoglobin and haematocrit levels[25]. In rare situations of advanced hematoma with haemorrhage, surgical intervention in the form of laparotomy drainage with haemostasis must be considered after analysis of the patient's hemodynamic and clinical status[26,27]. In those cases, it is necessary to monitor the patient in the postoperative period with instruments such as computed tomography or ultrasound.

PERFORATION

According to the studies performed in the last decade, the incidence of ERCP-related perforation ranges

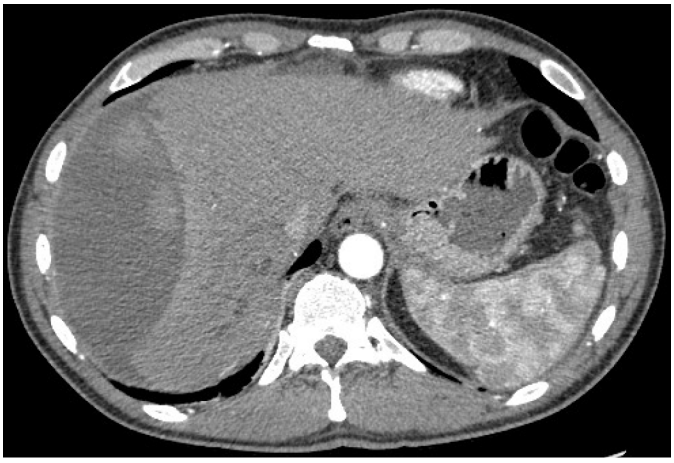

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Figure 1 Computed tomography image presenting an example of advanced hepatic hematoma of the right lobe.

from 0.08% to 0.7%, with endoscopic sphincterotomy and guidewire injury being the most assumed etiologies[28,29]. Suggested risk factors associated with post-ERCP duodenal perforation include biliary stricture dilatation, sphincterotomy, sphincter of Oddi dysfunction, and common bile duct dilation. Patients with surgically altered anatomy (*i.e.*, due to the previous Billroth II or Roux-en-Y operation) are at higher risk of bowel perforation[30].

ERCP-related perforations can be divided into four different types, according to the cause mechanism and the need of a surgical intervention. Types of ERCP-related perforations according to Stapfer *et al*[31] are shown in Table 2.

In terms of prevention, it is crucial to recognize the risk factors before the procedure. Complicated cases should be handled by skillful and experienced endoscopists. Patients with a history of previous surgical anatomy alterations might be considered for "endoscopic scanning" in order to evaluate the conditions before the main procedure. A balloon dilatation over the guidewire might be helpful in preparing the way for a duodenoscope into the strictures[32]. Type II perforations can be avoided by a cautiously performed sphincterotomy with stepwise incisions.

Surgery is usually required in cases of type I or type II perforations, though the decision should be made taking into account the clinical state of the patient and the severity of the leak. Endoscopic treatment is possible for smaller-range perforations where endoloop application combined with clipping or placing a covered metal stent prevents the need of a surgical intervention[33,34]. Type III duodenal perforations, including the ones related to the migration of the stents, can also be treated with endoscopic clipping[35].

STENT RELATED COMPLICATIONS

Occlusion is one of the most common complications resulting from inserting plastic or metal biliary and pancreatic stents during the procedure of ERCP. In cases of malignant strictures, this rather late negative outcome is a result of the progression of the primary disease[36]. The group of rare complications related to stenting include migration, misplacement, and dislodgement, with the latter resulting, in some cases, in intestinal hemorrhage[37,38] (Figure 2).

Patients undergoing endoscopic stent placement are at a risk of stent migration in approximately 3.5%, with the risk factors including bile duct benign stenosis, stenosis of the lower bile duct, and bile duct diameter being less than 10 mm[39]. A migrating stent can lead to the formation of different types of fistulas, such as bronchobiliary, bile duct-duodenum, and pancreatic-gastric[40,41]. Other possible and less common complications due to a migrating stent include the previously mentioned perforation of the duodenum and further parts of the gut.

An example of a duodenum injury caused by a migrating stent can be found in a recent case reported by Perez *et al*[42], considering a young female who underwent ERCP stenting due to hepatobiliary tuberculosis. Due to severe abdominal pain, the patient underwent a laparotomy with peritoneal lavage and tube jejunostomy. The operation confirmed a duodenal perforation from a biliary stent migration. The complication led to bacterial peritonitis resulting in a septic shock and the death of the patient. In another case of a migrating stent, described by Paikos *et al*[43], a patient diagnosed with cholangiocarcinoma required ERCP due to the progressive obstructive jaundice. The procedure involved placement of a plastic stent. Nevertheless, the jaundice persisted despite the procedure. The second ERCP revealed an active ulcer of the duodenum with the stent trapped in it. The patient's condition rapidly worsened,

Table 2 Types of endoscopic retrograde cholangiopancreatography-related perforations according to Stapfer *et al*[31]

TYPE I	Perforation of the lateral/medial duodenal wall, caused by the endoscope. It usually results in a large leak and requires immediate surgical treatment
TYPE II	Sphincterotomy related periampullary perforations of various severity.
TYPE III	Bile duct or duodenal perforation caused by migrating stents or biliary baskets presenting with a smaller-size leakage
TYPE IV	Guide-wire related perforation with retroperitoneal air present in the X-ray. It usually does not require surgical intervention

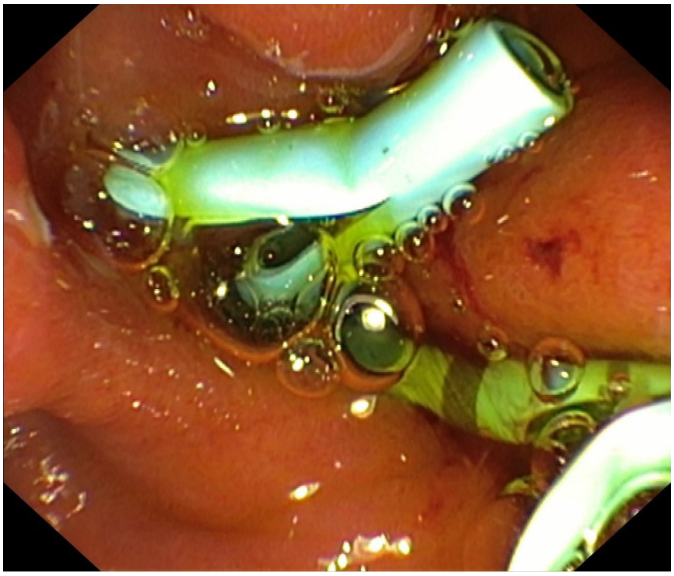

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Figure 2 Procedure of placing stents in the common bile duct.

resulting in respiratory arrest and heart failure.

BASKET IMPACTION

The conventional treatment for choledocholithiasis includes papillotomy and extracting the stones with a Dormia basket. Removal of larger stones might require additional techniques in which the stone is mechanically fragmented before the extraction[44]. Lithotripsy is effective in 79%-92% of the choledocholithiasis cases[45,46] with the success of the procedure depending mostly on the stone size/bile duct size ratio[47]. One of the rare complications that might occur during the procedure is the impaction of the biliary basket, with a incidence rate of 0.26%[4]. The point of the impaction is usually located at the ampulla but it may also be localized in the main pancreatic duct or the intrahepatic ducts [48,49].

The retrieval of the basket might become impossible due to different reasons, not only the size of the deposit. The calcification of the stone causes its hardening to the point where a lithotriptor is unable to crush it. Cases like this require surgical management, such as choledochomy with cholecystectomy[50]. In rare situations, the extraction of the basket might not be possible *via* choledochotomy and duodenotomy, and must be performed during an emergency operation[51]. Laparoscopic management of impacted Dormia baskets has been presented in a few reports describing common bile duct exploration with choledochoscope and retrieving the trapped basket with a grasper or another biliary basket[52,53].

CONCLUSION

Rare post-ERCP complications have a low incidence rate but should not be underestimated, since the possible outcomes might be unpredictable. It is important to be aware of the uncommon adverse effects and their clinical presentation in order to diagnose the problem as soon as possible, and implement the relevant treatment. Are we able to avoid those infrequent complications completely though?

The prevention starts before the ERCP procedure itself by acknowledging the risk factors and recognizing cases more exposed to rare, but potentially dangerous incidents. This relates especially to patients with a history of previous abdominal operations (adhesions as a risk factor of splenic injury, and prior Billroth II procedure increasing the risk of post-ERCP bowel perforation)[12,30]. In demanding cases, procedures should be carefully performed by experienced and skillful endoscopists with expertise in the matter[54]. Technical difficulties, though challenging, can be overcome by choosing an appropriate approach, suitable for the specific problem. As most of the rare complications are unexpected, it is very important to pay close attention to the patient's post-ERCP condition and hemodynamic status. In cases of a splenic or hepatic injury, manifestations such as abdominal pain in the left or right upper quadrant, respectively, indicate the need for further investigation, especially when combined with peritoneal symptoms and decrease of the haemoglobin level[18,23]. When unexpected complications occur, a decision needs to be made on whether the management of the problem should be conservative or surgical, and the physician must be prepared to adopt adequate treatment immediately.

FOOTNOTES

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SYSTEMATIC REVIEWS

Review with meta-analysis relating North American, European and Japanese snus or smokeless tobacco use to major smoking-related diseases

Peter Nicholas Lee, Katharine Jane Coombs, Janette Susan Hamling

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Abstract

BACKGROUND

While extensive information exists relating cigarette smoking to the risk of lung cancer, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD) or acute myocardial infarction (AMI), and stroke, far less information is available on risks from moist snuff ("snus") or smokeless tobacco (ST) in United States/Canada, Europe or Japan.

AIM

To summarize data from the selected countries on risks of the four diseases associated with current ST or snus use.

METHODS

Publications in English in 1990-2020 were considered that, based on epidemiological studies in North America, Europe or Japan, estimated risks of lung cancer, COPD, IHD/AMI, or stroke according to use of ST or snus. The studies should involve at least 100 cases of the disease considered, and not be restricted to those with specific other diseases. Medline literature searches were conducted, selecting papers initially from examination of titles and abstracts, and then from full texts. Further papers were sought from reference lists in selected papers, reviews and meta-analyses. For each disease, relative risk estimates adjusted at least for age were extracted relating ST or snus use to risk, and combined using random-effects meta-analysis. The estimates were mainly for current vs. never or non-current use, but results for ever *vs* never use were also considered.

RESULTS

Seven publications reported results for ST use from six United States studies. The

most useful results came from four studies which provided results for current vs. never use. Random-effects meta-analyses of these results showed an increased risk for each disease, clearest for lung cancer (relative risk 1.59, 95% confidence interval 1.06-2.39, based on 4 estimates) and COPD (1.57, 1.09-2.26, n = 3), but also significant (at P < 0.05) for IHD (1.26, 1.10-1.45, n = 4) and stroke (1.27, 1.03-1.57, n = 4). Also including results for ever vs. never use from two other studies increased the lung cancer estimate to 1.80 (1.23-2.64, n = 6), but had little effect on the other estimates. For snus, 16 publications described results from 12 studies, one in Norway and the rest in Sweden. There were no results for COPD, and only three for lung cancer, with these reporting a relative risk of 0.80 (0.40-1.30) for current *vs* never use. More extensive data were available for IHD/AMI and stroke. Using the latest results from each study, combined estimates for current vs. never use were 1.00 (0.91-1.11, n = 5) for IHD/AMI and 1.05 (0.95-1.17, n = 2) for stroke, while for current vs. non-current use they were 1.10 (0.92-1.33, n = 9) for IHD/AMI and 1.12 (0.86-1.45, n = 9) for stroke. Meta-analyses including earlier results from some studies also showed no significant association between snus use and IHD/AMI or stroke. No relevant results were found for Japan.

CONCLUSION

Risks of smoking-related diseases from snus use in Scandinavia are not demonstrated, while those from ST use in the United States are less than from smoking.

Key Words: Smokeless tobacco; Moist snuff; Lung disease; Cardiovascular disease; Meta-analysis; Review

Core Tip: United States studies show that, in never users of other products, current smokeless tobacco use associates with a significant (P < 0.05) increase in risk of the four major smoking-related diseases, with relative risks, compared to never users, of almost 1.6 for lung cancer and chronic obstructive pulmonary disease (COPD) and 1.3 for ischaemic heart disease (IHD)/acute myocardial infarction (AMI) and stroke. This increase is substantially less than for smoking. In Scandinavia, current snus use, does not significantly increase risk of IHD/AMI, stroke or lung cancer, with no data for COPD. Smokers unwilling to quit might consider these smokeless products.

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INTRODUCTION

It is well established[1,2] that cigarette smoking markedly increases the risk of a range of diseases, particularly lung cancer, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD) and acute myocardial infarction (AMI), and stroke. Meta-analyses[3] have shown that in North American and European populations, current cigarette smokers, compared with those who have never smoked cigarettes, have about a ten-fold increase in risk of lung cancer, with the extent of the increase rising with amount smoked and earlier age of starting. Relative risks (RRs) exceed three for COPD and, in younger individuals, two for cardiovascular disease[4]. Pipe and cigar smoking is also associated with a clear increase in risk of smoking-related disease[2].

Here, we study the association between current use of smokeless tobacco (ST) and four major smoking-related diseases (lung cancer, COPD, IHD/AMI, and stroke). Our analyses are based on studies published from 1990, and separate out the effects of ST as used in North America, and the effects of moist snuff ("snus") as mainly used in Sweden and neighbouring countries. Coupled with a separate ongoing attempt to provide updated meta-analyses relating the same diseases to current cigarette, cigar and pipe smoking, our results should help to provide a good picture of the relative effects of the different nicotine products on the major smoking-related diseases.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 1990 to 2020 which provide results relating use of current ST or snus) in non-smokers to the risk of lung cancer, COPD, IHD/AMI or stroke, based on epidemiological cohort or case-control studies conducted in North America, Europe or Japan, and involving at least 100 cases of the disease of interest. The studies selected should not be restricted to those with specific other diseases.

Literature searches

The search procedures are described in detail in Supplementary material and are summarized below. First, separate literature searches on Medline were conducted for lung cancer, COPD or cardiovascular disease, the aim being to identify from these searches not only publications that described studies satisfying the inclusion criteria, but also meta-analyses and reviews that may themselves cite other relevant publications. Then, for each of the three searches, a print-out of the Medline output for title and abstract was examined by Katharine J Coombs (Coombs KJ) to identify publications of possible relevance, the selection then being checked by Peter N Lee (Lee PN), with any disagreements resolved in discussion. The selected publications (and where relevant supplementary files and also other publications linked to them in the Medline search) were then obtained, and examined by Lee PN, and classified as either an accepted publication possibly including relevant data, a reject (giving reason), a relevant review or a relevant meta-analysis. The suggested rejects were then checked by Coombs KJ, with any disagreements resolved. Then additional accepted publications not detected by the Medline searches were sought from examination of reference lists of the accepted papers and of the relevant reviews and meta-analyses.

The accepted publications from the three searches combined were then examined to eliminate those giving results superseded by a later publication, those not providing new data, and those not providing results relating current ST or snus use specifically for the four diseases of interest.

Meta-analyses

Using standard methods[5] individual study RR estimates were combined using fixed-effect and random-effects meta-analysis, with the significance of between-study heterogeneity also estimated.

For studies on ST use in North America, preference was given to results for those who had never used cigarettes, pipes or cigars which compared current and never ST use, but results from studies which only compared ever and never ST use were also considered in some meta-analyses.

For studies on snus use, use of pipes and cigars was disregarded as this was often not reported, and such use is rare in Scandinavia. RRs comparing current snus users both with never users and with non-users (*i.e.* non-current users, including both former and never users) were separately considered, as a number of studies only presented results compared to non-use. In some cases these estimates were derived from data separately by current, former and never use. Only age-adjusted RR estimates were considered, with the estimates adjusted for the most other factors generally being used.

RESULTS

Literature searches

The results of the searches are given in detail in Additional File 1 and are summarized below and in Figure 1.

For lung cancer, 131 papers were identified in the Medline searches, with 32 considered possibly relevant from examination of title and abstract, and a further 12 identified from comments on these papers. Examination of the full text from the 44 papers led to 10 being accepted as providing apparently relevant study data, with 23 being reviews or meta-analyses and 11 rejected for various reasons.

For COPD, the Medline searches identified 46 papers with six initially considered possibly relevant based on title and abstract, and no further papers identified from comments. The full text examination led to one of the six papers being accepted and three rejected, with the other two being reviews.

For cardiovascular diseases, the Medline searches identified 308 papers, with 80 initially considered possibly relevant, a number extended to 97 after identification of comments on these papers. Of these 27 were accepted, with 52 being reviews or meta-analyses and 18 rejected.

Examination of reference lists in accepted papers, reviews and meta-analyses led to ten further papers being considered possibly relevant, but only one of these was a paper describing relevant results (for COPD). The total of 39 accepted papers for the diseases combined, was then reduced to 26, as three had been accepted in two separate searches, four did not give results for non-smokers, one did not separate results for IHD and stroke, and five were only comments on other accepted papers and provided no new data. Of the 26 papers, 18 gave results for snus, and eight for ST as used in the United States (US), considered separately below. No relevant results were found for Japan.

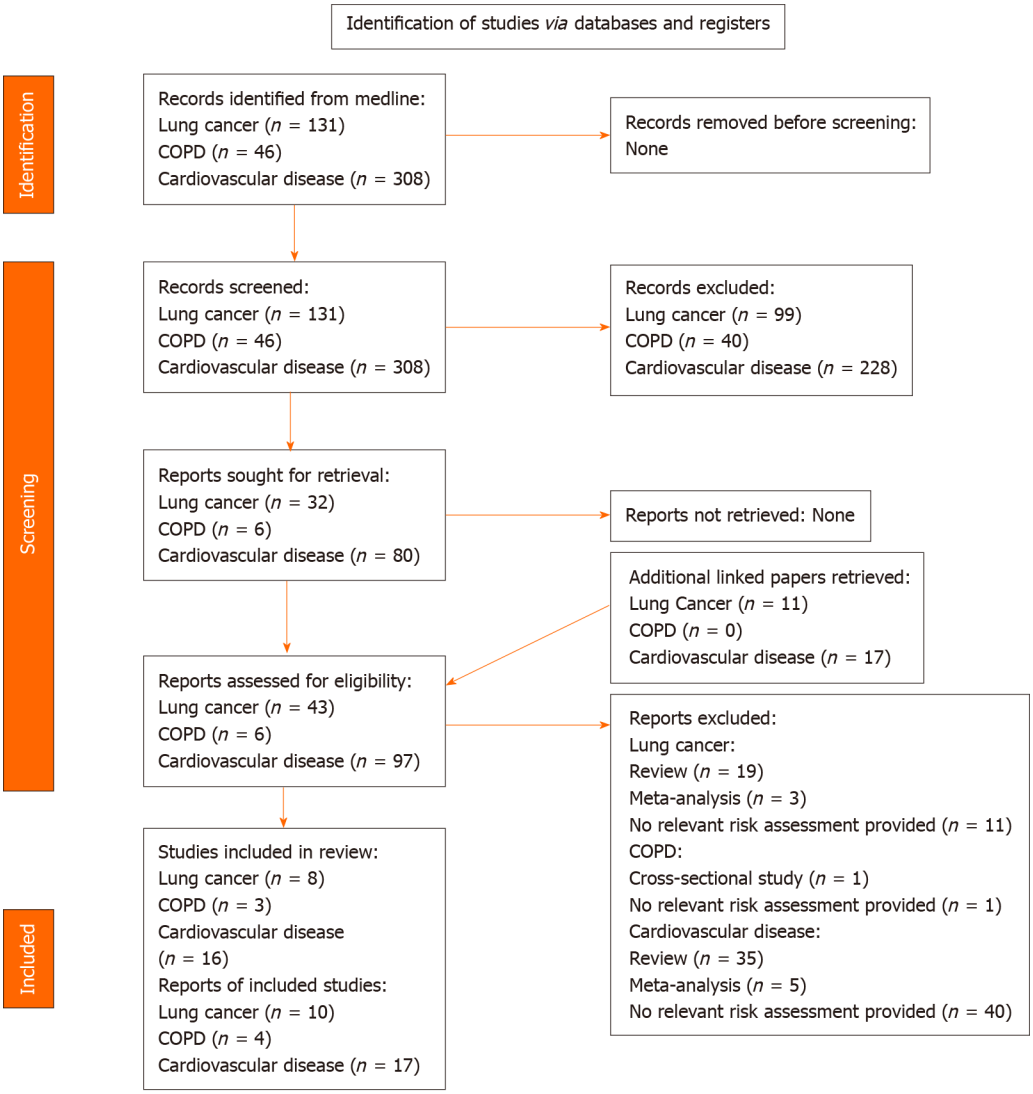

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Figure 1 Literature searches. COPD: Chronic obstructive pulmonary disease.

ST use in the US

Each of the eight publications identified[6-13] reports results from a prospective study. Results from one [10] were not considered further as a later publication[11] provides corrected results from the same study.

The most relevant results, comparing risks for current *vs* never ST users in those who had never used cigarettes, pipes or cigars, come from four studies. For Cancer Prevention Studies I and II (CPS-I and CPS-II), separate results for each of the four diseases are available in one publication[9]. For the National Longitudinal Mortality Study (NLMS), results for IHD and stroke from one publication[13] are preferred to those from another[8], due to the longer follow-up considered, though results for lung cancer are only available from the latter publication[8]. For the National Health Interview Surveys (NHIS), the results from one publication[11] are preferred, as they provide results for all four diseases, and for a longer follow-up than do other publications[8,12].

Less useful are results from two studies. For the Agricultural Health Study (AHS), the results[7] are only for lung cancer, and only compare ever and never ST use. For the first National Health and Nutrition Examination Survey (NHANES), the results[6], for all the diseases except COPD, only compare ever and never ST use, with pipe and cigar smokers not excluded.

Table 1 gives a summary description of the six studies considered, including timing, population studied, and relevant diseases considered, as well as the ST exposure index used and whether pipe and cigar smokers are excluded from the results for never smokers.

Table 2 gives the RRs and 95% confidence intervals (CIs), both as reported for the individual studies and as estimated for the combined studies using random-effect meta-analysis, as well as the available results by sex, and the adjustment factors taken into account. Two studies report results only for males, three for sexes combined and only one for the sexes separately. All the RRs were adjusted for age and a

Table 1 Studies considered in analyses of smokeless tobacco risk among never smokers in the United States

Study	Ref.	Study type[1]	Timing	Population	Diseases considered	Excludes pipe/cigar	Exposure index
Main sources							
CPS-I[2]	Henley *et al*[9], 2005	P	1959 to 1971	Families of volunteers' friends and neighbours	LC, COPD[3], IHD, Stroke	Yes	Current *vs* never
CPS-II[2]	Henley *et al*[9], 2005	P	1982 to 2000	Families of volunteers' friends and neighbours	LC, COPD[4], IHD, Stroke	Yes	Current *vs* never
NHIS[5]	Inoue-Choi *et al*[10], 2019; Inoue-Choi *et al*[11], 2020	P	1991-2010 to 2015	Civilian non-institutionalized	LC, COPD[6], IHD, Stroke	Yes	Current *vs* never
NLMS[7]	Timberlake *et al*[13], 2017	P	1985-2011 to 2011	Civilian non-institutionalized	IHD, Stroke	Yes	Current *vs* never
NLMS[7]	Fisher *et al*[8], 2019	P	1993-2005 to 2010	Civilian non-institutionalized	LC	Yes	Current *vs* never
Other sources							
NHANES[8]	Accortt *et al*[6], 2002	P	1971-75 to 1992	Civilian non-institutionalized	LC, IHD, Stroke	No	Ever *vs* never
AHS[9]	Andreotti *et al*[7], 2017	P	1993-97 to 2010-11	Pesticide applicators and their spouses	LC	Yes	Ever *vs* never

[1]Prospective study.
[2]CPS: Cancer Prevention Study.
[3]Respiratory symptom diseases (ICD7 470-527).
[4]Chronic obstructive pulmonary disease (ICD9 490-492, 496).
[5]NHIS: National Health Interview Surveys.
[6]Chronic lower respiratory disease (ICD10 J40-J47).
[7]NLMS: National Longitudinal Mortality Study.
[8]NHANES1: First National Health and Nutrition Examination Survey.
[9]AHS: Agricultural Health Study.
COPD: Chronic obstructive pulmonary disease.

varying list of other factors, including sex where relevant.

The combined evidence from the main studies (CPS-I, CPS-II, NHIS, NLMS) shows a statistically significant increase in risk relating to current ST use which is somewhat greater for lung cancer (RR 1.59, 95%CI: 1.06-2.39) and COPD (1.57, 1.09-2.26) than for IHD (1.26, 1.10-1.45) and stroke (1.27, 1.03-1.57). Including also the evidence from the other two studies (AHS, NHANES) somewhat increased the combined RR estimate for lung cancer (to 1.80, 1.23-2.64) but left the RRs for the other three diseases virtually unchanged. Significant evidence of heterogeneity between the estimates was only seen in the analyses for IHD, where due to a rather higher estimate from NHIS, the associated *P* value was 0.019 for the estimate based only on the four main results, and 0.015 when also including the results from NHANES.

There is also information from three of the studies on variation in risk by type of ST (chewing tobacco or snuff). For CPS-II[9] RRs were reported, for lung cancer, IHD and stroke, respectively of 1.97 (95%CI: 1.10-3.54), 1.25 (1.03-1.51) and 1.38 (1.02-1.86) for exclusive chewing tobacco use, and of 2.08 (0.51-8.45), 1.59 (1.06-2.39) and 0.62 (0.23-1.67) for exclusive snuff use. For AHS[7] the RR of lung cancer for chewing tobacco of 2.20 (0.98-4.97) was similar to that of 2.21 (1.11-4.42) for overall ST use. No result was given for snuff, as there were only three cases of lung cancer in the exposed group. For NLMS[13] RRs for IHD were 1.11 (0.88-1.42) for exclusive chewing tobacco and 1.30 (1.03-1.63) for exclusive snuff use. In all three studies, the RRs did not vary significantly by type of ST.

Snus use in Scandinavia

Of the 18 publications on snus[14-31], one[16] describes results from a study in Norway, with the rest describing studies in Sweden. Most describe results from a single study, but one[14] presents separate results from two studies, while two[20,21] present results from eight studies, one for AMI and the other for stroke. All the available results are for males.

Two papers were not considered further. One[30] only reported results for ever *vs* never snus use, reported RRs in never smokers only for combined cardiovascular death (RR 1.15, 95%CI: 0.97-1.37) and respiratory death (0.8, 0.2-3.0), and did not separate out results for IHD/AMI, stroke or COPD. The other[14] mainly considered heart failure, the limited results for AMI being unrestricted to non-smokers and not adjusted for any potential confounding factors.

Table 2 Relative risks in analyses of smokeless tobacco risk among never smokers in the United States

Study	Sex	Lung cancer	Chronic obstructive pulmonary disease	Ischaemic heart disease	Stroke	Adjustment factors
Main sources						
CPS-I	M	1.08 (0.64-1.83)	1.86 (1.12-3.06)	1.12 (1.03-1.21)	1.46 (1.31-1.64)	Age, alc, asp, bmi, edu, ex, fat, f/v, race
CPS-II	M	2.00 (1.23-3.24)	1.28 (0.71-2.32)	1.26 (1.08-1.47)	1.40 (1.10-1.79)	Age, alc, asp, bmi, edu, emp, ex, fat, f/v, race
NHIS	M + F	1.43 (0.51-4.01)	1.35 (0.39-4.76)	1.66 (1.30-2.13)	1.09 (0.56-2.11)	Age, edu, race, sex, year
NLMS	M + F	2.98 (0.91-9.76)	-	1.24 (1.05-1.46)	0.92 (0.67-1.27)	Lung cancer: age, edu, hea, inc, race, sexIHD and CVD: age, edu, inc, race, sex
Random-effects meta-analysis		1.59 (1.06-2.39) (*n* = 4)	1.57 (1.09-2.26) (*n* = 3)	1.26 (1.10-1.45) (*n* = 4)	1.27 (1.03-1.57) (*n* = 4)	
Other sources						
NHANES	M	-	-	0.6 (0.3-1.2)	0.7 (0.2-2.0)	Lung cancer: age, alc, ex, f/v, pov, race, regIHD: age, alc, bmi, chol, ex, f/v, pov, race, sbpCVD: age, alc, ex, f/v, pov, race, sbp
NHANES	F	9.1 (1.1-75.4)	-	1.4 (0.8-2.2)	1.0 (0.3-2.9)	
AHS	M + F	2.21 (1.11-4.42)	-	-	-	Age, alc, edu, race, reg, sex
All sources						
Random-effects meta-analysis		1.80 (1.23-2.64) (*n* = 6)	1.57 (1.09-2.26) (*n* = 3)	1.24 (1.08-1.43) (*n* = 6)	1.24 (1.02-1.52) (*n* = 6)	

Alc: Alcohol, asp: Aspirin use; bmi: Body mass index; chol: Cholesterol; edu: Education; emp: Employment, ex: Exercise; f/v: Fruit and vegetable intake; hea: Health status; inc: Income; pov: Poverty; reg: Region; sbp: Systolic blood pressure; year: Year of survey.

The other 16 studies all present results for snus use in non-smokers or non-regular smokers, in some where the comparison is between current and non-use rather than between current and never use, and one where it is between ever and never use. Table 3 gives details, by study and publication, of the study type, timing, population, relevant diseases considered, and the unexposed group considered. In total there are results from 12 studies, with multiple publications describing results from some studies. For no study did any of the publications present simple updates of results given in another publication. All but the Two Counties study is of prospective design, though some results from the MONICA study are based on case-control analyses.

From Table 3 it can be seen that there are no results at all for COPD (or a closely related endpoint) and only three publications present results for lung cancer. The most useful result[29] is based on follow-up of construction workers interviewed in 1978-92, including 15 cases in current users and three in former users, with a RR of 0.80 (95%CI: 0.40-1.30) for current vs. never ST use and of 0.80 (0.45-1.45) for current *vs* non ST use. An earlier result from this study[17] can be ignored, as it is based on no more than three lung cancer cases in current users, and based on interviews in 1971-74, when coding of smoking status was problematic[29]. A RR of 0.96 (0.26-3.56) from the Norway study[16] is for ever *vs* never use and based on only three cases in ever users. No meta-analyses seemed to be worth conducting for lung cancer.

As illustrated in Table 4, much more evidence is available for IHD/AMI and stroke, both for current vs. non snus use and for current *vs* never use, each RR estimate being adjusted for age and varying other factors. Based on the estimate from the latest publication, where data for a study provides a choice, Table 5 shows no evidence of an increased risk in current snus users, whether the comparison group is never users (IHD/AMI: RR 1.00, 95%CI: 0.91-1.11; stroke: 1.05, 0.95-1.17), or is non users (IHD/AMI: 1.10, 0.92-1.33; stroke 1.12, 0.86-1.45). No significant association is also seen when, less satisfactorily, all available RRs are combined, regardless of whether in some studies some disease occurrences may be counted more than once.

DISCUSSION

The results of the meta-analyses for ST use in the US show that, in those who have never used cigarettes, cigars or pipes, current use, compared to never use, is associated with a significant increase in risk of all four major smoking-related diseases studied, the increases estimated from the four main sources of data

Table 3 Studies considered in analysis of current snus use among non-smokers in Scandinavia

Study[1]	Source	Study type[2]	Timing	Population	Diseases considered	Unexposed snus[3]
CWC	Bolinder *et al*[17], 1994	P	1971-74 to 1985	Construction workers	LC, IHD, stroke	Non
	Hergens *et al*[23], 2007		1978-93 to 2004		AMI	Never
	Luo *et al*[29], 2007		1978-92 to 2004		LC	Never
	Hergens *et al*[24], 2008		1978-92 to 2003		CVD	Never
	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014		1978-93 to 2004		AMI, stroke	Non
MALMÖ	Janzon and Hedblad [27], 2009	P	1991-96 to 2004	Population-based, Malmö city	AMI, stroke	Non
	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014				AMI, stroke	Non
MONICA	Asplund *et al*[15], 2003	NCC	1986-99 to 2000	Population-based, Norrbotten and Västerbotten counties	CVD	Non
	Wennberg *et al*[31], 2007	NCC	1986-99 to 1999		AMI	Never
	Huhtasaari *et al*[25], 1992	CC	1989-91		AMI	Non
	Huhtasaari *et al*[26], 1999	CC	1991-93		AMI	Non
	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	P	1986-2004 to 2004		AMI, stroke	Non
NMC	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	P	1997 to 2004	Participant in charity walk	AMI, stroke	Non
NORWAY	Boffetta *et al*[16], 2005	P	1964-67 to 2001	Population sample and relatives of emigrants	LC	Ever vs never
SALLS	Johansson *et al*[28], 2005	P	1988-89 to 2000	Civilian non-institutionalized	IHD	Non
SALT	Hansson *et al*[19], 2009	P	1998-2002 to 2005	Twins born in Sweden 1926-1958	IHD, stroke	Never
	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014		1998-2002 to 2004		AMI, stroke	Non
Scania-PHC	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	P	2002 to 2004	Population-based, Skåne County	AMI, stroke	Non
Stockholm-PHC	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	P	2002 to 2004	Population-based, Stockholm County	AMI, stroke	Non
ULF	Haglund *et al*[18], 2007	P	1988-89 to 2003	Civilian, non-institutionalized	IHD, stroke	Non
Two Counties	Hergens *et al*[22], 2005	CC	1992-94	Randomly selected, Stockholm and Västernorrland counties	AMI	Never
WOLF	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	P	1992-98 to 2004	Employed in three counties	AMI, stroke	Non

[1]CWC: Construction workers cohort; MONICA: Monitoring of trends in cardiovascular disease; NMC: National March Cohort; PHC: Public Health Cohort; SALLS: Swedish Annual Level of Living Survey; SALT: Screening across the lifespan twin study; ULF: Swedish survey of living conditions; WOLF: Work, lipids and fibrinogen.
[2]CC: Case control; NCC: Nested case control, P: Prospective.
[3]Exposed group: Current unless stated. In some studies the unexposed group may include non-regular tobacco users.

(CPS-I, CPS-II, NHIS, NLMS) being almost 30% for IHD and stroke and almost 60% for COPD and lung cancer. These increases are less than those associated with cigarette smoking, *e.g.*[4]) and suggest that ST, as used in the US, is a safer, but not harmless, alternative method of nicotine exposure than cigarette smoking for smokers not willing to quit. While some of the publications we consider[6,10] have concluded that an excess risk of smoking-related disease associated with ST use in the US has been

Table 4 Relative risks in analyses of ischaemic heart disease/acute myocardial infarction and stroke in relation to current snus use among never smokers in Scandinavia

Study	Source[1]	Current *vs* never		Current vs non		Adjustmentfactors[2]
		IHD/AMI	Stroke	IHD/AMI	Stroke	
CWC	Bolinder *et al*[17], 1994	-	-	1.35 (1.13-1.62)[3]	1.29 (0.83-1.99)[3]	Age, res
CWC	Hergens *et al*[23], 2007	1.02 (0.92-1.14)	-	1.03 (0.93-1.15)	-	Age, BMI, res
CWC	Hergens *et al*[24], 2008	-	1.05 (0.95-1.17)	-	1.06 (0.96-1.18)	Age, BMI, res
CWC	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	-	-	1.01 (0.90-1.14)	1.03 (0.90-1.17)	Age, BMI[4]
MALMÖ	Janzon and Hedblad[27], 2009	-	-	0.75 (0.30-1.80)	0.59 (0.20-1.50)	Age, BMI, dia, hyp, mar, occ, phys
MALMÖ	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	-	-	1.00 (0.37-2.70)	1.23 (0.50-2.99)	Age, BMI[4]
MONICA	Asplund *et al*[15], 2003	-	-	-	0.87 (0.41-1.83)	Age, chol, cohort, edu, dia, hyp, mar, year
MONICA	Wennberg *et al*[31], 2007	0.82 (0.46-1.43)	-	0.85 (0.48-1.50)	-	Age, BMI, chol, edu, phys, res, year
MONICA	Huhtasaari *et al*[25], 1992	-	-	0.89 (0.62-1.29)	-	Age
MONICA	Huhtasaari *et al*[26], 1999	-	-	0.58 (0.35-0.94)	-	Age, chol, dia, edu, her, hyp, mar, res
MONICA	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	-	-	0.77 (0.35-1.69)	0.65 (0.23-1.80)	Age, BMI[4]
NMC		-	-	No IHD cases in current snus users	1.28 (0.40-4.10)	Age, BMI[4]
SALLS		1.41 (0.61-3.28)	-	-	-	Age, BMI, dia, hyp, phys
SALT	Hansson *et al*[19], 2009	0.85 (0.51-1.41)	1.18 (0.67-2.08)	0.85 (0.51-1.40)	1.15 (0.66-2.02)	Age, chol, dia, hyp
SALT	Hansson *et al*[20], 2012; Hansson *et al*[21], 2014	-	-	1.56 (0.98-2.48)	0.98 (0.52-1.83)	Age, BMI[4]
Scania-PHC		-	-	1.90 (0.90-4.00)	3.17 (1.50-6.70)	Age, BMI[4]
Stockholm-PHC		-	-	1.21 (0.48-3.08)	0.58 (0.14-2.45)	Age, BMI[4]
ULF		-	-	1.15 (0.54-2.41)	1.01 (0.35-2.92)	Age, heal, ill, phys, res, ses
Two Counties		0.73 (0.35-1.50)	-	0.73 (0.35-1.51)	-	Age, area
WOLF		-	-	3.30 (0.63-17.1)	0.96 (0.28-3.30)	Age, BMI[4]

[1]See Table 2 for source if the study is only analysed by one publication or by the two pooled analyses by Hansson *et al*[20] only.
[2]Abbreviations used: BMI: Body mass index; chol: Cholesterol; dia: Diabetes; edu: Education; heal: Self-reported health; her: Heredity; hyp: Hypertension; ill: Self-reported longstanding illnesses; mar: Marital status; occ: Occupation; phys: Physical activity; res: Region of residence; ses: Socioeconomic status; year: Recruitment year.
[3]Estimated from results given for two groups by age at entry to the study.
[4]Body mass index adjusted for in the analyses of stroke, but not acute myocardial infarction.
All results are for men. Where results in any row are given for both comparison groups (never and non) for the same disease, the result for the comparison group non were estimated from data provided in the source paper.

shown, some are more cautious, regarding the evidence as limited[9,13].

Limitations of the evidence for US ST include the fact that a number of the studies considered are quite old, with three of the seven studies summarized in Table 1 involving follow-up periods ending over 20 years ago, ignoring the possibility that the nature of the products studied may have changed over time. Another limitation is the fairly sparse evidence comparing risk by type of ST product. Although this does not suggest any marked differences in risk between those who use chewing tobacco or use snuff, the data are insufficient to reliably detect smaller differences. Also, it is possible that some misclassification of smoking status has taken place, with some of the effects attributed to ST use actually being a consequence of unreported current or past smoking of cigarettes, pipes or cigars.

Table 5 Meta-analyses of ischaemic heart disease/acute myocardial infarction and stroke results in relation to snus use among never smokers in Scandinavia

Disease	Comparison group	All data or latest	Random-effects meta-analysis relative risk (95%CI)	Heterogeneity		
				Chi sq	DF	*P* value
IHD/AMI	Never	Latest	1.00 (0.91-1.11)	2.33	4	NS
	Non	All	1.04 (0.92-1.18)	24.87	15	0.052
		Latest	1.10 (0.92-1.33)	9.18	8	NS
Stroke	Never	Latest	1.05 (0.95-1.17)	0.16	1	NS
	Non	All	1.06 (0.98-1.14)	12.69	13	NS
		Latest	1.12 (0.86-1.45)	10.26	8	NS

Where the comparison group is non users, there are (see Table 4) estimates for some studies from multiple publications. For these studies, the estimate "Latest" includes only the result from the latest publication, while the estimate "All" includes all the results. Where the comparison group is never users, no study provides more than one estimate. NS: Not significant ($P \geq 0.1$).

Even if the magnitude of the effect on risk of current ST use in the US may be somewhat inaccurately measured in our meta-analyses, there seems little doubt that it is substantially less than that for cigarette smoking. For lung cancer, for example, RRs for current cigarette smoking for the US have been estimated as 11.68 in one meta-analysis[3], with RRs increasing with increasing amount smoked and earlier age of starting to smoke, and higher for squamous cell carcinoma than for adenocarcinoma. While we have not attempted to quantify risk of ST use in the US by amount or duration of use, or by subdivision of the diseases considered, this does not affect the conclusion that the risks of the four diseases for ST are less than for cigarette smoking.

The results of our meta-analyses for current snus use, based on studies in Scandinavia, show no clear evidence of any increased risk, whether the comparison group is never or non-users. While there is little evidence for lung cancer, and there are no useful results for COPD, the evidence for cardiovascular disease is based on as many as 12 studies, the results from some being reported in multiple publications (see Table 4). As shown in Table 5, RR estimates for IHD/AMI and for stroke vary only from 1.00 to 1.12, and none are statistically significant. Though a lack of effect cannot be demonstrated, and it is possible that there is a true small increase in risk by perhaps about 5%, it seems likely that any increase is less than for US ST, and much less than that for cigarette smoking. Certainly the great majority of the publications from which we derived data[14-16,18-22,25-31] considered that no increased risk in current snus users had been demonstrated for any of the smoking-related diseases we considered, many concluding that components of tobacco smoke other than nicotine appear to be involved in the relationship of smoking with heart disease and stroke. However, possible effects were noted for cardiovascular disease[17] based on early and unreliable data[29], fatal AMI and fatal stroke[23,24] and for heart failure[14]. The at most very weak association of snus with the smoking-related diseases considered was also the conclusion of a review of the evidence on snus[32], though this review also noted a possible effect of snus on reduced survival from AMI and on heart failure, arguing that further investigation was needed to investigate possible confounding by socio-economic status or other factors.

In the last few years there have been a number of reviews and meta-analyses on the effects of ST, *e.g.* [33-42], many unrestricted to effects in the US and Scandinavia, and some restricted to specific diseases. Where effects are claimed, they often relate to products used in Africa or Asia, *e.g.*[42], or to other diseases, such as oral or pancreatic cancer. For oral cancer, however, evidence of an increased risk from snus has not emerged from meta-analyses[32], while for US ST any increase is mainly evident in studies before 1980[43]. Also, for pancreatic cancer, claims of any increased risk associated with snus use[33,34] are weakly based, with the evidence for any association with ST use essentially disappearing[32] following publication of pooled analyses[44,45]. For lung cancer, the reviews, *e.g.*[33,34,38,46] generally consider that no increased risk from snus has been demonstrated, though one[39] points to increased risk from US ST. COPD is little considered in the reviews, though one[39] does refer to the increased risk seen in the CPS-I study shown in Table 2. The risks of IHD/AMI and stroke are more extensively considered in the reviews, and some, *e.g.*[35] refer to a possible increase in risk of fatal AMI and stroke. However, this increase is mainly dependent on the results for US ST, where we have found a significant increase in our analyses. For snus, where the evidence considered derives from studies of fatal cases only, of non-fatal cases only, or of first occurrences of a case (fatal or non-fatal), where separate results are not always reported by fatality, there is no clear evidence of an increased risk specifically in fatal cases[32]. As noted in this review, confounding may occur due to snus users reporting disease later, or having less medical care when they do. Even if, for some reason, there is a slight adverse effect of snus on fatal AMI and stroke, it is clearly less than for cigarette smoking. This conclusion is consistent with a recent follow-up of almost 75000 patients admitted with a first percutaneous intervention, which found

that snus use was not associated with increased mortality, new revascularisation or hospitalisation for heart failure[47].

Taken as a whole, the conclusions reached in the reviews are consistent with our findings that, for the four major diseases considered, effects of the smokeless products commonly used in the US are less than those for cigarette smoking, and they are not clearly evident for Swedish snus. Our analyses provide no information on risks from ST as used in Africa and Asia.

CONCLUSION

Studies in the US show that, in those who never used other tobacco products, current ST use is associated with an increased risk of the four major smoking-related diseases. However, this increase, though statistically significant (at $P < 0.05$), is much less than for cigarette smoking. Scandinavian studies show no significant increase in risk of IHD/AMI, stroke or lung cancer in current snus users, with no data available for COPD. Though the data have limitations, providing information only on risks from the major smoking-related diseases, and none on risks from the smokeless products used in Africa or Asia, our findings clearly show that risks of the diseases considered from US ST and snus use are much less than for smoking.

ARTICLE HIGHLIGHTS

Research background

There are extensive data on the risks from cigarette smoking, but far less on the risks from moist snuff ("snus") or smokeless tobacco (ST) as used in Western populations and Japan.

Research motivation

To obtain recent evidence as part of a project comparing risks from use of various tobacco products.

Research objectives

To summarize data relating snus and ST use in North America, Europe and Japan to risk of the four main smoking related diseases – lung cancer, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD) (including acute myocardial infarction (AMI) and stroke.

Research methods

Medline searches sought English publications in 1990-2020 providing data on risks of each of the diseases relating to current (or ever) use of snus or ST in the selected regions. The studies had to include at least 100 cases of the disease considered, and not be based on individuals with specific diseases. Relative risk estimates adjusted at least for age were extracted for each study and combined using random-effects meta-analyses.

Research results

Six United States studies provided ST results. For current vs. never use (4 studies), significant increases were seen for each disease, with the RRs higher for lung cancer (1.59) and COPD (1.57) than for IHD/AMI (1.26) and stroke (1.25). Including also results for ever vs. never use, increased the lung cancer RR to 1.80, but little affected the other RRs. Twelve Scandinavian studies provided snus results, with no data on COPD. For the other diseases, RRs for current vs. never use were never significant, the highest RR being 1.05 for stroke. There were no relevant studies in Japan.

Research conclusions

Risks from ST use in North America are much less than for smoking, while no risks were demonstrated for snus.

Research perspectives

The results suggest that smokers unwilling to give up nicotine may substantially reduce their risk of the four diseases by switching to ST (as used in North America) or snus.

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FOOTNOTES

Author contributions: Lee PN planned the study; Literature searches were carried out by Coombs KJ and checked by Lee PN; Statistical analyses were carried out by Hamling JS and checked by Lee PN; Lee PN drafted the text, which was checked by Coombs KJ and Hamling JS.

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META-ANALYSIS

Evidence analysis on the utilization of platelet-rich plasma as an adjuvant in the repair of rotator cuff tears

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Abstract

BACKGROUND

Platelet-rich plasma has been gaining popularity as an agent for biological augmentation either as the sole treatment modality or as an adjunct to surgical repair. There is substantial discrepancy in the results of the published meta-analyses; and the true efficacy and role of using autologous platelet-rich plasma (PRP) at the time of rotator cuff repair is still ambiguous.

AIM

To performed this systematic overview on the overlapping meta-analyses that analyzed autologous PRP as an adjuvant in the repair of rotator cuff tears and identify the studies which provide the current best evidence on this subject and generate recommendations for the same.

METHODS

We conducted independent and duplicate electronic database searches in PubMed, Web of Science, Scopus, Embase, Cochrane Database of Systematic Reviews, Reference Citation Analysis and the Database of Abstracts of Reviews of Effects on September 8, 2021 to identify meta-analyses that analyzed the efficacy of PRP as an adjuvant in the repair of rotator cuff tears. Methodological quality assessment was made using Oxford Levels of Evidence, AMSTAR scoring and AMSTAR 2 grades. We then utilized the Jadad decision algorithm to identify the study with the highest quality to represent the current best evidence to generate the recommendation.

RESULTS

Twenty meta-analyses fulfilling the eligibility criteria were included. The AMSTAR scores of the included studies varied from 6-10 (mean: 7.9). All the included studies had critically low reliability in their summary of results due to their methodological flaws according to AMSTAR 2 grades. Significant heterogeneity was observed in the reporting of VAS, function outcome scores (long-term UCLA score, ASES score, SST score), operative time and long-term re-tear rates. Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

CONCLUSION

Based on this systematic overview, we give a level II recommendation that intra-operative use of PRPs at the bone-tendon interface can augment the healing rate, reduce re-tears, enhance functional outcome and mitigate pain in patients undergoing arthroscopic rotator cuff repair. LP-PRP possibly offers the greatest benefit in terms of healing rates, as compared with other platelet preparations.

Key Words: Platelet-rich plasma; Rotator cuff tears; Meta-analyses; Functional outcome; Re-tear; Recommendation

Core Tip: Platelet-rich plasma has been gaining popularity as an agent for biological augmentation either as the sole treatment modality or as an adjunct to surgical repair. There is growing evidence on the positive effects of platelet-derived autologous growth factors on collagen production, cell proliferation, tissue revascularization and tendon regeneration thereby making them useful as an augment to arthroscopic rotator cuff repair. Based on our analysis, we found that the intra-operative use of PRPs at the bone-tendon interface can augment the healing rate, reduce re-tears, enhance functional outcome and mitigate pain in patients undergoing arthroscopic rotator cuff repair.

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INTRODUCTION

Despite substantial improvements and huge strides made in the surgical procedures and the fixation constructs employed in the repair of rotator cuff tears, high failure rates persist to remain a major cause for concern[1]. The reported failure rates of rotator cuff repairs vary between 8 and 94%[1-4]; and multitudinous factors including age, systemic comorbidities, smoking status, size of tear, degree of fatty infiltration and surgical approaches or techniques have been purported to determine the outcome in these patients[5].

With the understanding that there is still room for significant improvement, the need for employing additional modalities for ameliorating healing in this setting has been growingly acknowledged[6]. It has been well-demonstrated that degenerated rotator cuff tissue has substantially compromised microcirculation, as compared with normal, healthy tissue[7]. Moreover, the fibro-vascular scar at the region of the bone-tendon interface following repair of the rotator cuff tear is of poorer quality in comparison with the innate tissue[8]. Since these aforementioned biological factors have been postulated to be the potential underlying cause for impaired tendon healing capacity after surgical repair, a significant degree of promise has been recently placed on biological augmentation strategies for enhancing tissue healing after rotator cuff repair surgeries[1,9].

Platelet-rich plasma (PRP) is a platelet concentrate which is prepared by centrifugation of autologous whole blood; and contains various growth factors including platelet-derived growth factor, insulin-like growth factor, transforming growth factor-β, epidermal growth factor and vascular endothelial growth factor. Based on the preparations and constitution (leukocyte content and fibrin architecture), PRP have been classified as pure PRP, leucocyte and PRP (L-PRP), leucocyte and platelet-rich fibrin (L-PRF) and pure platelet-rich fibrin (P-PRF)[1-6]. PRP and platelet-rich fibrin matrix have been gaining popularity as agents for biological augmentation in diverse sub-specialties of orthopedic surgery, either as the sole treatment modality or as an adjunct to surgical repair[8,9]. There is growing evidence from animal-based models on the positive effects of platelet-derived autologous growth factors on collagen production, cell proliferation, tissue revascularization and tendon regeneration in the setting of operative arthroscopic rotator cuff repair (ARCR)[10,11]. Nevertheless, there is substantial discrepancy in the results of the published meta-analyses; and the true efficacy and role of using PRP at the time of rotator cuff repair is still ambiguous[12-16].

The overall purpose of the current study was to perform a detailed systematic review of the existing meta-analyses evaluating the role of PRP in patients undergoing rotator cuff repair; and to specifically provide answers to the following research questions, namely: (1) To evaluate the effect of this strategy on overall clinical outcome scores; (2) To evaluate the reduction in re-tear or failure rates; (3) To analyze the evolution and variations in the techniques of procurement and application of PRP across different studies; (4) To critically analyze and interpret the best currently available evidence and provide recommendations; and (5) To discern the major gaps in the existing literature and identify the scope for future research on this subject.

MATERIALS AND METHODS

We present herewith a systematic overview of meta-analyses, performed by duly cohering the guidelines of the Back Review Group of Cochrane Collaboration[17]; and aim to report the same based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18].

Search strategy

Two reviewers performed an independent literature search for systematic reviews with meta-analysis evaluating PRP therapy along with surgical repair for rotator cuff tear. The comprehensive search was performed on the electronic databases including PubMed, Web of Science, Scopus, Embase, Cochrane Database of Systematic Reviews, Reference Citation Analysis and the Database of Abstracts of Reviews of Effects on September 8, 2021. Our search was neither restricted to any specific language nor confined to any particular period. The electronic search strategy was designed in accordance with the Peer Review of Electronic Search Strategy (PRESS) guidelines[19]. The keywords used for the search included: "Platelet-rich Plasma", "PRP", "rotator cuff repair", "rotator cuff tear", "clinical outcome", "re-tear rate", "failure rate", "Systematic Review", "Meta-analysis" together with Boolean operators such as "AND", "OR" and "NOT". A manual search of the key journals was made; and reference list of the selected articles was searched to identify studies not identified in the primary search. Additionally, a search was also made in the International prospective register of systematic reviews for any ongoing review which is nearing completion. All the studies meeting the inclusion criteria were included and analyzed. Any discrepancy between the two reviewers was resolved through discussion until a consensus was achieved. The PRISMA flow chart for the study selection into systematic overview has been shown in Figure 1.

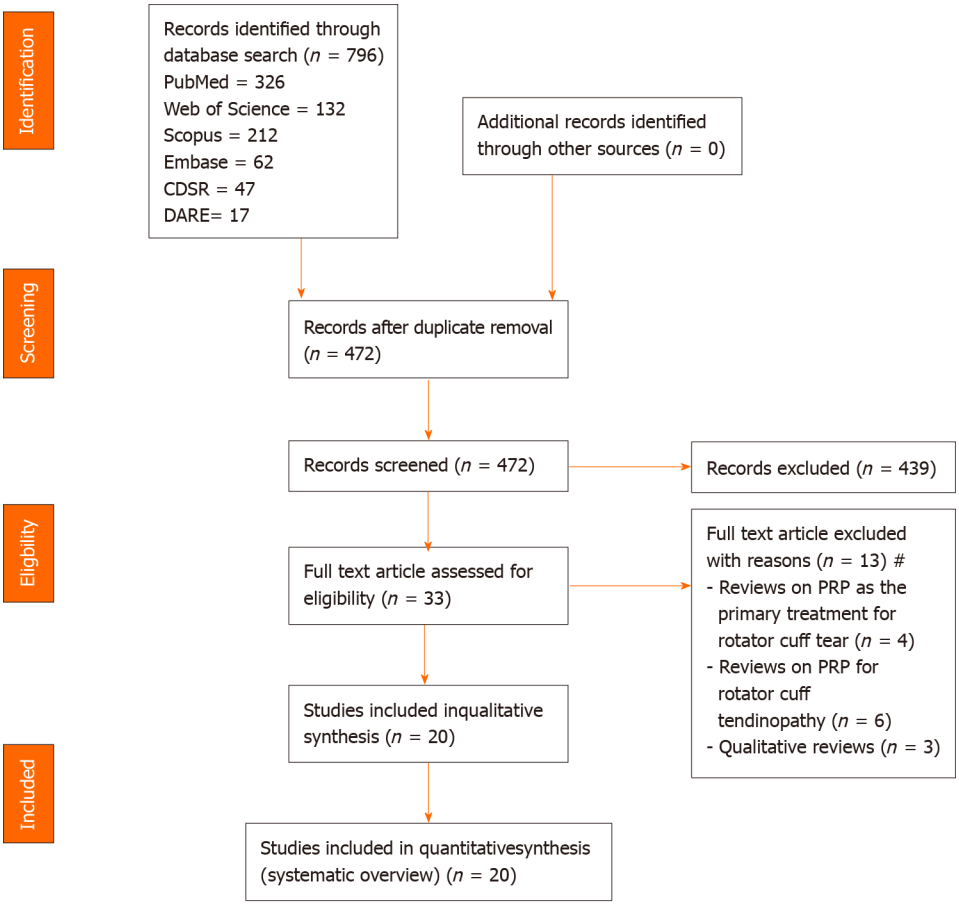

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Figure 1 PRISMA flow diagram of the included studies.

Inclusion criteria

Review articles were included in our study if they satisfied the following criteria: Systematic review with meta-analysis comparing surgical repair with and without PRP for rotator cuff tears. Studies which analyzed at least one of the outcome measures like Visual analog scale (VAS) score, Disabilities of the Arm, Shoulder and Hand (DASH) score, Constant score, University of California Los Angeles (UCLA) score, American Shoulder and Elbow Surgeons (ASES) score, Simple Shoulder Test (SST) score, operating time, patient satisfaction, tendon healing and re-tear rates.

Exclusion criteria

Narrative reviews, systematic reviews without data pooling/meta-analysis, systematic reviews with mixed intervention groups, correspondence articles, pre-clinical studies, studies on animal models and cadaveric studies were excluded.

Data extraction

Data was extracted from meta-analyses by two reviewers independently. Notably, data extracted from the studies included: First author details, date of last literature search performed, year and journal of publication, number, and nature of studies included, language restrictions, criteria for inclusion and exclusion for studies, databases used for literature search, software employed for analysis, subgroup/sensitivity analysis, analysis of publication bias, conflict of interest, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary, and I^2 statistic value of variables in each meta-analysis. Disagreements were settled by consensus.

Assessment of quality of study methodology

The methodological quality of included reviews was evaluated using Oxford Levels of Evidence[20]. Additionally, the Assessment of Multiple Systematic Reviews (AMSTAR)[21] and its updated grading tool AMSTAR 2[22] were also used to assess their methodological robustness with good validity and reliability[23]. Two reviewers independently assessed quality of methodology of the included studies. Disagreements were settled by consensus.

Heterogeneity assessment

I^2 test was used for the assessment of heterogeneity[24]. When $I^2 > 50\%$ and $P < 0.1$, heterogeneity is deemed to exist among included trials; and the reviewers evaluated whether the studies utilized sensitivity or subgroup analyses to assess the reasons for heterogeneity and strengthen the robustness of pooled data.

Application of Jadad decision algorithm

Variability in the findings among included meta-analyses was interpreted with the help of Jadad decision algorithm. As per Jadad *et al*[25], possible reasons for discordance in the results among studies include differences in study question, inclusion and exclusion criteria, quality assessment, data pooling/extraction and statistical analysis. Currently, this is the most commonly used algorithm for generating recommendations among meta-analyses with discordant results[26-29]. Two reviewers used this algorithm independently to arrive at a single meta-analysis representing the current best evidence in order to generate recommendations.

RESULTS

Search results

A comprehensive search of the electronic database generated 838 articles which were subjected to an initial screening for removing duplicate articles. This yielded 514 articles. Further screening of title and abstract resulted in the exclusion of 481 articles. Therefore, 33 articles qualified for reviewing the full-text. Upon full-text review by both reviewers, 13 were excluded. Finally, 20 meta-analyses were included in this systematic review[30-46,1,47,48]. These overlapping meta-analyses were published in different journals between 2012 and 2021; and the number of studies included in them ranged between 5 and 19 (Table 1). The publication years of the included studies in these meta-analyses ranged between 2008 and 2020 as shown in Supplementary Table 1.

Search methodology of the meta-analyses

Although the included meta-analyses made a comprehensive literature search, the search databases employed were not similar. Sixteen, 1 and 7 studies searched PubMed, Embase and Medline databases, respectively. While 2 of them searched the Cochrane library, one searched Web of Science. 18 searched Scopus, 16 Google Scholar, 3 Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, 2 China National Knowledge Infrastructure (CNKI) database, 1 Wan fang and 2 meta-analyses searched VIP database. Of the 20 studies, 4 included studies only in English[1,42,43,46] while 7 others mentioned no linguistic restriction in their search criteria[30,33,38,40,41,44,45]. Further details regarding the search methodology employed in the included meta-analyses has been presented in Table 2.

Methodological quality

Using Oxford Levels of Evidence, the quality of included studies was determined based on the nature of primary studies considered in the analysis. Of the 20 studies analyzed, 6 were of level-II evidence, one level-III and the rest of them were of level III evidence (Table 3). Among the 20 studies, 12 used RevMan5.3, 4 used Stata software, 1 used open meta, 2 used R-foundation for data analyses; while in one study, the software employed was not mentioned (Table 3). Additionally, three studies utilized the GRADE system, 12 studies performed sensitivity analysis and 16 conducted sub-group analysis to explore the heterogeneity in their results. Eleven studies assessed for possible publication bias.

As shown in Table 4, AMSTAR scores of included studies ranged between 6 and 10 (mean 7.8). Based on AMSTAR-2 grading, none of the studies were without any critical methodological flaw in the conduction of meta-analysis. Among all included studies, the meta-analysis by Zhang *et al*[30] was found to be of the highest quality with an AMSTAR score of 10/11 (Table 4). However, this study also suffered from critical methodological flaws of including status of publication (*i.e.* grey literature) as a criterion for inclusion and did not provide the list of (included and excluded) studies.

Assessment of heterogeneity

All the studies included used I^2 statistic for heterogeneity assessment. Mild heterogeneity was noted in short-term UCLA score, tendon healing rates and patient satisfaction. Heterogeneity in the reporting of DASH score, Constant score and short-term re-tear rate was moderate; while heterogeneity of VAS, long-term UCLA score, ASES score, SST score, operative time and long-term re-tear rates was significant (Table 5). It is of utmost importance to probe into source of discordance among included studies, as recommendations generated are put into clinical practice and for developing public health-care policies [49]. The heterogeneity of results among the meta-analyses was primarily due to variation in the nature of primary studies included (other than RCTs).

Table 1 Characteristics of the included studies

Sl. No	Ref.	Publication date	Publication journal	Literature search date	No. of studies included
1	Chahal *et al*[32], 2012	June 14, 2012	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	December 30, 2011	5
2	Moraes *et al*[31], 2013	December 23, 2013	*Cochrane Database of Systematic Reviews*	March 25, 2013	19
3	Zhang *et al*[30], 2013	July 12, 2013	*PLoS One*	April 20, 2013	7
4	Li *et al*[33], 2014	June 7, 2014	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	May 1, 2013	7
5	Zhao *et al*[29], 2014	September 30, 2014	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	September, 2013	8
6	Warth *et al*[35], 2014	November 13, 2014	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	September, 2013	11
7	Vavken *et al*[36], 2015	March 12, 2015	*The American Journal of Sports Medicine*	August 1, 2014	13
8	Cai *et al*[38], 2015	October 8, 2015	*Journal of Shoulder and Elbow Surgery*	January, 2015	5
9	Xiao *et al*[37], 2016	October 30, 2016	*International Journal of Clininical and Experimental Medicine*	February 1, 2016	15
10	Hurley *et al*[40], 2018	February 21, 2018	*The American Journal of Sports Medicine*	March 24, 2017	18
11	Han *et al*[39], 2019	June 20, 2019	*Journal of Orthopaedic Surgery and Research*	September, 2016	13
12	Wang *et al*[41], 2019	July 29, 2019	*PLoS One*	September 15, 2018	8
13	Chen *et al*[42], 2019	November 19, 2019	*The American Journal of Sports Medicine*	December, 2017	18
14	Cavendish *et al*[43], 2020	May 1, 2020	*Journal of Shoulder and Elbow Surgery*	May 23, 2018	16
15	Hurley *et al*[44], 2020	July 30, 2020	*The American Journal of Sports Medicine*	March, 2020	13
16	Yang *et al*[45], 2020	October 14, 2020	*Nature research*	February 15, 2020	7
17	Zhao *et al*[46], 2020	November 18, 2020	*Journal of Shoulder and Elbow Surgery*	March, 2020	10
18	Ryan *et al*[1], 2021	March 17, 2021	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	June, 2020	17
19	Xu *et al*[48], 2021	July 13, 2021	*The Orthopaedic Journal of Sports Medicine*	June 20, 2020	14
20	Li *et al*[47], 2021	May 27, 2021	*Arthroscopy: The Journal of Arthroscopic and Related Surgery*	October 29, 2020	

Results of Jadad decision algorithm

The pooled results from each included meta-analysis are presented in Figure 2. To identify the study which provides the best possible evidence to generate treatment recommendations, the Jadad decision algorithm was adopted. Two authors independently applied the decision algorithm to determine the meta-analysis with the highest quality to develop recommendation on the use of PRP in ARCR. Considering that all the 20 studies aimed to answer similar clinical questions despite analyzing a varied spectrum of primary studies, the study with the highest quality was selected on the basis of its methodological quality, restrictions involved (such as language or publication status), databases involved and analysis protocols adopted (Figure 3).

Based on this algorithm, the meta-analysis by Zhang *et al*[30] was determined to be the highest-quality study. This study observed no major benefits on overall clinical outcomes and re-tear rate following PRP administration in full-thickness rotator cuff tears; while a reduction in the rate of re-tears was demonstrated for small- and medium-sized tears. However, the selected study is also not free of critical methodological flaws based on AMSTAR 2 criteria. Hence, we analyzed the rationale for the development of the succedent systematic reviews as in Table 6 and tried to understand the evolution, variation in the techniques of procurement and application of PRP across different studies with due consideration to the high-quality evidence developed in the recent years and arrived at the following results.

Significant heterogeneity was observed in the reporting of VAS, function outcome scores (long-term UCLA score, ASES score, SST score), operative time and long-term re-tear rates. Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in

Table 2 Search methodology used by each study

Sl. No	Search parameters	Chahal (2012)	Moraes (2013)	Zhang (2013)	Li (2014)	Zhao (2015)	Warth (2015)	Vavken (2015)	Cai (2015)	Xiao (2016)	Hurley (2018)	Han (2019)	Wang (2019)	Chen (2019)	Cavendish (2020)	Hurley (2020)	Yang (2020)	Zhao (2021)	Ryan (2021)	Xu (2021)	Li (2021)
1	Publication language restriction	X	X	NA	X	X	X	X	NA	X	NA	X	NA	√	√	NA	NA	√	√	X	NA
2	Publication status restriction	X	NA	NA	NA	X	NA	NA	NA	X	X	NA	NA	X	NA	X	NA	NA	NA	X	NA
3	PubMed	√	X	√	√	√	√	√	√	√	X	√	√	√	√	X	√	√	√	X	√
4	Medline	√	√	X	X	X	X	X	X	X	√	X	X	√	X	√	X	X	√	√	X
5	Embase	X	X	X	√	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	Cochrane library	X	X	X	√	X	X	X	X	X	X	X	X	X	X	X	X	X	X	√	X
7	Web of Science	X	√	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	Scopus	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	X	√	√
9	Google Scholar	√	√	√	X	√	X	√	X	√	√	√	√	√	X	√	√	√	√	√	√
10	CINAHL	X	X	X	X	X	X	X	√	√	X	X	X	X	X	X	X	X	X	X	√
11	AMED	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12	CNKI	X	X	X	X	X	X	X	X	√	X	X	X	X	X	X	√	X	X	X	X
13	Wan Fang	X	X	X	X	X	X	√	X	X	X	X	X	X	X	X	X	X	X	X	X
14	CBM literature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
15	VIP	X	X	X	X	X	X	X	X	X	√	X	X	X	X	√	X	X	X	X	X

AMED: Allied and Complementary Medicine; CBM: Chinese BioMedical database; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNKI: Chinese National Knowledge Infrastructure; NA: Not available; VIP: Chinese Scientific Journals Database.

improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

Major conclusions from the individual studies

Different studies employed specific criteria to include studies with an aim to provide more useful and relevant information as compared to the previously-published literature. Chen *et al*[42] (2019), Hurley *et*

Table 3 Methodological information of each study

Sl. No	Search parameters	Chahal (2012)	Moraes (2013)	Zhang (2013)	Li (2014)	Zhao (2015)	Warth (2015)	Vavken (2015)	Cai (2015)	Xiao (2016)	Hurley (2018)	Han (2019)	Wang (2019)	Chen (2019)	Cavendish (2020)	Hurley (2020)	Yang (2020)	Zhao (2021)	Ryan (2021)	Xu (2021)	Li (2021)
1	Primary study design	RCT, CCT,RCS	RCT	RCT	RCT	RCT	RCT CCT	RCT	RCT	RCTCCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
2	Level of Evidence	III	I	I	II	I	II	I	I	II	I	I	I	I	II	I	I	II	I	I	II
3	Software Used	RevMan 5.3	RevMan 5.3	RevMan 5.3	NA	RevMan 5.3	Open Meta	STATA 10	RevMan 5.3	RevMan 5.3	RevMan 5.3	RevMan 5.3	RevMan 5.3	STATA 15.1	STATA 13	R Foundation (netmeta package Version 0.9-6 in R)	RevMan 5.3	RevMan 5.3	R Foundation for Statistical Computing, Vienna, Austria	STATA 15	RevMan 5.3
4	GRADE Used	X	√	X	X	√	X	X	X	X	X	X	√	X	X	X	X	X	X	X	X
5	Sensitivity Analysis	√	√	X	√	√	√	√	X	√	X	√	√	√	X	X	X	√	X	X	√
6	Subgroup Analysis	√	√	√	X	√	√	√	√	X	√	√	√	√	√	X	√	√	√	√	X
7	Publication Bias	X	√	√	X	√	√	√	√	√	X	√	√	√	√	X	X	X	X	X	X

CCT: Controlled clinical trial; GRADE: Grading of Recommendations Assessment, Development and Evaluation system; NA: Not available; RCTs: Randomized controlled trials; RCS: Retrospective cohort study.

al[44] (2020), Zhao *et al*[46] (2021), Ryan *et al*[1] (2021) and Li *et al*[47] (2021) compared the effects of PRP preparations on the basis of their relative leukocyte concentrations[1,42,44,46,47].

The initial studies by Chahal *et al*[32] (2012), Moraes[31] (2013), Zhang *et al*[30] (2013), Li *et al*[33] (2014), Zhao *et al*[34] (2014) and Xiao *et al*[37] (2016) did not reveal any benefit following PRP application [31-34,37]. Warth *et al*[35] (2014), Hurley *et al*[44] (2018) and Xu *et al*[48] (2021) observed that PRP was more helpful in enhancing the healing rates of large-sized tears[44,48]. Vavken *et al*[36] (2015) and Cai *et al*[38] (2015) reported better outcome following PRP application in small- to medium-sized tears[36,38]. The recent studies published by Han *et al*[39] (2019), Wang *et al*[41] (2019), Chen *et al*[42] (2019), Yang *et al*[45] (2020) and Cavendish *et al*[43] (2020) concluded that intraoperative PRP application significantly enhanced the short- and long-term clinical outcome and mitigated the re-tear rates after RC repair[39,41-43,45]. The recently-published literature [Hurley *et al*[44] (2020), Zhao *et al*[46] (2021), Ryan *et al*[1] (2021), Li *et al*[47] (2021) and Xu *et al*[48] (2021)] also seemed to demonstrate better outcome (functional scores and re-tear rates) with LP-PRP, as compared with LR-PRP[1,33,44,46,48]. The individual data of the included studies are presented in Table 6.

Table 4 AMSTAR scores and AMSTAR 2 grading for included studies

Sl. No	AMSTAR domains	Chahal (2012)	Moraes (2013)	Zhang (2013)	Li (2014)	Zhao (2015)	Warth (2015)	Vavken (2015)	Cai (2015)	Xiao (2016)	Hurley (2018)	Han (2019)	Wang (2019)	Chen (2019)	Cavendish (2020)	Hurley (2020)	Yang (2020)	Zhao (2021)	Ryan (2021)	Xu (2021)	Li (2021)
1	Was a priori design provided?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	Were there duplicate study selection and data extraction?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
3	Was a comprehensive literature search performed?	1	1	0	1	0	0	1	0	1	1	0	0	1	0	1	1	0	0	1	1
4	Was the status of publication (*i.e.* grey literature) used as an inclusion criterion?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	Was a list of studies (included and excluded) provided?	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	Were the characteristics of the included studies provided?	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
7	Was the scientific quality of the included studies assessed and documented?	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1
9	Were the methods used to combine the findings of studies appropriate?	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
10	Was the likelihood of publication bias assessed?	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0
11	Was the conflict of interest stated?	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1
	Total AMSTAR score	8	8	10	8	8	7	8	6	8	8	8	8	7	9	8	8	6	7	8	8
	Critical Methodological Flaw	3	3	1	3	2	2	3	5	2	3	2	3	4	1	3	3	4	4	3	2

Non-Critical Flaw	1	1	1	1	1	3	1	1	2	1	1	1	1	1	1	1	2	1	1	1
AMSTAR 2 Grade	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CL: Critically low.

DISCUSSION

To date, numerous RCTs have analyzed the efficacy of adjuvant PRP therapy in patients undergoing surgical repair of RC tears[6,30,39]. Although theoretically, biological augmentation with PRP can potentially enhance healing and mitigate failure rates after arthroscopic rotator cuff repair, our understanding of the exact role of PRP therapy in this scenario is still ambiguous[9,33]. Limited sample sizes, heterogeneity in the treatment protocols, PRP preparations and techniques employed; and the paucity of long- term results have been the major limitations of the currently published studies on this subject[1,6].

To further strengthen the results, multiple meta-analyses have been conducted to consolidate the findings of more recent RCTs, so as to provide the higher level of evidence on the effectiveness of the intervention in operatively-treated RC tears[6]. However, the spectra of primary studies included in the recent analysis and the databases utilized for study inclusion are still discordant[1,37,48]. Hence, a systematic overview of these overlapping meta-analyses was planned in order to identify the highest quality study among the available studies; as well as to formulate and generate recommendations regarding the use of adjuvant PRP in such situations.

Platelets are a source of high concentrations of different growth factors (like platelet-derived growth factor, transforming growth factor-beta, fibroblast growth factor, vascular endothelial growth factor and epidermal growth factor) which can potentially stimulate cell proliferation. They form a temporary matrix which can fill the defects and thereby provide a scaffold for cell migration and tissue remodeling [34]. The earliest meta-analysis on this subject was published by Chahal *et al*[32] in 2013. Although they observed marginal benefits in small and moderate sized tears, there was no major improvement in the overall re-tear rates or shoulder-specific outcomes after ARCR in larger or at-risk tears. Following this, in a Cochrane review, Moraes *et al*[31] reviewed studies involving intra-operative application of PRP; and concluded marginal benefits of PRP administration, especially with respect to improvements in short-term VAS and short-term re-tears. There has been a recent surge in the number of meta-analyses published on this subject since 2020[1,34,47,48]. While a majority of the older meta-analyses failed to show any major benefit of PRP therapy in this cohort of patients, more recent studies seem to re-iterate the potential benefits of adjuvant PRP treatment as evident from Figure 2. Older age, number of tendons involved, large tear size, duration of pre-operative symptoms and degree of pre-operative fatty degeneration have been postulated as some of the major factors predictive of high post-operative re-tear rates[32]. Table 6 discusses in detail the observations of each of these meta-analyses and enlists the reasons put forth by authors on the need for performing an additional meta-analysis in the presence of multiple pre-existing studies in the literature.

Among all the initial meta-analyses, the study with an excellent quality of methodology and a larger sample size and minimal heterogeneity was published by Zhang *et al*[30] in 2013. This study also

Table 5 I^2 statistic values of variables analyzed in each meta-analysis

Sl. No	Outcome variables	Chahal (2012)	Zhang (2013)	Moraes (2013)	Li (2014)	Zhao (2015)	Warth (2015)	Vavken (2015)	Cai (2015)	Xiao (2016)	Hurley (2018)	Han (2019)	Wang (2019)	Chen (2019)	Hurley (2020)	Yang (2020)	Cavendish (2020)	Zhao (2021)	Ryan (2021)	Xu (2021)	Li (2021)
1	VAS Score – Short term			29.9%+						0%-	38%-		0%-			60.5%+		0%+	0%+	0%+	
2	VAS Score – Long term			67%-			0%-			0%-	0%-	0%+	0%-	87.5%-	0%+	0%-		0%+		4%+	63%+
3	DASH Score – Short term									0%-			32%-			30%-					
4	DASH Score – Long term			0%-						NR-			0%-			0%-					32%-
5	Constant Score – Short term									30%+			0%+			0%+				23%+	
6	Constant Score – Long term	NR-	17%-	50%+	86%-	0%-	26%-		0%-	0%-	0%-	0%+	0%-	30.7%+	0%+	0%-		19%+	36%+	47%+	0%+
7	UCLA Score – Short term									0%+			8.9%+			0%+				0%+	
8	UCLA Score – Long term	NR-	0%-	35.18%-	75%-	0%-	0%-		60%-	47%-	0%-	47%+	12%+		0%+	0%-		49%+	64.18%-	63%+	46%+
9	ASES Score		0%-	0%-	46%-		58%-		0%-	54%-	0%-	26%-						0%-	41%-	52%-	0%+
10	SST Score	NR-	47%-	0%+	90%-		0%-		0%-	47%-		0%+							0%+		0%-
11	Operative time									85%-											
12	Patient Satisfaction			0%-						0%-											
13	Tendon healing rate								0%+	0%-					0%+			10%-			
14	Retear rate – Short term		0%-	25%+				15.2%-		30%-			0%+					0%+		0%-	
15	Retear rate – Long term	0%+	11%-	14%-	22%-	43%-		0%-	0%-	71%-		0%+	0%-	0%+	0%+	0%+	0%+	0%+	NA+	4.7%+	22%+

ASES: American Shoulder and Elbow Surgeons; DASH: Disabilities of the Arm, Shoulder and Hand; SST: Simple Shoulder Test; UCLA: University of California Los Angeles; VAS: Visual analog scale.

concluded that adjuvant PRPs could reduce the re-tear rates in small and medium-sized rotator cuff tears but not in massive or full-thickness tears. The meta-analyses by Li *et al*[33] (2014) and Zhao *et al*[34] (2014) incorporated a few more later-published RCTs. Both these studies did not reveal any major benefits of PRPs in terms of both clinical outcome scores and re-tear rates.

Warth *et al*[35] (2014) conducted a meta-regression analysis to evaluate the effect of 6 different co-variates (level of studies included, tear size, single- *vs* double-row repairs, types of PRP preparation, manual *vs* commercially available PRP preparations; and method of application of PRP) on overall clinical and structural outcome. They concluded that Constant scores were significantly improved when the PRPs were applied over the tendon-bone interface; and re-tears were significantly reduced in tears larger than 3 cm which were repaired using the double-row technique. In contrast, both the meta-analysis [Vavken *et al*[36]; Cai *et al*[38] (which included only RCTs)] published following this study revealed no benefit in large, full-thickness tears. In both these studies, PRPs enhanced healing rates only in small- to moderate-sized tears. Additionally, Vavken *et al*[36] concluded that despite its biological effectiveness; at the present costs, the use of PRPs is not a cost-effective strategy in arthroscopic repair of small- to moderate-sized RC tears. Another meta-analysis by Xiao *et al*[37] (2016) tried to enhance the power of the analysis by including both level I and II studies. Nevertheless, they too failed to reveal any major benefit in terms of both clinical outcome and re-tear rates. By being less selective in including studies for analysis, the quality of the meta-analysis also significantly deteriorated as compared to previous studies.

Between 2016 and 2018, many new RCTs were performed; and 4 new meta-analyses were published in 2018 and 2019 which included these recent studies as well. Hurley *et al*[40] (2018; involving 18 studies) compared PRP and platelet-rich fibrin (PRF) in ARCR. They concluded that PRPs improved pain score (short-term and long-term), Constant score and re-tear rates in RC tears of all sizes. Another similar study by Han *et al*[39] (involving 13 RCTs) also reported reduced re-tear rate and meliorated clinical outcome with PRP therapy in ARCR. Wang *et al*[41] (2019; included only 8 RCTs) observed good outcomes with PRPs when administered in ARCRs with a single-row technique. Chen *et al*[42] (2019) performed another higher quality meta-analysis (involving 18 level 1 studies) and concluded that long-term re-tear rates were significantly improved with PRP therapy. Additionally, the functional outcome scores (Constant score, UCLA score – at long- and short-terms) and VAS scores were better in the PRP-treated group. They also performed detailed sub-group analysis in 3 different categories and concluded that: a. Functional outcome measures were more significantly improved when multiple tendons were torn or ruptured, b. Leukocyte-rich PRP (LR-PRP) group had much better improvement in Constant scores as compared with LP-PRP, and c. Patients receiving gel-preparations of PRP had significantly greater Constant scores than their respective comparison groups. They also assessed the minimal clinically important differences (MCID) for these patient-related outcome (PRO) measures. It was concluded that although significant improvements were observed in multiple functional outcome measures in the PRP-treated patient group, none reached their respective MCID. They opined that despite a reasonable number of publications on this subject, limited data availability, substantial study heterogeneity and poor methodological quality hampered our ability to reach firm conclusions regarding PRPs.

Recent meta-analyses and their observations

Between 2020 and 2021, 7 new meta-analyses have been published on this topic. Owing to the availability of better quality, larger-scale RCTs over the recent years, these recent meta-analyses have been able to put forth stronger recommendations regarding the administration of PRPs. Cavendish *et al*[43] reported 16 RCTs and prospective trials (1045 participants), Hurley *et al*[44] included 13 RCTs (868 participants), Yang *et al*[45] analyzed 7 RCTs published between 2013 and 2018 (541 participants), Zhao *et al*[46] involved 10 RCTs (742 participants), Ryan *et al*[1] included 17 RCTs (1104 participants), Li *et al*[47] evaluated 23 RCTs (1440 patients) and Xu *et al*[48] studied 14 RCTs (923 patients). Hurley *et al*[44] analyzed RCTs comparing LP- or LR-PRP against controls, Zhao *et al*[46] evaluated studies involving LP-PRP, Ryan *et al*[1] evaluated 4 different types of PRPs (pure platelet-rich plasma [P-PRP], leukocyte and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte and platelet-rich fibrin); and Li *et al*[47] analyzed RCTs comparing PRP or PRF to controls in ARCR. The remaining 3 studies included all RCTs evaluating the overall role of PRPs (with or without comparison to a control group)[43,45,48].

All the 7 recent meta-analyses support the role of PRPs in ARCR. Overall, based on their recommendations, PRPs are preferably delivered intra-operatively at the bone-tendon interface for the best possible outcome. Cavendish *et al*[43] reported that PRPs significantly reduce the failure rates after ARCR, irrespective of the size of tear. Xu *et al*[48] demonstrated substantially improved re-tear rates following intra-operative use of PRP in large- or massive-sized tears. Hurley *et al*[44] concluded that LP-PRP reduces re-tear, enhances healing potential and improves PRO, as compared with a control. Nevertheless, they could not make any strong recommendations regarding its superiority or inferiority as a biological augment, in comparison with LR-PRPs. Even in the meta-analysis by Zhao *et al*[46], LP-PRP was demonstrated to significantly reduce medium- and long-term post-operative re-tear rates in patients undergoing ARCR, irrespective of the size of tear and the technique of repair. Nevertheless, when defined in terms of MCID, the use of LP-PRP failed to reveal any clinically meaningful benefits in terms of post-operative VAS and PRO measures. Among the 4 different types of PRP employed, only P-

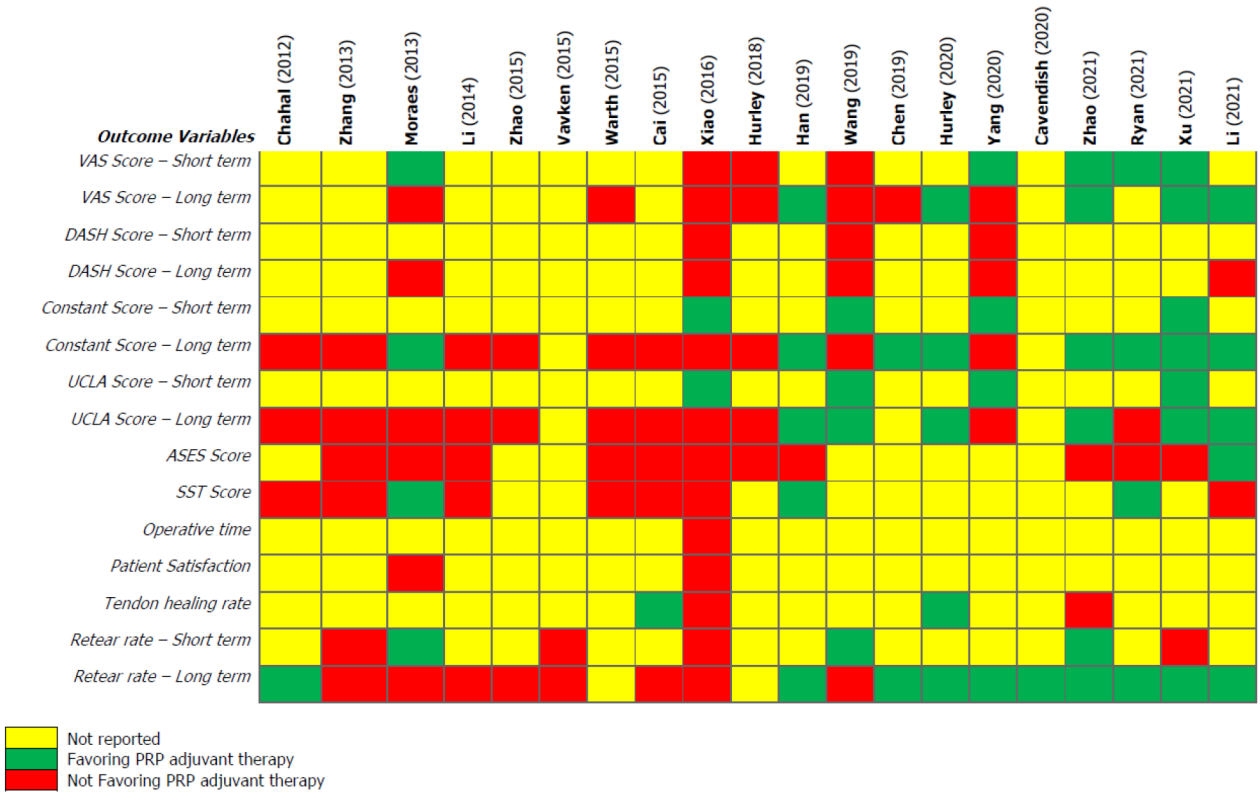

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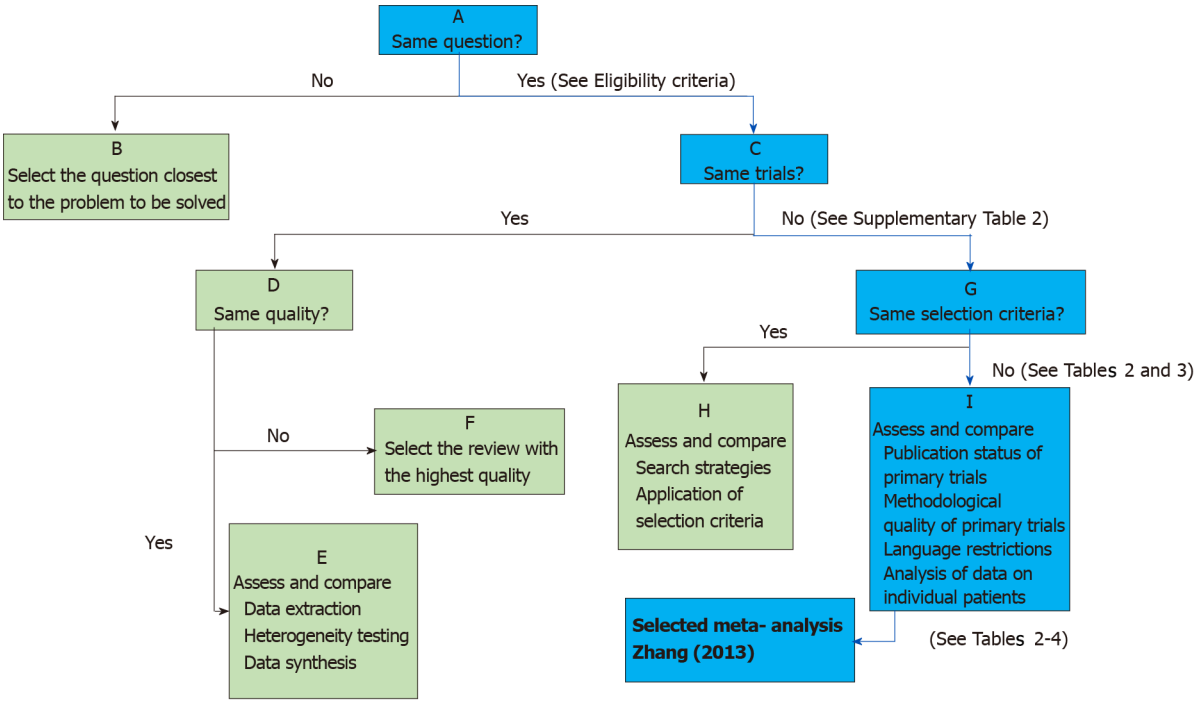
Figure 2 Pooled results of each included meta-analyses along with their heterogeneity. ASES: American Shoulder and Elbow Surgeons; DASH: Disabilities of the Arm, Shoulder and Hand; SST: Simple Shoulder Test; UCLA: University of California Los Angeles; VAS: Visual analog scale.



DOI: 10.13105/wjma.v10.i3.143

Figure 3 Flowchart of Jadad decision algorithm.

PRP demonstrated statistically significant improvement in re-tear rate and Constant score. Theoretically, LP-PRP enhances the formation of normal collagen and mitigates the synthesis of inflammatory mediators. On the other hand, LR-PRP augments the cell catabolism and inflammatory response, both of which are not conducive for tendon healing. Therefore, in acute traumatic RC tears, use of LR-PRP may

Table 6 Systematic Reviews or Meta-analyses with their level of evidence with the authors' rationale for repeating the systematic review along with their concluding remarks

Sl. No.	Ref.	Date of publication	Date of last literature search	Level of evidence	Rationale for repeating meta-analysis	Conclusion
1	Chahal *et al* [32], 2012	June 14, 2012	December 30, 2011	III	Earliest meta-analysis	No effect of PRP on overall retear rates or shoulder-specific outcomes after ARCR
2	Moraes *et al* [31], 2013	December 23, 2013	March 25, 2013	I	Only included studies with intra-operative PRP application after ARCR	Some benefit of PRP in improving pain with comparable rates of retear (after 2 yr) between PRP and non-PRP groups
3	Zhang *et al* [30], 2013	July 12, 2013	April 20, 2013	I	Included studies with high methodological quality and provided results without significant heterogeneity supported by larger number of patients	No benefit of PRP on overall clinical outcomes and retear rate in full-thickness rotator cuff tears and decrease in rate of retears with PRP for small- and medium-sized rotator cuff tear
4	Li *et al*[33], 2014	June 7, 2014	May 1, 2013	II	All high-quality (7 studies) RCTs included (compared with previous studies)	No benefit with PRP regarding retear and clinical outcomes for ARCR
5	Zhao *et al* [29], 2014	September 30, 2014	September, 2013	I	Newer RCTs as compared with previous meta-analysis	No benefit of PRP in ARCR of full-thickness tears in terms of similar retear rates and clinical outcomes
6	Warth *et al* [35], 2014	September 13, 2014	September, 2013	II	Meta-regression analyses to evaluate the effects of 6 covariates such as inclusion of Level II studies, initial tear size, single- *vs* double-row repair constructs, varying PRP preparation, manual *vs* commercially available PRP preparation systems, method of PRP application on overall clinical and structural outcomes	No statistically significant differences in outcome scores or retear rate with the use of PRP. However, significant improvement in Constant scores when PRPs applied at tendon-bone interface and significant reduction in retear rate with PRP in tears > 3 cm repaired with double-row technique
7	Vavken *et al*[36], 2015	March 12, 2015	August 1, 2014	I	To know if addition of PRP to ARCR results in statistically relevant as well as clinically meaningful reduction in retear rates along with analysis of its safety with difference in complication rates and its cost-effectiveness	PRP proved to be an effective and safe way of reducing retear rates in the arthroscopic repair of small- and medium-sized rotator cuff tears. However, no evidence to support its use in large and massive tear
8	Cai *et al* [38], 2015	October 8, 2015	January, 2015	I	Meta-analysis of level I studies	PRP in full-thickness rotator cuff repairs showed no statistically significant difference in clinical outcome but demonstrated significant reduction in failure-to-heal rate for small-to-moderate tears
9	Xiao *et al* [37], 2016	October 30, 2016	February 1, 2016	II	All level I and II evidence studies – included to enhance power of meta-analysis (15 studies)	No significant difference in the re-tear rates and clinical efficacy
10	Hurley *et al* [40], 2018	February 21, 2018	March 24, 2017	I	First study to find that PRP was associated with significant improvement in tendon healing rates in tears > 3 cm with 9 new studies that have been published till Cai *et al*[38], 2015	Use of PRP in rotator cuff repair improves the healing rates, pain levels, and functional outcomes. But PRF shows no benefit in improving tendon healing rates or functional outcomes
11	Han *et al* [39], 2019	June 20, 2019	September, 2016	I	Inclusion of new RCTs, as compared with previous meta-analysis with improved pooled effect size	PRP treatment with ARCR showed decreases retear rate and improves clinical outcome
12	Wang *et al* [41], 2019	July 29, 2019	September 15, 2018	I	To ensure homogeneity of data, only studies using PRP in full-thickness tears included along with addition of new high-level RCTs	PRP improved the short-term outcomes such as pain, retear rate, and shoulder function after ARCR in full-thickness rotator cuff tears. PRP when used in single-row fixation of ARCR demonstrated improved clinical outcomes.
13	Chen *et al* [42], 2019	September 19, 2019	December, 2017	I	Exclusively reviewed only level 1 RCTs with multiple sub-groups, and comparative quantitative analysis with MCID on effects of LR-PRP *vs* LP-PRP, gel *vs* non-gel preparations, and tendon-specific outcomes analyzed	Long-term retear significantly decreased with PRP. Several PROs such as constant score, VAS, retear rate significantly improved in PRP-treated patients. However, all analyzed PROs failed to reach the 5% MCID threshold. Hence authors neither recommended nor discouraged the use of PRP for rotator cuff injuries

14	Cavendish *et al*[43], 2020	May 1, 2020	May 23, 2018	II	Included 7 out of 16 studies published in the past 4 yr with larger sample size to reduce risk of type II error noted in previous studies	Intraoperative use of PRP reduces the failure risk following rotator cuff repair and has a consistent effect regardless of tear size and showed 25% reduction in the overall risk of failure in rotator cuff repairs
15	Hurley *et al* [44], 2020	July 30, 2020	March, 2020	I	To ascertain whether there is evidence to support the use of LP- or LR-PRP as an adjunct to ARCR	LP-PRP reduces rate of retear and/or incomplete tendon healing after ARCR and improves patient-reported outcomes as compared with control whereas whether LP-PRP improves the tendon healing rate when compared with LR-PRP remained unclear
16	Yang *et al* [45], 2020	October 14, 2020	February 15, 2020	I	Inclusion of studies that dealt with PRP application on bone–tendon interface only during arthroscopic repair and studies that administered only PRP and not any other platelet-rich matrix to lower bias caused by different materials. All included RCTs were conducted on patients with full thickness rotator cuff tear who received diagnoses based on preoperative MRI or sonography	Application of PRP shown to be beneficial in reducing the retear rate and improving the functional outcomes during the short-term follow-up of single-row repair
17	Zhao *et al* [46], 2020	November 18, 2020	March, 2020	II	Meta-analysis of level I and II studies based on MCID values to comprehensively assess clinical efficacy of LP-PRP only for ARCR mainly to avoid heterogeneity due to different types of PRP	LP-PRP - significantly reduces the postoperative retear rate in medium and long term regardless of tear size and method used for repair. But no clinically meaningful effects in terms of postoperative pain and patient-reported outcomes were noted
18	Ryan *et al* [1], 2021	March 17, 2021	June, 2020	I	Involved stratified pooled data on basis of leukocyte concentration, liquid and solid formulation, and all 4 types of PRP (P-PRP, P-PRF, LP-PRP, LP-PRF)	This analysis demonstrates significant reductions in retear when rotator cuff repair is augmented with PRP. LP-PRP appears to be most effective formulation, resulting in significantly improved retear rates and clinical outcome scores when compared with controls
19	Xu *et al* [48], 2021	May 27, 2021	October 29, 2020	II	Analyzed PRP and PRF separately and PRP was sub grouped into leukocyte-poor and leukocyte-rich PRP. Compared with study by Hurley *et al* 5 more RCTs included. Cochrane Collaboration risk of bias tool- adopted and retear rate was analyzed based on duration of follow-up into 2 subgroups with a cut off of 2 yr	PRP in ARCR improved pain and functional outcome, reduces retear rates. PRF improved only the Constant score. Significant reduction of retear rate in leukocyte-poor PRP when followed-up > 2 yr
20	Li *et al*[47], 2021	July 13, 2021	June 20, 2020	I	Strict eligibility criteria enforced in the inclusion of RCTs along with subgroup analysis, based on PRP preparation, time of administration, size of tear, type of repair, to assess the real utility of PRP	ARCR with PRP significantly improved long-term retear, shoulder pain and long-term shoulder function scores and intraoperative application of leukocyte-poor plasma for large to massive tears contributed to significant decrease in retear rates

ARCR: Arthroscopic rotator cuff repair; LP: Leukocyte poor; LP-PRF: Leucocyte poor – platelet rich fibrin; LP-PRP: Leucocyte poor – platelet rich plasma; LR: Leucocyte rich; MCID: Minimum clinically identifiable difference; P-PRF: Pure platelet rich fibrin; P-PRP: Pure platelet rich plasma; PRF: Platelet rich fibrin; PRO: Patient reported outcomes; PRP: Platelet rich plasma; RCTs: Randomized controlled trials.

impair post-operative tissue healing. These recent meta-analyses also seem to indicate the superiority of LP-PRP (over LR-PRP) in ARCR[48]. Thus, despite multiple studies published on this topic, the literature is still unclear on whether the use of PRP is more beneficial in massive and full-thickness tears or smaller and partial thickness injuries[36,38,44,48]. A majority of the studies in the literature have also not clearly determined the correlation between the type of RC repair and the effect of PRP application [29-40,42-48]. However, two recent studies [Wang *et al*[41] (2019) and Yang *et al*[45] (2020)] have shown better outcome with PRP use following single-row RC repairs[6,41].

These recent studies have also cautioned regarding significant heterogeneity in the available preparations of PRPs, which leads to inconsistent outcome and difficulty in making strong recommendations in favor or against this treatment modality. Yang *et al*[45] demonstrated a significant decrease in re-tears as well as a substantial improvement in short-term pain severity (VAS) and short-term functional outcome (Constant and UCLA scores). In a sub-group analysis, they also demonstrated meliorated outcomes (in terms of VAS, functional scores and re-tear) in both single- and double-row repair groups. In a comparison study by Li *et al*[47] between PRP and PRF, PRP demonstrated significant improvement in pain, functional outcome and re-tears; while PRF only improved Constant score.

Directions for future

Although PRP has been considered as a minimally-invasive effective non-operative treatment methodology for partial RC tears[50], its utility as an adjuvant in the ARCR needs further refinement to preclude the heterogeneity in the results obtained and achieve consistent beneficial effects of the additive intervention performed. For example, role of repeat administration of PRP and utility of scaffolds as a medium of sustained delivery of the growth factors from the platelet concentrate may provide even more beneficial effects compared to the single direct use post-ARCR[51]. Although our systematic overview establishes the efficacy of PRP as an adjuvant to ARCR, there remains heterogeneity among the study results obtained due to the variability in the preparation and the utility of PRP. To clarify these aspects, blinded RCTs investigating the above-mentioned lacunae are required in the future.

Limitations

This study has some limitations. The quality of the meta-analyses identified in our study were of Level I/II evidence due to the quality of the included primary studies in them. Hence, we were unable to provide a level I recommendation on the utility of PRP in ARCR with the existing literature. This systematic overview may be influenced by the limitations and biases involved in the meta-analyses and their primary studies. Moreover, selecting the meta-analysis of highest quality based on the Jadad algorithm generates recommendations based on the results of the selected meta-analysis at the cost of studies missed from their primary search as highlighted in Supplementary Table 1. Moreover, we identified many recent meta-analyses, apart from the meta-analysis selected through the Jadad algorithm, which had the power of the recent RCTs on the subject. Hence, we resorted to give collaborative documentation based on all the recent evidence though they lack the methodological robustness of the study identified by the Jadad algorithm thereby making the final level of recommendation that was achieved out of this study to be Level II. Heterogeneity was noted across the studies in terms of their methods of preparation, use of activators and method of application of PRP which could have accounted for the variability noted across the primary studies and the meta-analyses that included them into analysis.

CONCLUSION

Based on our systematic overview of the existing meta-analyses, we could observe that despite multiple publications on this subject over the past years, methodological quality of the included studies and heterogeneity in protocols employed across different individual trials continue to remain major impediments in clearly defining the role of PRPs in ARCR. Nevertheless, the recent meta-analysis published over the past 2 years to 3 years seems to indicate a clear benefit of intra-operative use of PRPs at the bone-tendon interface in terms of post-operative pain, functional outcome and re-tear rates (irrespective of the type of repair performed). Although the older studies supported its role in only small to moderate tears, recent studies indicate a definite benefit in tears of all sizes (including massive ones). Among the different preparations used, LP-PRP possibly offers the greatest benefit as a biological augment in these situations.

ARTICLE HIGHLIGHTS

Research background

Platelet-rich plasma has been gaining popularity as an agent for biological augmentation either as the sole treatment modality or as an adjunct to surgical repair.

Research motivation

There is growing evidence on the positive effects of platelet-derived autologous growth factors on collagen production, cell proliferation, tissue revascularization and tendon regeneration thereby making them useful as an augment to arthroscopic rotator cuff repair.

Research objectives

The overall purpose of the current study was to perform a detailed systematic review of the existing meta-analyses evaluating the role of PRP in patients undergoing rotator cuff repair; and to specifically provide answers to the following research questions, namely: (1) To evaluate the effect of this strategy on overall clinical outcome scores; (2) To evaluate the reduction in re-tear or failure rates; (3) To analyze the evolution and variations in the techniques of procurement and application of PRP across different studies; (4) To critically analyze and interpret the best currently available evidence and provide recommendations; and (5) To discern the major gaps in the existing literature and identify the scope for

future research on this subject.

Research methods

We then utilized the Jadad decision algorithm to identify the study with the highest quality to represent the current best evidence to generate the recommendation.

Research results

Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

Research conclusions

Based on this systematic overview, we give a Level II recommendation that intra-operative use of PRPs at the bone-tendon interface can augment the healing rate, reduce re-tears, enhance functional outcome and mitigate pain in patients undergoing arthroscopic rotator cuff repair.

Research perspectives

LP-PRP possibly offers the greatest benefit in terms of healing rates as compared with other platelet preparations.

FOOTNOTES

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META-ANALYSIS

Is cellular therapy beneficial in management of rotator cuff tears? Meta-analysis of comparative clinical studies

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Abstract

BACKGROUND

Mesenchymal stromal cell (MSC)-based cellular therapy promotes type I collagen

production, enhance mechanical strength of tissues, and enhance biology at the bone-tendon interface, which primarily explains their potential clinical utility in rotator cuff (RC) tears.

AIM

To analyze the efficacy and safety of cellular therapy utilizing MSCs in the management of RC tears from clinical studies available in the literature.

METHODS

We conducted independent and duplicate electronic database searches including PubMed, Embase, Reference Citation Anallysis, Web of Science, and Cochrane Library in August 2021 for studies analyzing the efficacy and safety of cellular therapy (CT) utilizing MSCs in the management of RC tears. Visual Analog Score (VAS) score for pain, American Shoulder and Elbow Surgeons (ASES) score, Disability of the Arm, Shoulder, and Hand score, Constant score, radiological assessment of healing, and complications such as retear rate and adverse events were the outcomes analyzed. Analysis was performed in R-platform using OpenMeta [Analyst] software.

RESULTS

Six studies involving 238 patients were included for analysis. We noted a significant reduction in VAS score for pain at 3 mo (weighed mean difference [WMD] = -2.234, $P < 0.001$) and 6 mo (WMD = -3.078, $P < 0.001$) with the use of CT, which was not maintained at long-term follow-up (WMD = -0.749, $P = 0.544$). Concerning functional outcomes, utilization of CT produced a significant short-term improvement in the ASES score (WMD = 17.090, $P < 0.001$) and significant benefit in functional scores such as Constant score (WMD = 0.833, $P = 0.760$) at long-term follow-up. Moreover, we also observed significantly improved radiological tendon healing during the long-term follow-up (odds ratio [OR] = 3.252, $P = 0.059$). We also noted a significant reduction in the retear rate upon utilization of CT in RC tears both at short- (OR = 0.079, $P = 0.032$) and long-term (OR = 0.434, $P = 0.027$) follow-ups. We did not observe any significant increase in the adverse events directly related to cellular therapy, as compared with the control group (OR = 0.876, $P = 0.869$).

CONCLUSION

Based on our comprehensive and critical review, we could observe that the utilization of CT in RC tear significantly reduced pain severity at 3 and 6 mo, improved short-term functional outcome, enhanced radiological tendon healing, and mitigated retear rates at both short- and long-term follow-ups. The literature also confirmed the relative safety of using MSC therapy in patients presenting with RC tears.

Key Words: Mesenchymal stromal cell; Bone-marrow derived mesenchymal stromal cell; Adipose-derived mesenchymal stromal cell; Rotator cuff tear; Cellular therapy; Meta-analysis

Core Tip: Biological augmentation of rotator cuff tears with mesenchymal stromal cell-based cellular therapy significantly reduces the pain severity and improves the functional outcome at 3 and 6 mo based on our critical review of clinical studies on the subject. Moreover, we noted enhanced radiological tendon healing, and mitigated retear rates at both short- and long-term follow-ups. We have also established the safety of using cellular therapy in patients presenting with rotator cuff tears.

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INTRODUCTION

Rotator cuff (RC) tear is a common shoulder pathology, whose prevalence ranges from 4% in asymptomatic individuals younger than 40 years to 54% in patients aged over 60 years[1]. The etiology

of these tears is multifactorial, and has been variously attributed to traumatic, mechanical, and inflammatory processes[2]. It has been well-demonstrated that the natural course of non-operatively managed RC tears in the majority of patients is a progressive deterioration of the anatomical tear without spontaneous regression of symptoms[3]. On the other hand, although surgical repair of a torn RC potentially aids in restoring the shoulder function as well as arresting the tear progression[4], the failure rates range between 0 and 78%, thereby giving room for improvement[5].

In view of obtaining predictable and consistent results in the management of RC tears, biological adjuvants like platelet-rich plasma (PRP) and stem cells (SC) have been tried to augment the regeneration of damaged RCs and improve the outcome following surgical repair[6]. Recently, mesenchymal stromal cells (MSCs) have been successfully employed in diverse animal and human models in the repair of various musculoskeletal structures like cartilages, bones, muscles, and tendons [7]. These cells (usually extracted from bone marrow or adipose tissue) possess a unique attribute described as "multipotency", which denotes their ability to differentiate into other tissues of mesenchymal origin[2,8]. When delivered using appropriate scaffolds, these modalities of cellular therapy (CT) have shown great promise in enhancing the outcome following RC tears too[2,8-13]. MSCs are thought to promote type I collagen production, enhance mechanical strength of tissues, and ameliorate biology at the bone-tendon interface, which primarily explains their potential clinical utility in RC tears[8-13]. The concentrates of these cells may be delivered into the region of tendon injury, either *via* image-guided injections or through arthroscopic approach (intra-operatively)[8-13]. However, the major barriers to regular use of MSCs include lack of standardized techniques for preparation, inadequate clinical evidence, and potentially high cost:benefit ratios.

With this backdrop, in order to further enhance the understanding of their utility with clinical evidence on utilization of MSC-based CT in the management of RC tears, we performed a meta-analysis of clinical studies available in the literature to systematically analyze the efficacy and safety of CT utilizing MSCs in the management of RC tears.

MATERIALS AND METHODS

We performed this meta-analysis following the guidelines made out by the Back Review Group of Cochrane Collaboration[14] and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15].

Search strategy

Two reviewers performed an independent electronic literature search for studies evaluating the efficacy and safety of MSC-based CT in the management of RC tears. We searched the following databases: PubMed, Embase, Reference Citation Analysis, Web of Science, and the Cochrane Library up to August 2021. No language or date restrictions were applied. Keywords used for the search were as follows: "Cellular therapy", "Mesenchymal Stromal Cells", "Stem Cell Therapy", "Mesenchymal Stromal Cells", "Bone marrow", "Adipose", "Rotator cuff tear", and "Supraspinatus tear". We have presented the search strategy used in one of the included databases in Supplementary Material 1. We also looked into the references of the included studies to identify additional studies that were not identified in the primary search. Based on the specified inclusion and exclusion criteria set as a priori, studies were analysed for inclusion into the analysis. In case of discrepancy between the authors upon selection of studies into the analysis, discussion was made until a consensus was obtained. PRISMA flow diagram of inclusion of studies in the analysis is given in Figure 1.

Inclusion criteria

The PICOS criteria to include the studies into the review were as follows:

Population: Patients with RC tears.

Intervention: MSC-based biological therapy.

Comparator: Placebo.

Outcomes: Visual Analog Score (VAS) score for pain, American Shoulder and Elbow Surgeons (ASES) score, Disability of the Arm, Shoulder and Hand (DASH) score, Constant score, ultrasonogram (USG) or magnetic resonance imaging (MRI) based assessment of healing, and complications such as retear rate and adverse events reported.

Study design: Comparative clinical studies (CCSs).

Exclusion criteria

Studies that had the following characteristics were excluded from the inclusion into the review: *In vitro* studies on stem cell therapy for tendon injury; Observational studies and non-comparative interven-

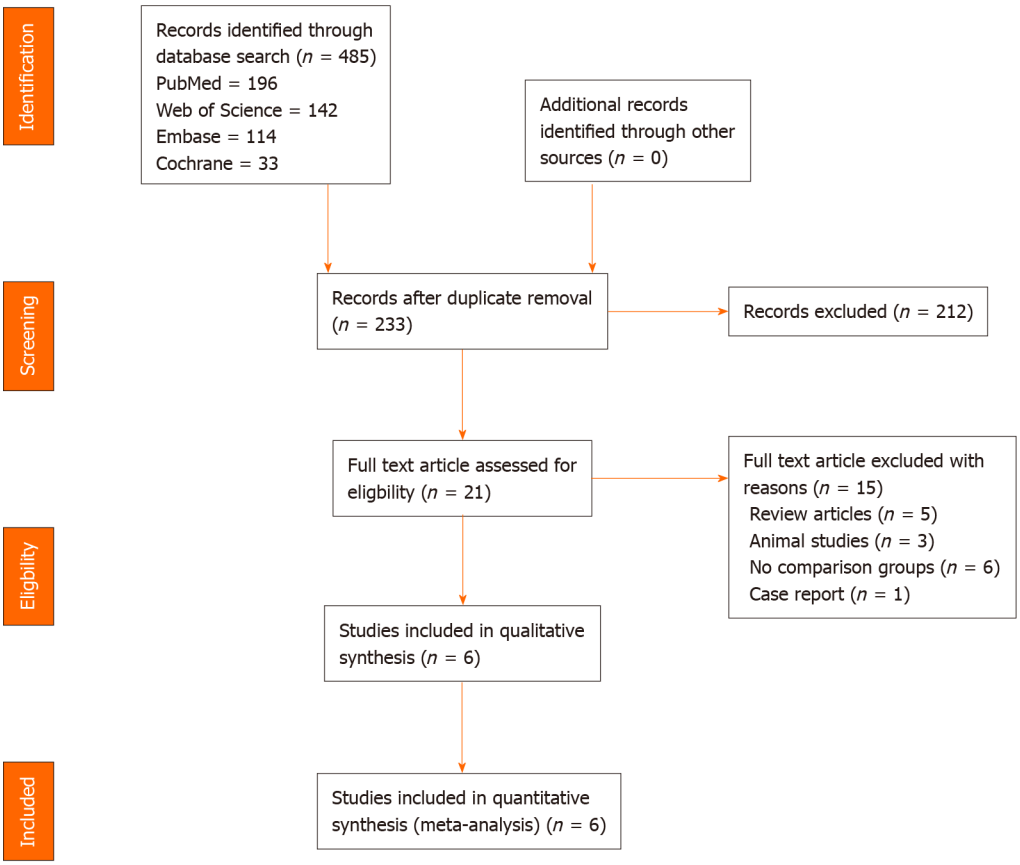

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Figure 1 PRISMA flow diagram of the included studies.

tional studies on RC tears; Animal model studies of tendon injury investigating stem cell therapy; and Review articles on CT for RC tears.

Data extraction

The following relevant data from the included studies were retrieved by two reviewers for analysis.

Study characteristics: Year of publication, authors, country, nature of the study, level of evidence, and number of enrolled patients.

Baseline characteristics: Age, gender proportions, nature of RC tear, intervention for both the groups, source of MSC utilized, delivery method of MSCs, follow-up duration, and assessment parameters utilized.

Efficacy outcomes: VAS score for pain, ASES score, DASH score, Constant score, and USG/MRI based assessment of healing.

Safety outcomes: Complications such as retear rate and adverse events reported in the included studies.

In case of any disagreement between the authors in data collection, it was resolved by discussion until a consensus was achieved.

Risk of bias and quality assessment

Two reviewers independently assessed the methodological quality of the included studies based on the ROB2 tool of Cochrane Collaboration for randomized studies. It consists of five domains of bias assessment including bias in randomization process, bias due to deviation from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selective reporting of results[16]. Similarly, the methodological quality of the non-randomized comparative studies were assessed using ROBINS-1 tool of Cochrane Collaboration which have seven domains of bias assessment including confounding bias and bias in intervention classification apart from the five domains described previously for randomized studies[17].

Statistical analysis

We conducted the meta-analysis in the R-platform with OpenMeta [Analyst][18]. We utilized odds ratio

(OR) with 95% confidence interval (CI) for dichotomous outcomes and weighted mean difference (WMD) with 95%CI for continuous variable outcomes. We analyzed the heterogeneity in the included studies using the I^2 test[19]. In case of I^2 value < 50% and P value > 0.1, a fixed-effects model was used for evaluation. Otherwise, a random-effects model was used. We considered a P value < 0.05 to be significant. We also performed sensitivity analysis and subgroup analysis to analyse the source of heterogeneity when it existed. Funnel plot and normal quantile plot were used for the publication bias assessment of the outcomes in the included studies along with Egger's regression test.

RESULTS

Search results

Electronic database search resulted in 485 articles which, after initial screening for duplicate removal, gave a total of 233 articles. Title and abstract screening were done in those 233 articles and 212 of them were excluded. Twenty-one articles were qualified for full-text review, of which 15 were excluded. A list of articles excluded from full-text review with reasons is presented in Supplementary Material 2. We included six studies[2,8-12] (3 randomized controlled trials[2,9,12], 1 prospective controlled study[8], and 2 retrospective comparative studies[10,11]) with 238 patients for meta-analysis. PRISMA flow diagram of study selection is given in Figure 1. We excluded most of the studies since they did not have a comparator group in their study design, which resulted in a low number of included studies for analysis. Considering the specificity of the research question, we considered it would be useful if a meaningful result could be arrived with the analysis of the comparative studies identified based on the predefined screening protocol. Four of the included six studies[2,8,11,12] utilized MSCs from bone marrow, while the remaining two studies[9,10] used adipose tissue as their source of MSCs. Only two of the included six studies[8,12] utilized platelet-rich plasma as an adjuvant to the cellular therapy intervention being used in them. We noted wide variability in the cellular dosage utilized in the included studies with a mean dosage of 141.15 ± 327.75 × 10^6 cells. While three studies[2,10,11] compared the intervention against the surgical repair of RC tears, two studies[8,12] compared it against exercise therapy, and one study[9] against steroid injection. There was also no uniformity among the included studies for the outcome measures utilized to analyze the efficacy of the intervention. The general characteristics of the studies included are given in Table 1. The protocols of intervention used in the case and control groups along with the measures of outcome assessment are given in Table 2.

Quality assessment

The methodological quality of the included studies evaluated as per the RoB2 tool and ROBINS tool is presented in Figure 2. None of the included studies had a high risk of bias to be excluded from the analysis.

Efficacy outcomes

Visual Analog Scale score for pain: We analyzed five studies[2,8-10,12] comparing the VAS outcome upon using CT for RC tears against controls at varied time points. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, a random-effects model was used for analysis. We stratified the analysis based on the duration of follow-up in the included studies and found that upon utilizing CT in the management of RC tears, an overall significant reduction in VAS score for pain was noted compared to the controls (WMD = -1.408, 95%CI [-2.231, -0.585], P < 0.001). However, upon stratification of the studies based on the duration of their follow-up, it was noted that the pain reduction was not significant at < 3 mo (WMD = -0.399, 95%CI [-1.134, 0.335], P = 0.287), which improved significantly at 3 mo (WMD = -2.234, 95%CI [-2.711, -1.757], P < 0.001) and 6 mo (WMD = -3.078, 95%CI [-3.634, -2.521], P < 0.001). Upon analyzing the VAS scores at 1 year (WMD = -0.749, 95%CI [-3.167, 1.670], P = 0.544), and > 2 years (WMD = 0.3, 95%CI [-0.171, 0.771], P = 0.256), it was noted that the significance of the VAS reduction was lost at long-term follow-up as shown in Figure 3. Hence, utilization of CT produced a significant reduction of pain in the initial periods of inflammation and healing cascade caused by the injury and surgical repair procedure while in the long term, since the lesion heals in the surgical comparator groups, we did not note any significant difference (Figure 3).

ASES score

We analyzed two studies[8,9] comparing the ASES outcome upon using CT for RC tears against controls at varied time points. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, a random-effects model was used for analysis. We stratified the analysis based on the duration of follow-up in the included studies and found that upon utilizing CT in the management of RC tears, an overall significant improvement in ASES score was noted compared to the controls (WMD = 17.090, 95%CI [9.122, 25.057], P < 0.001). However, upon stratification of the studies based on the duration of their follow-up, it was noted that the functional improvement based on ASES score improvement was not significant at 3 wk (WMD = 12.052, 95%CI [-14.499, 38.603], P = 0.374),

Table 1 Characteristics of included studies (*n* = 6)

No.	First author	Year	Country	Study design	Sample size	Cases/controls	MSC source	PRP	Cellular dosage (10^6 cells)	Comparator intervention	Case age (SD)	Control age (SD)	Case male: Female	Control male: Female	Follow-up timeline (mo)
1	P Hernigou	2014	France	RCS	90	45/45	BM-MSC	No	0.051	Surgery	61 ± 4.5	61 ± 4.5	21:24	20:25	6, 120
2	YS Kim	2017	Korea	RCS	70	35/35	AD-MSC	No	4.46	Surgery	59.2 ± 3.4	57.6 ± 2.9	15:20	13:22	28.3
3	SJ Kim	2018	Korea	PCS	24	12/12	BM-MSC	Yes	1	Exercise therapy	54.9 ± 7.6	59.6 ± 7.2	05:07	08:04	0.7, 3
4	JR Lamas	2019	Spain	RCT	13	8/5	BM-MSC	No	20	Surgery	57.8 ± 6.5	61.8 ± 3.8	06:02	02:03	12
5	C Centeno	2020	USA	RCT	25	14/11	BM-MSC	Yes	810	Exercise therapy	46 ± 11	49 ± 11	09:05	05:06	1, 12
6	JL Hurd	2020	USA	RCT	16	11/5	AD-MSC	No	11.4	Steroid	64.6 ± 9.6	57.6 ± 6.2	08:03	05:00	6, 12

AD: Adipose derived; BM: Bone marrow derived; MSC: Mesenchymal stem cell; PCS: Prospective controlled study; RCS: Retrospective comparative study; RCT: Randomized controlled trial; SD: Standard deviation; USA: United States of America.

which improved significantly at 3 mo (WMD = 18.919, 95%CI [5.802, 32.036], P = 0.005) and 6 mo (WMD = 21.000, 95%CI [16.177, 25.823], P < 0.001) as shown in Figure 4A.

Constant score

We analyzed two studies[2,8] comparing the Constant scores upon using CT for RC tears against controls at varied time points. There was no significant heterogeneity observed between the included studies (I^2 < 50%, P = 0.181). Hence, a fixed-effects model was used for analysis. We stratified the analysis based on the duration of follow-up in the included studies and found that upon utilizing CT in the management of RC tears, we did not find any significant improvement in the Constant score compared to the controls (WMD = 0.833, 95%CI [-4.517, 6.182], P = 0.760). Both the studies included in the analysis compared the outcomes at 1 and 2 years (Figure 4B).

Radiological healing

We analyzed five studies[2,9-12] reporting the MRI-based healing of RC tears upon using CT for RC tears against controls at varied time points. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, a random-effects model was used for analysis. We stratified the analysis based on the duration of follow-up in the included studies and found that upon utilizing CT in the management of RC tears, we did not note an overall significant difference in the healing of RC tears based on repeat MRI compared to the controls (OR = 3.252, 95%CI [0.958, 11.037], P = 0.059). However, upon stratification of the studies based on the duration of their follow-up, it was noted that the MRI based healing of the RC tears was significantly better at long-term follow-up compared to the controls (OR = 8.125, 95%CI [2.868, 23.019], P < 0.001) as shown in Figure 4C.

Hence, utilization of CT produced significant improvement in functional outcomes in short term based on the ASES score. Although similar consistent significant long-term benefit in function scores such as Constant score was not found in long term, significant radiological improvement in the tendon

Table 2 Biological treatment protocol of the included studies (*n* = 6)

Ref.	MSC type	MSC source	Rotator cuff tear nature	Preparation method	Cellular dosage (10^6 cells)	Treatment group intervention	Control group intervention	Outcome measures
Hernigou *et al*[11]	BM-MSC	Auto	Full thickness	150 mL of bone marrow aspirate was serially centrifuged to result in 12 mL of BMAC	0.051	Arthroscopic rotator cuff repair followed by injection of BMAC of 4 mL in bone-tendon junction, and 8 mL in the bone at the site of the footprint	Arthroscopic rotator cuff repair only	USG and MRI guided tear size assessment
Kim *et al* [4]	AD-MSC	Auto	Full thickness	The raw lipoaspirates were processed to obtain SVF using enzymatic digestion method using 0.075% collagenase	4.46	Arthroscopic rotator cuff repair followed by injection of AD-MSCs in SVF loaded in 2 mL of fibrin glue scaffold into the tendon-bone approximation and over the repaired tendon	Arthroscopic rotator cuff repair only	VAS, Constant score, UCLA scores, MRI guided tear size assessment
Kim *et al* [8]	BM-MSC	Auto	Partial thickness	BMAC from BIOMET MarrowStim Mini kit and PRP from BIOMET GPS III kit	1	USG guided injection of 2 mL BMAC with 1 mL of PRP	Rotator cuff exercises taught by experienced physical therapist done daily on their own for 3 mo	VAS, MMT scores, ASES, USG guided tear size assessment
Lamas *et al*[2]	CE-BM-MSC	Auto	Full thickness	The BM-MSCs isolated from aspirates were expanded during a 2-wk period	20	Open rotator cuff repair with autologous bone marrow in combination with a type I collagen membrane (OrthADAPT)	Open rotator cuff repair with a type I collagen membrane (OrthADAPT™)	VAS, Constant score, MRI guided tear size assessment
Centeno *et al*[12]	BM-MSC	Auto	Both partial and full thickness	90 mL of bone marrow aspirate was serially centrifuged to a resultant 1-3 mL of buffy coat that is collected. In addition, 60mL of intravenous blood was drawn to isolate PRP and platelet lysate	810	USG guided injection of 1-2 mL of injectate with 60% by volume of BMAC, 20% of PRP, and 20% of platelet lysate	Stretches in all planes along with non-weighted exercises involving scapular stabilizing muscles, triceps, and the rotator cuff muscles for 3 mo	DASH score, SANE, MRI guided tear size assessment
Hurd *et al* [9]	AD-MSC	Auto	Partial thickness	Transpose RT/Matrase system	11.4	USG guided injection of 5 mL of AD-MSCs	Single injection of 80 mg of methylprednisolone in 2 mL plus 3 mL of 0.25% bupivacaine	Adverse events, ASES, SF-36 score, VAS, MRI guided tear size assessment

AD: Adipose derived; Auto: Autologous; ASES: American shoulder and elbow surgeons; BM: Bone marrow derived; BMAC: Bone marrow aspirate concentrate; CE: Culture expanded; DASH: Disability of the arm, shoulder and hand; MMT: Manual muscle test; PRP: Platelet rich plasma; MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cells; SANE: Single assessment numeric evaluation; SF-36 score: Short form 36 score; SVF: Stromal vascular fraction; UCLA: University of California, Los Angeles; USG: Ultrasonogram; VAS: Visual analog score.

healing was noted in long term.

Retear rate

We analyzed five studies[2,8-11] reporting retear of RC tendons following RC tear management using CT against controls at varied time points. We did not note a significant heterogeneity among the included studies ($I^2 < 50\%$, $P = 0.392$). Hence, a fixed-effects model was used for analysis. We stratified the analysis based on the duration of follow-up in the included studies and found that upon utilizing CT in the management of RC tears, we noted an overall significant reduction in the retear rate compared to the controls (OR = 0.371, 95%CI [0.183, 0.751], $P = 0.006$). Upon stratification of the studies based on the duration of their follow-up, it was noted that utilization of CT for RC tears resulted in a significant reduction of retear rate both at short- (OR = 0.079, 95%CI [0.008, 0.804], $P = 0.032$) and long-term (OR = 0.434, 95%CI [0.207, 0.910], $P = 0.027$) follow-ups compared to the controls as shown in Figure 5A.

Adverse events

Five studies[2,8-10,12] reported adverse effects with a low heterogeneity among the included studies

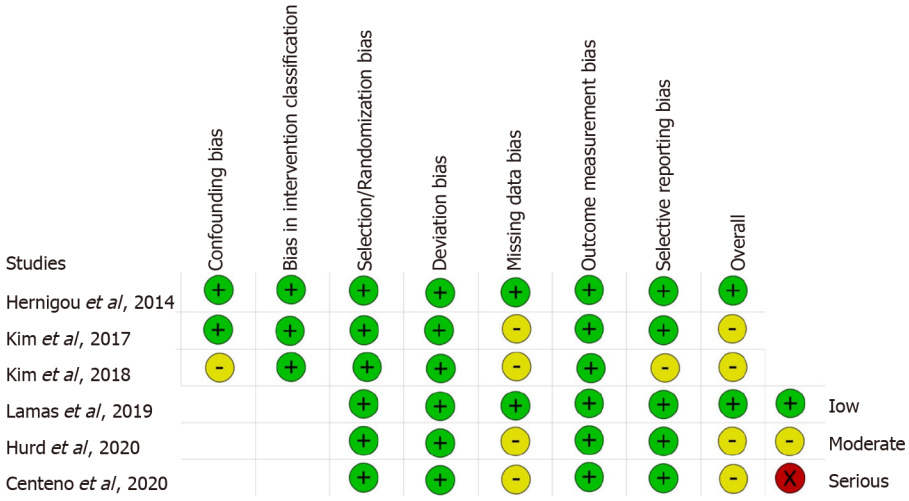

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Figure 2 Methodological quality and risk of bias assessment of all the included studies.

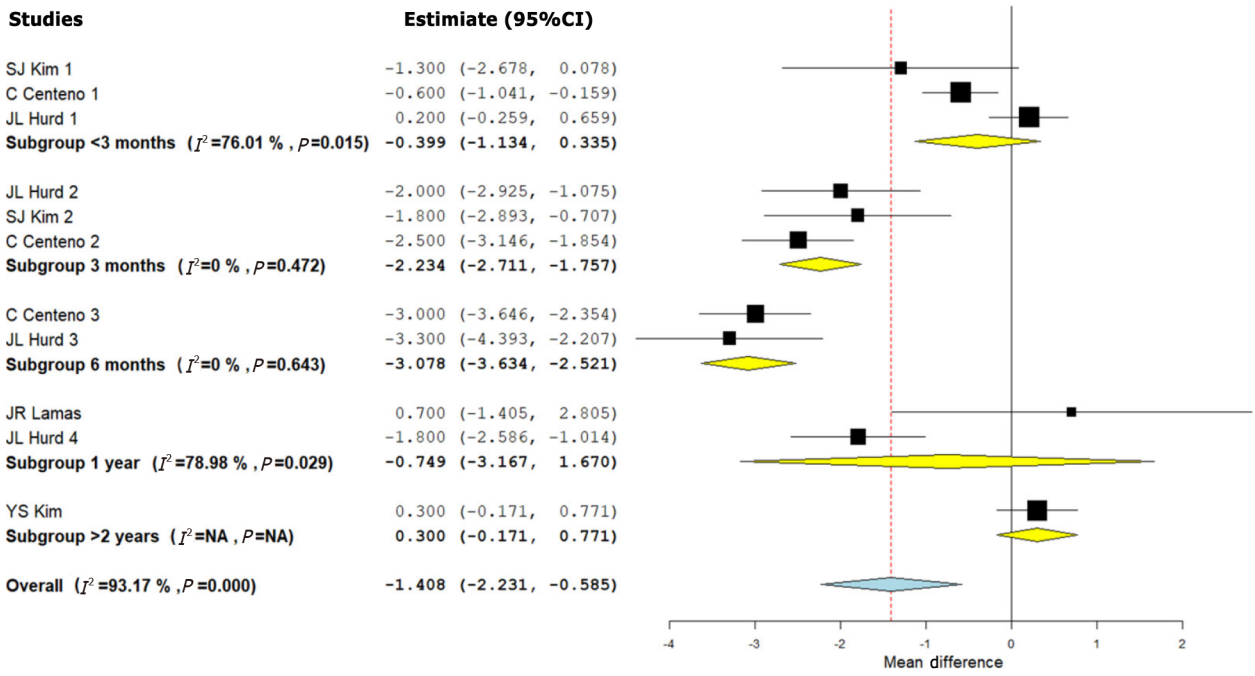

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Figure 3 Forest plot of the included studies analyzing the Visual Analog Scale score outcomes at varied time points compared to their controls.

upon utilization of CT in RC tear management (I^2 = 0.0%, P = 0.990). Hence, a fixed-effects model was used for analysis. On analysis, we did not find any significant increase in the adverse events compared to the controls (OR = 0.876, 95%CI [0.182, 4.212], P = 0.869) as shown in Figure 5B. No major serious adverse events with permanent effects such as death, tumor, or immune reaction to the intervention were noted during follow-up.

Sensitivity analysis

A sensitivity analysis was performed in each analysis. All the results (VAS score for pain, ASES score, Constant score, radiological healing, and complications such as retear rate and adverse events) maintained their consistency in significance even upon sequentially omitting each study in the meta-analysis. Similar consistency was noted upon reanalysis of the results by changing to a random-effects model. We performed subgroup analysis of outcomes with significant heterogeneity based on the duration of their follow-up and presented accordingly (Figures 3-5). We explored into the heterogeneity of the results based on the source, dosage of MSCs, and nature of RC tear (complete/partial) but we did

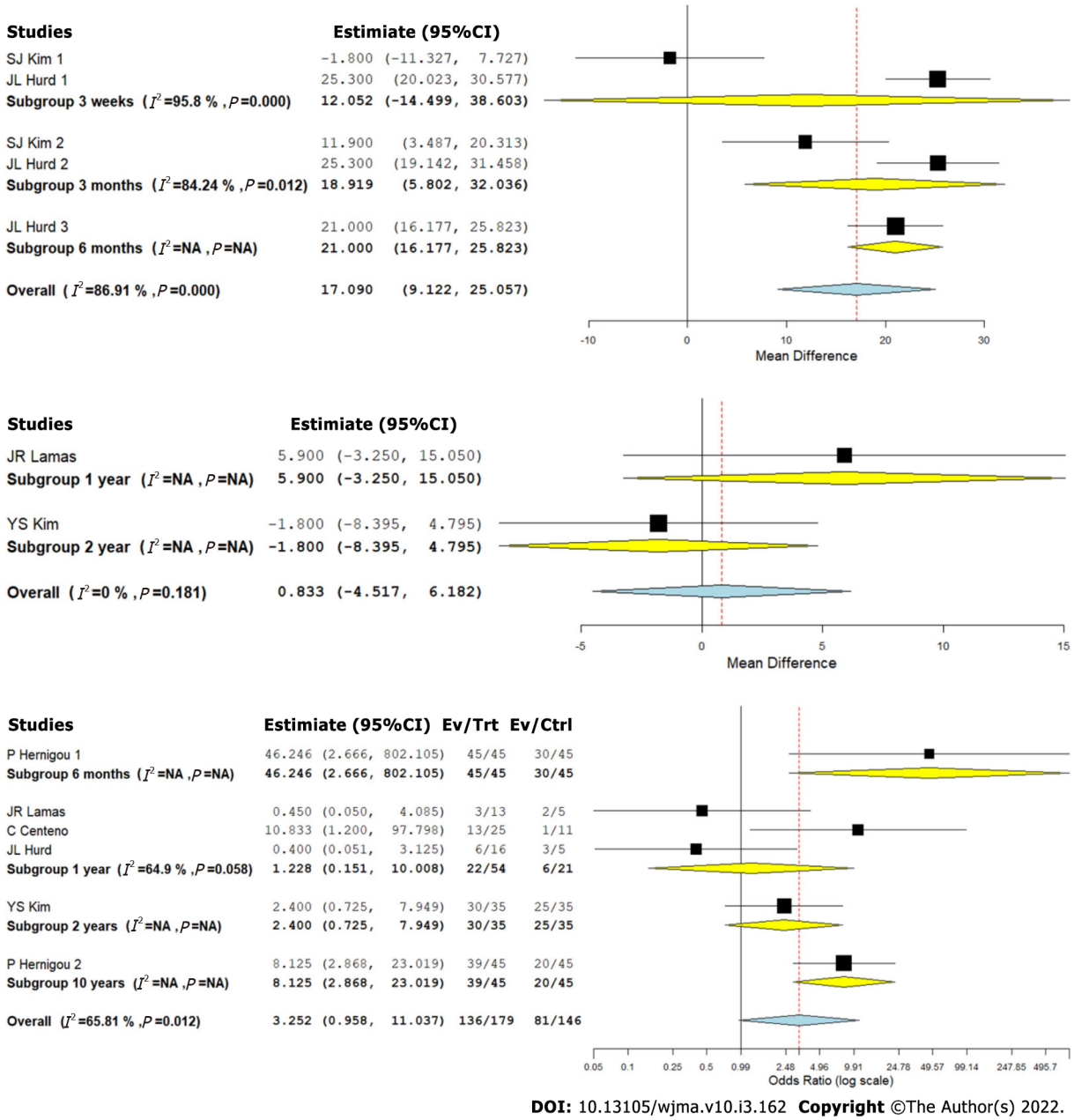

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Figure 4 Forest plot of the included studies analyzing the functional outcomes at varied time points compared to their controls. A: American Shoulder and Elbow Surgeons score; B: Constant score; C: Magnetic resonance imaging -based healing of rotator cuff tear.

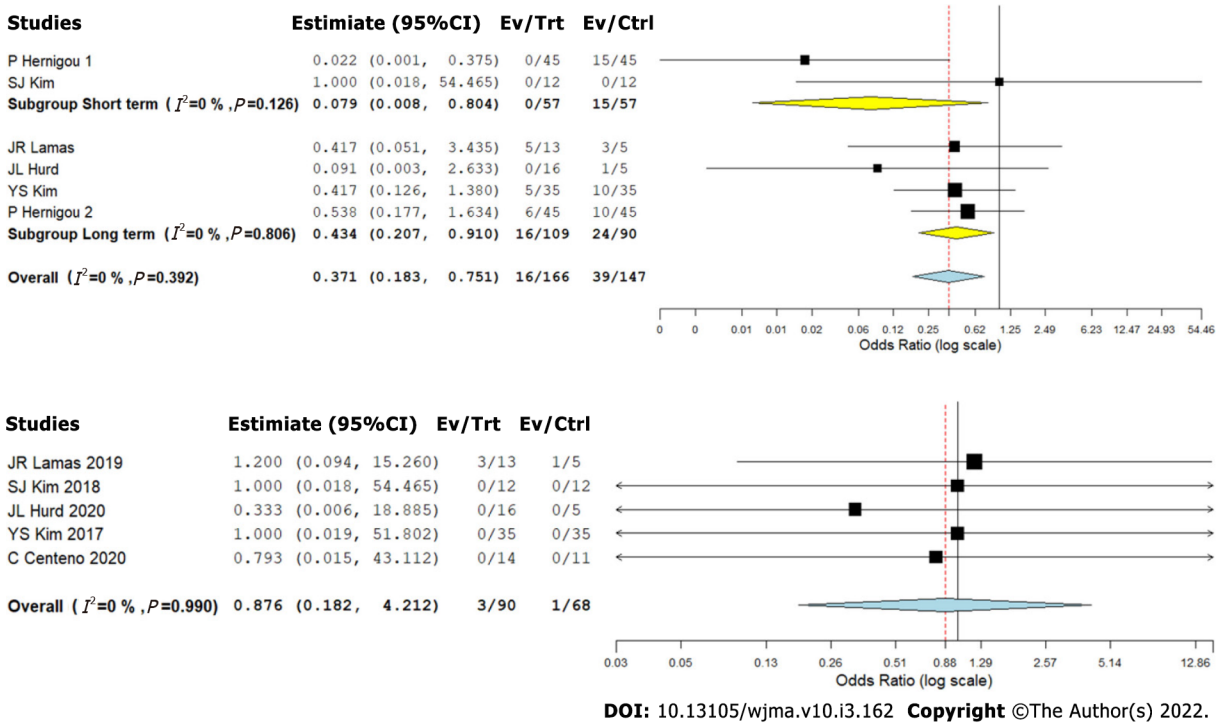
not find any significant change in the summary of results obtained as shown in Supplementary Materials.

Publications bias

We utilized the funnel plot, normal quantile plot, and Egger's regression test to analyze the publication bias in the reporting of studies on the subject analyzed. We did not find any significant publication bias by funnel plot and normal quantile plot as shown in Figure 6 or by Egger's regression test (P = 0.019). We noted that all the studies were close to the 95%CI without significant heterogeneity in their distribution about the axes, implying minimal publication bias.

DISCUSSION

The lifetime chance of sustaining an RC tear has been reported to range between 25% and 40%[20], and the rate continues to rise with increasing age. Given the global increase in the elderly population, it is estimated that RC pathologies will continue to place immense demands on the overall healthcare system worldwide[21]. Among the non-surgical options, although local corticosteroid infiltration is highly



DOI: 10.13105/wjma.v10.i3.162

Figure 5 Forest plot of the included studies analyzing the complications at varied time points compared to their controls. A: Retear rate; B: Adverse events.

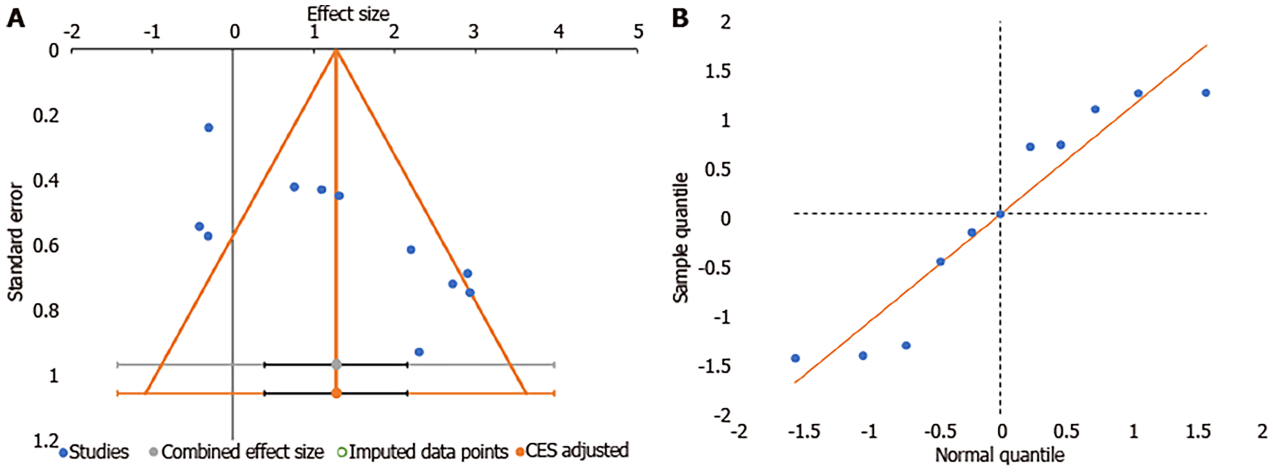


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Figure 6 Publication bias assessment with funnel plot and quantile plot for Visual Analog Scale score in the included studies.

popular, it has been associated with a high incidence of RC rupture resulting from an enhanced induction of non-tenocyte differentiation of human tendon stem cells[9]. With progressive advancements in arthroscopic procedures, surgical implantation for RC pathologies has increased tremendously over the past decade[21]. Consequently, the rate of retear has also worsened, with an overall reported incidence as high as 15% to 40%, irrespective of the surgical technique employed[22]. To overcome these aforementioned reasons, research efforts in the recent past have focused on enhancing the outcomes following management of RC tears, through advancements in surgical indications and decision making, novel surgical and non-surgical interventions, as well as improvements in rehabilitative strategies[2,8-12]. Over the past decade, one promising augmentative approach is the incorporation of biological agents into surgical and non-surgical strategies. In this context, the potential role of MSCs as biological adjuncts in RC injuries has been increasingly acknowledged[2,8-12].

Following an injury to a tendon, various physiological healing cascades are initiated. The earliest response is acute inflammation, which includes the recruitment of cells like leukocytes and thrombocytes to the site of injury[23]. These inflammatory cells further recruit various growth factors

like transforming growth factor-beta (TGF-beta), platelet-derived growth, insulin-like growth factor, and fibroblast growth factor[24]. During the next proliferative stage of healing, these recruited cells stimulate the production of type-3 collagen and temporary extracellular matrix[24]. Finally, the remodeling phase occurs at around 1 to 2 mo following the injury where the type-3 collage gradually gets replaced by type-1 collagen. Biological augmentation techniques utilize these body's natural healing processes especially during the inflammatory and proliferative phases to facilitate the enhancement of tendon healing. PRP is a component of blood with a high concentration of platelets, which releases growth factors essential for tissue healing[25]. Hypocellularity is postulated as a major reason underlying the relatively unsatisfactory outcome following PRP injection[9]. In other words, there is a mismatch between the growth factors released by PRP and the insufficient number of stem cells at the site of RC tear[9,22]. Recent reports, therefore, seem to suggest that biological augmentative therapy involving MSCs circumvents this problem and offers greater benefits, as compared to PRP-alone administration[9].

In the current meta-analysis, we included six CCSs (3 RCTs – 238 patients), which discussed the influence of MSCs in RC tears[2,8-12]. While the effect of adjuvant MSCs was compared to the surgically-treated control RC injury population in 3 studies[2,10,11], non-surgically managed control population was included in the remaining trials[8,9,12].

Among the 3 studies involving conservatively-managed RC tear patients, Hurd *et al*[9] discussed the role of MSCs in partial injuries. Partial RC tendon ruptures are broadly classified based on location (articular, bursal, and interstitial), depth (grade 1 < 3 mm, grade 2 3-6 mm, grade 3 ≥ 6 mm), and tear area[9]. It has been reported that articular-sided RC tears are more common and have relatively lower healing rates, given the poorer vascularity[9,12,24]. Hurd *et al*[9] demonstrated that injection of adipose-derived into pathological RC tissues resulted in a reduced recruitment of inflammatory cells, enhanced tendon regeneration with mitigated scarring, improved collagen fiber arrangement, greater load-to-failure, and enhanced tensile strength of the injured tendons. They recommended that stem cell delivery can be a promising non-surgical option in these types of partial injuries with a relatively poor prognosis for healing.

Influence of MSC therapy on pain severity and functional outcome scores

The two main clinical parameters assessed in the reviewed studies were pain severity by VAS score[2,8-10,12] and functional outcome measures by ASES[8,9] and Constant scores[2,8]. We could observe significant heterogeneity in the reporting of both these parameters.

Based on our analysis, we could observe a significant improvement in the VAS score for pain at 3 and 6 mo in all patients who underwent CT. However, beyond this initial period, MSC therapy did not result in any significant difference compared to the control group. This observation was consistently reported by all the included studies[2,8-10,12]. A probable explanation for the observed effect could be due to the augmented healing in the treated group of patients demonstrating superior pain control during the early post-operative period.

The reviewed studies used ASES and Constant scores to report the functional outcome during follow-up. In the two studies[8,9] which reported the ASES scores, the outcome was significantly better at 3 and 6 mo following CT. However, the studies did not reveal any significant difference in ASES scores, before and after this time point (*i.e.*, at 3 wk, 1 year, and 2 years). Both the studies that evaluated the Constant score compared the outcome at 1 and 2 years[2,8]. The above findings were in concordance with the results of the pain scores in the included studies showing early augmented healing and functional benefit in the intervention group compared to the controls.

Influence of MSC therapy on radiological healing

The radiological healing was assessed in 5 studies[2,9-12] based on MRI. In contrast to our findings regarding the pain score and functional outcome, there was a statistically significant improvement in the radiological healing of the lesions at long-term follow-up (1 and 2 years). It has been well-acknowledged that the use of appropriate scaffolds is necessary to preserve the optimal survival, as well as reparative and differentiation capacities of MSCs[25]. BMAC-PRP complexes have previously been shown to enhance healing in diabetic ulcers, osteochondral deficiencies, and spinal injuries. Additionally, studies have also reported a synergistic effect of BMAC-PRP complexes in the healing of tendon injuries[8,25]. Two of the studies included in our analysis also utilized PRP in addition to BM-MSCs[8,12].

Thus, our review suggests that the use of BMAC-PRP complexes in RC tears can be a potentially rewarding treatment option. Kim *et al*[8] reported that the proliferation of tenocytes and tendon stem cells, followed by synthesis of collagen type 3 by tenocytes at 6 wk post-injury, was enhanced by BMAC-PRP complexes. Therefore, in their study, they indicated that biological augmentation with these complexes may potentially result in more anatomical healing of the tears. In the study by Hernigou *et al*[11], augmentation with MSCs significantly improved the healing, quality, and the structural integrity of arthroscopically-repaired RC tears, as assessed by ultrasound and MRI performed at 6 mo and 10-year follow-up time points.

Influence of MSC therapy on retear rates

Based on the evidence from five studies[2,8-11], we could observe that the use of CT resulted in a significant reduction in the retear rates, at both the short-term as well as long-term follow-up. This corroborated our finding that CT resulted in better radiological healing of the lesions. The studies by Hernigou *et al*[11] and Kim *et al*[10], which included a total of 80 patients treated with MSCs in addition to arthroscopic RC repair, revealed a statistically significant improvement in the rate of tendon healing, structural integrity of healed tendon, and mitigated number of retears at both short-term and long-term follow-up. In the study by Hernigou *et al*[11], 87% of patients in the MSC group had intact tendon integrity at 10-year follow-up, as against 44% in the control population.

Safety of MSC therapy

In one of the included studies[2], high failure rates secondary to detrimental inflammatory processes activated by a xenograft scaffold were reported similarly in both MSC and control groups. Apart from this issue that was unrelated to MSCs, none of the reviewed studies reported any significant adverse events directly related to the use of CT in patients with RC tears.

Limitations

Our analysis had some limitations. We could not find blinding to be established in most of the studies included in the analysis which might invite room for bias from patients or observers with regard to the treatment given. We also noted heterogeneity across many reported outcomes in the included studies, which might be due to the variability in the follow-up time and the treatment protocols followed in the individual studies as shown in Table 2. However, we tried to address the impact of follow-up period through our stratified analysis of results at different time points to arrive at a meaningful conclusion. Moreover, patients in various stages of the disease process were included in the studies, which could have also contributed to the heterogeneity of their results.

CONCLUSION

Based on our comprehensive and critical review of the available literature analyzing the efficacy and safety of CT utilizing MSCs in the management of RC tears, we could observe that the utilization of CT significantly reduced pain severity at 3 and 6 mo, improved short-term functional outcome, enhanced radiological tendon healing, and mitigated retear rates at short- and long-term follow-up. The literature did not reveal any major adverse events directly related to MSC therapy in patients presenting with RC tears.

We recommend a large-scale, multicentric trial analyzing autologous and allogeneic sources of MSCs with standardized dosage and intervention protocol, evaluated with established outcome measures both at short- and long-term follow-up to further confirm the results of our analysis.

ARTICLE HIGHLIGHTS

Research background

Rotator cuff (RC) tear is a common shoulder pathology, whose prevalence ranges from 4% in asymptomatic individuals younger than 40 years to 54% in patients aged over 60 years. The etiology of these tears is multifactorial, and has been variously attributed to traumatic, mechanical, and inflammatory processes. It has been well-demonstrated that the natural course of non-operatively managed RC tears in the majority of patients is a progressive deterioration of the anatomical tear without spontaneous regression of symptoms. On the other hand, although surgical repair of a torn RC potentially aids in restoring the shoulder function as well as arresting the tear progression, the failure rates range between 0 and 78%, thereby giving room for improvement.

Research motivation

Recently, mesenchymal stromal cells (MSCs) have been successfully employed in diverse animal and human models in the repair of various musculoskeletal structures like cartilages, bones, muscles, and tendons. These cells (usually extracted from bone marrow or adipose tissue) possess a unique attribute described as "multipotency", which denotes their ability to differentiate into other tissues of mesenchymal origin. When delivered using appropriate scaffolds, these modalities of cellular therapy (CT) have shown great promise in enhancing the outcome following RC tears, too. MSCs are thought to promote type I collagen production, enhance mechanical strength of tissues, and ameliorate biology at the bone-tendon interface, which primarily explains their potential clinical utility in RC tears. The concentrates of these cells may be delivered into the region of tendon injury, either *via* image-guided injections or through arthroscopic approach (intra-operatively). However, the major barriers to regular

use of MSCs include lack of standardized techniques for preparation, inadequate clinical evidence, and potentially high cost:benefit ratios.

Research objectives

To analyze the efficacy and safety of CT utilizing MSCs in the management of RC tears from clinical studies available in the literature.

Research methods

We conducted independent and duplicate electronic database searches including PubMed, Embase, Web of Science, and Cochrane Library on August 2021 for studies analyzing the efficacy and safety of CT utilizing MSCs in the management of RC tears. Visual Analog Score (VAS) score for pain, American Shoulder and Elbow Surgeons (ASES) score, Disability of the Arm, Shoulder and Hand score, Constant score, radiological assessment of healing, and complications such as retear rate and adverse events were the outcomes analyzed. Analysis was performed in R-platform using OpenMeta [Analyst] software.

Research results

Six studies involving 238 patients were included for analysis. We noted a significant reduction in VAS score for pain at 3 mo (WMD = -2.234, $P < 0.001$) and 6 mo (WMD = -3.078, $P < 0.001$) with the use of CT, which was not maintained at long-term follow-up (WMD = -0.749, $P = 0.544$). Concerning functional outcomes, utilization of CT produced a significant short-term improvement in the ASES score (WMD = 17.090, $P < 0.001$) and significant benefit in functional scores such as Constant score (WMD = 0.833, $P = 0.760$) at long-term follow-up. Moreover, we also observed a significantly improved radiological tendon healing during the long-term follow-up (OR = 3.252, $P = 0.059$). We also noted a significant reduction in the retear rate upon utilization of CT in RC tears both at short- (OR = 0.079, $P = 0.032$) and long-term (OR = 0.434, $P = 0.027$) follow-up. We did not observe any significant increase in the adverse events directly related to CT, as compared with the control group (OR = 0.876, $P = 0.869$).

Research conclusions

Based on our comprehensive and critical review of the available literature analyzing the efficacy and safety of CT utilizing MSCs in the management of RC tears, we could observe that the utilization of CT significantly reduced pain severity at 3 and 6 mo, improved short-term functional outcome, enhanced radiological tendon healing, and mitigated retear rates at short- and long-term follow-up. The literature did not reveal any major adverse events directly related to MSC therapy in patients presenting with RC tears.

Research perspectives

We recommend a large-scale, multicentric trial analyzing autologous and allogeneic sources of MSCs with standardized dosage and intervention protocol, evaluated with established outcome measures both at short- and long-term follow-up to further confirm the results of our analysis.

FOOTNOTES

Author contributions: Muthu S conducted the research along with Viswanathan VK; Jeyaraman N, Patel K, Chellamuthu G, Jeyaraman M, and Khanna M helped in the conduction of the study; all authors have read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have a conflict of interest over the subject presented.

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META-ANALYSIS

Clinical outcomes of the omicron variant compared with previous SARS-CoV-2 variants; meta-analysis of current reports

Mohsen Karbalaei, Masoud Keikha

Specialty type: Infectious diseases

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Grade B (Very good): B
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Grade D (Fair): 0
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Abstract

BACKGROUND

Omicron (B.1.1.529) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern; however, there is no comprehensive analysis regarding clinical features, disease severity, or clinical outcomes of this variant.

AIM

To compare the clinical characteristics of infection with omicron and previous variants of SARS-CoV-2.

METHODS

We searched major international databases consisting ISI Web of Science, PubMed, Scopus, MedRxiv, and *Reference Citation Analysis* to collect the potential relevant documents. Finally, clinical features, *e.g.*, death rate, intensive care unit (ICU) admission, length of hospitalization, and mechanical ventilation, of infection with SARS-CoV-2 omicron variant compared with previous variants were assessed using odds ratio and 95% confidence intervals by Comprehensive Meta-Analysis software version 2.2.

RESULTS

A total of 12 articles met our criteria. These investigated the clinical outcomes of infection with omicron variant compared with other variants such as alpha, beta and delta. Our results suggested that ICU admission, need for mechanical ventilation, and death rate were significantly lower for omicron than previous variants. In addition, the average length of hospitalization during the omicron wave was significantly shorter than for other variants.

CONCLUSION

The infectivity of omicron variant was higher than for previous variants due to

several mutations, particularly in the spike protein. However, disease severity was mild to moderate compared previous variants.

Key Words: SARS-CoV-2; COVID-19; Omicron; Infectious disease

Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron (B.1.1.529) is a variant of concern that was first identified on 24 November 2021 as a new global threat. However, due to the lack of comprehensive statistical analysis, clinical characteristics and disease outcomes of infection with omicron variant have remained unknown. Hence, the comparison of clinical profile between cases infected with this new variant and previous variants will lead to the establishment of a strategy regarding appropriate management and global control of this variant.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic that first emerged from Wuhan, China in December 2019. According to the World Health Organization (WHO), so far > 378 million cases, as well as 5.67 million deaths have occurred due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[1]. On 24 November 2021, the Network for Genomics Surveillance in South Africa (NGS-SA) reported a new variant of this virus from Gauteng Province, named omicron (B.1.1.529); the new variant was confirmed by WHO on 25 November 2021[2,3].

The omicron variant rapidly replaced the previous variants in South Africa and spread to other countries, so it quickly became a dominant variant. In the USA, approximately 95% of all new cases of COVID-19 were diagnosed as being caused by the omicron variant by January 2022[4,5].

The genome of this variant contains 26–32 mutations in the spike gene as well as 45–52 amino acid substitutions. these mutations are associated with increases in viral characteristics such as transmissibility, immune escape, and S gene target failure (SGTF). SGTF is due to the 69 to 70 deletion in the S gene of B.1.1.7[6-8]. Early studies have shown the inefficacy of current vaccines (vaccination schemes and booster doses) and the higher rate of re-infection with the omicron variant[9,10]. Based on animal model findings, the severity of symptoms as well as the viral load of the omicron variant were lower compared to the previously reported variants of SARS-CoV-2[11,12]. Clinical reports from Scotland, England, Canada, and the USA have also confirmed animal experiments[13-16]. However, the fourth global wave of COVID-19 caused by the omicron variant was not associated with increased hospitalization or death in comparison with previous SARS-CoV-2 variants[17].

Understanding the clinical characteristics, susceptibility factors, and immune response against the new SARS-CoV-2 variants could be useful strategies in managing these viruses and development of novel treatment options. In this study, we evaluated the clinical severity of SARS-CoV-2 omicron variant compared with previous variants.

MATERIALS AND METHODS

We searched global databases such as ISI Web of Science, PubMed, Scopus, MedRxiv, and Reference Citation Analysis (https://www.referencecitationanalysis.com/) using MeSH keywords such as "Omicron", "COVID-19", "SARS-CoV-2", "Disease severity", "Variant of concern", "ICU", "Intensive care unit", and "fourth wave". We retrieved all potential studies related to the clinical severity of SARS-CoV-2 omicron variant regardless of language and publication date. All eligible documents were carefully screened; required data including mean age, immunization status, mortality rate, intensive care unit (ICU) admission, length of hospitalization, and mechanical ventilation are summarized in Table 1. We also reviewed the bibliography of documents to avoid missing relevant articles. Finally, the severity of COVID-19 caused by omicron compared with previous SARS-CoV-2 variants was evaluated using odds ratio (OR) and 95% confidence interval (CI). We used a random-effect size due to the presence of significant heterogeneity (I^2 index and Cochrane *P* value test). Data were pooled using

Table 1 Characteristics of included studies

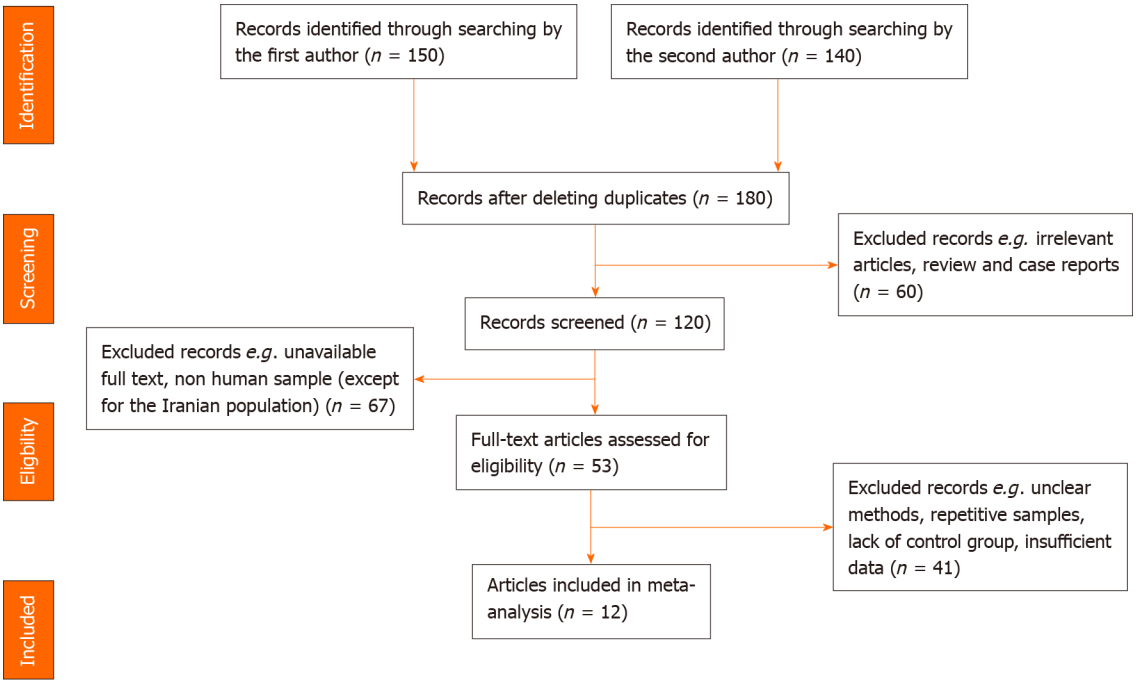
First author	Country	Mean age		Immunization		Death rate		ICU admission		Length of stay		Ventilation		Number of cases		Ref.
		Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	
Abdullah	South Africa	39	49.8	NA	NA	4.5%	21.3%	1%	4.3%	4	8.8	NA	NA	466	3962	[18]
Cloete	South Africa	4.2	NA	NA	NA	4	NA	7	NA	3.2	NA	7	NA	6287	NA	[19]
Christensen	USA	44.3	50.0	2497	101	38	170	NA	NA	3.2	5.1	49	144	4468	3149	[20]
Davies	South Africa	NA	NA	HR:0.41, 95%CI: 0.29-0.59		HR: 0.27, 95%CI: 0.19-0.38		NA	NA	NA	NA	NA	NA	5144	11609	[21]
Goga	South Africa	33	55	NA	NA	NA	NA	3%	16%	3	6	0.2%	8%	17650	22888	[22]
Lewnard	USA	NA	NA	6,981	784	1	12	4	20	5.5	15.8	0	11	52297	16982	[23]
Iuliano	USA	NA	NA	NA	NA	1854	1924	24776	24774	3	5	358	503	48238	25873	[24]
Maslo	South Africa	36	53	235	NA	27	520	180	1104	3	8	16	431	971	2628	[25]
Santos	Portugal	37.1	43.4	295	201	0	26	0	17	3.7	8.6	NA	NA	6581	9397	[26]
Torjesen	UK	NA	NA	NA	NA	NA	NA	9.9%	14%	1.7	6.6	2%	5.8%	NA	NA	[27]
Wang	USA	36.4	36.1	2.4%	3.1%	23	30	0.26%	0.78%	NA	NA	0.07%	0.43%	14054	563884	[28]
Wang	USA	1.49	1.73	NA	NA	NA	NA	0.14%	0.43%	NA	NA	0.33%	1.15%	7201	63203	[29]

ICU: Intensive care unit; NA: Not available; HR: Hazard ratio; CI: Confidence interval.

Comprehensive Meta-Analysis software version 2.2 (Biostat, Englewood, NJ, USA).

RESULTS

A total of 12 studies investigated the clinical outcomes of infection with SARS-CoV-2 omicron variant compared with other variants such as alpha, beta and delta (Figure 1). Eligible studies were performed in South Africa, USA, Portugal and UK from 2021 to 2022[18-29]. We pooled the data of 887 132 cases with positive PCR test for SARS-CoV-2, including 163 457 cases positive for omicron variant, as well as 723 675 cases positive for other variants.



DOI: 10.13105/wjma.v10.i3.177

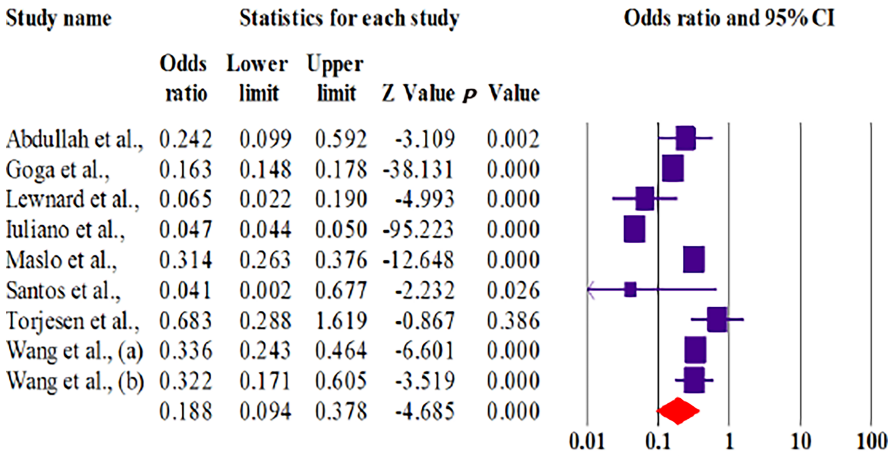
Figure 1 Flowchart of literature search and study selection process.

The mean age of patients infected with omicron variant was 28.93 ± 15 years. The frequency of events such as ICU admission, need for mechanical ventilation, and death rate for omicron variant was 0.8% (95% CI: 0.2%–3.7%; I^2: 99.89; P = 0.01; Egger's P = 0.01; Begg's P = 0.29), 0.2% (95% CI: 0.1%–0.5%; I^2: 95.75; P = 0.01; Egger's P = 0.16; Begg's P = 0.26), and 0.4% (95% CI: 0.1%–1.0%; I^2: 98.47; P = 0.01; Egger's P = 0.01; Begg's P = 0.45), respectively. The average length of hospitalization for omicron was significantly less than for other variants (3.36 ± 1 d *vs*. 7.98 ± 3 d; P < 0.05). The incidence of omicron infection among fully vaccinated individuals was 12.9% (95% CI: 5%–27%; I^2: 99.89; P = 0.01; Egger's P = 0.22; Begg's P = 0.40). the current findings revealed that the severity of infections caused by omicron was less than for previous infections caused by alpha, beta, and delta variants. The current findings are consistent with similar reports[30,31]. In comparing the fourth wave of COVID-19 caused by the omicron variant with previous waves, it should be said that the mean age for patients infected with omicron was ~13 years (28.93 ± 15 years), which was less than that for other variants (41.29 ± 17 years). There was a significant reduction in ICU admission (OR: 0.18; 95% CI: 0.094–0.37; P = 0.01; I^2: 99.05; P = 0.01; Egger's P = 0.2; Begg's P value: 0.07) (Figure 2). Our results suggested a significant reduction in the need for mechanical ventilation (OR: 0.135; 95% CI: 0.05–0.31; P = 0.01; I^2: 97.24; P = 0.01; Egger's P = 0.12; Begg's P = 0.26) among omicron cases (Figure 3). The mortality rate also declined among patients infected with omicron variant (OR: 0.17; 95% CI: 0.06–0.46; P = 0.01; I^2: 98.32; P = 0.01; Egger's P = 0.44; Begg's P = 0.71) compared with previous variants (Figure 4).

DISCUSSION

We found that the severity of COVID-19 caused by the SARS-CoV-2 omicron variant was significantly less than for previous variants; however, there was significant heterogeneity that could be due to differences in several factors such as study design, geographical region, time for assessment of clinical outcomes, and diverse conditions of included cases; publication bias was also significant. Recently, Zhao *et al*[32], showed that the omicron variant is less dependent on the TMPRSS2-mediated entry pathway, which leads to less-efficient replication and decreased viral load within the lungs. In addition, the omicron variant is more susceptible to interferons than other variants are, especially the delta variant [33]. Similar evidence could be a reasonable explanation for the lower severity of COVID-19 with the omicron variant, as confirmed by numerous observational studies[15].

The omicron variant nucleotide sequence has several mutations, especially 32 single substitutions in the spike protein that cause resistance to neutralizing antibodies, as well as inefficiency of current vaccines[34-36]. We revealed that omicron variant causes less severity of COVID-19 than previous variants; however, heterogeneity and publication bias were significant in our estimations (Figure 5). Further studies need to confirm the present findings.



DOI: 10.13105/wjma.v10.i3.177

Figure 2 Forest plot of the meta-analysis on intensive care unit admission for patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

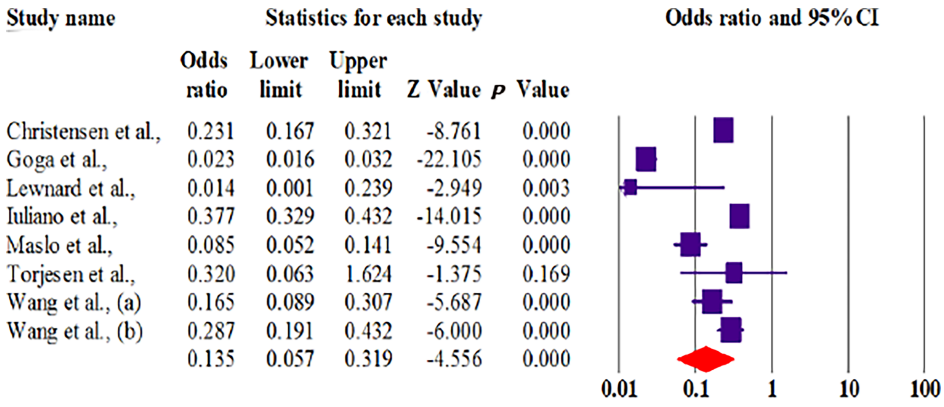


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Figure 3 Forest plot of the meta-analysis for need for mechanical ventilation in patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

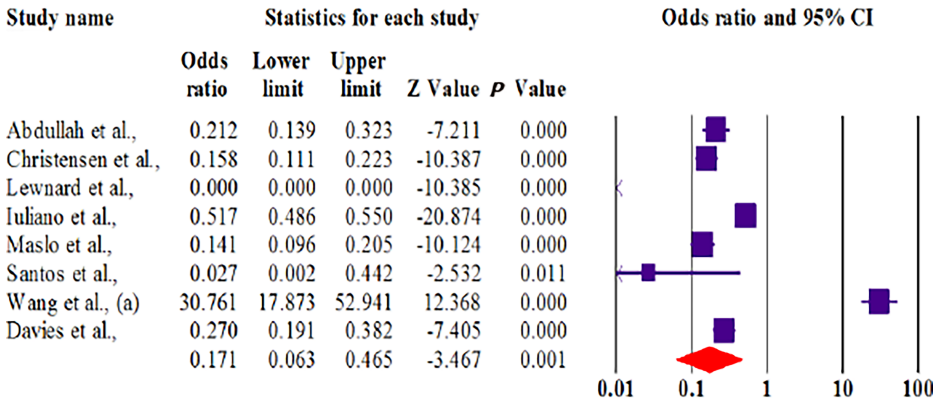

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Figure 4 Forest plot of meta-analysis of risk of mortality in patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

CONCLUSION

A new global increase in COVID-19 has been accompanied by the emergence of the SARS-CoV-2 omicron variant that is associated with less disease severity, as well as fewer ICU admissions, shorter

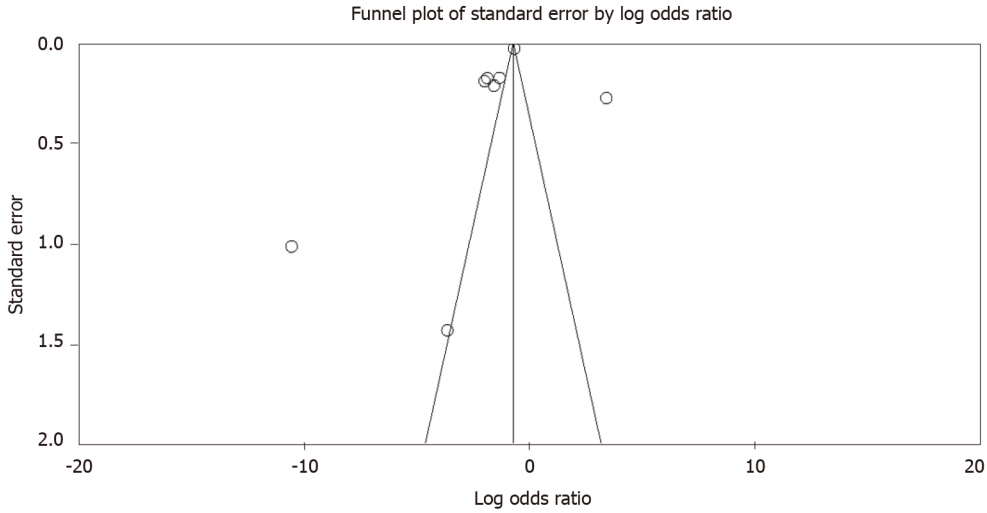

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Figure 5 Funnel plot of meta-analysis of disease severity of patients intfected with severe acute respiratory syndrome coronavirus 2 omicron variant compared with previous variants.

hospitalization, and lower mortality rate. Nonetheless, there is limited information about the effect of omicron on children, pregnant women, and immunodeficient individuals. Overall, omicron has been considered as the most contagious SARS-CoV-2 variant that affects children and young adults more than other groups. Continuation of the current situation can have deadly consequences for these age groups.

ARTICLE HIGHLIGHTS

Research background

Omicron (B.1.1.529) is a new variant of concern of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, there is no comprehensive analysis regarding clinical features, disease severity, and clinical outcomes of infection with this variant.

Research motivation

There is insufficient evidence regarding clinical characteristics, standard therapeutic regimen, and efficacy of currently available vaccines against the omicron variant.

Research objectives

This study was a comprehensive review and statistical analysis to compare the clinical characteristics of infection with the omicron and previous variants.

Research methods

We searched major international databases consisting ISI Web of Science, PubMed, Scopus, and MedRxiv to collect the potential relevant documents. Finally, clinical features, *e.g.*, death rate, intensive care unit (ICU) admission, length of hospitalization, and need for mechanical ventilation of patients infected with omicron variant compared with previous variants, were assessed.

Research results

Twelve articles met our criteria. These studies investigated the clinical outcomes of infection with SARS-CoV-2 omicron variant compared with other variants such as alpha, beta and delta. Our results suggested that ICU admission, need for mechanical ventilation, and death rate were significantly lower for omicron than previous variants. In addition, the average length of hospitalization during the omicron wave was significantly shorter than for other variants.

Research conclusions

The infectivity of the omicron variant was much higher than for previous variants due to the presence of several mutations, particularly in the spike protein. However, disease severity was mild to moderate disease compared with previous variants.

Research perspectives

We revealed that the disease severity of infection with omicron was lower than for previous variants. However, this variant was more contagious. Nevertheless, further investigation with larger samples is needed to confirm the present findings.

FOOTNOTES

Author contributions: Keikha M contribute in design of study, study conceptual, literature search, writhing the draft; Karbalaei M revision the draft and manuscript editing; all authors agree with publish in this journal.

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META-ANALYSIS

Difference in incidence of developing hepatocellular carcinoma between hepatitis B virus-and hepatitis C virus-infected patients

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Abstract

BACKGROUND

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. The reason why this difference in the incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We report the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

AIM

To investigate this, we surveyed the hazard ratio of inflammation for HCC development which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

METHODS
The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC identifying 8924 HBV-and 7376 HCV- infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV- infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

RESULTS
In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77] and that in the 8 studies of HCV-infected patients was 5.51 [3.08-9.83]. The HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. HR in HCV-infected patients was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

CONCLUSION
The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT between HBV and HCV infections.

Key Words: Hazard ratio of alanine aminotransferase; Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Elevated alanine aminotransferase

Core Tip: It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers. In HBV infection, alanine aminotransferase (ALT) is the second highest risk factor, and in HCV infection, ALT is the highest risk factor, for HCC development. The hazard ratio (HR) for developing HCC in the inflammatory state (serum ALT levels exceeded the normal range) was compared between HBV and HCV patients. In the 14 studies of HBV patients, the average HR was 2.74 as compared with 5.51 in the 8 studies of HCV patients (P = 0.0391). The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT for HCC development between HBV and HCV infections.

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INTRODUCTION

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers[1].

However, the reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We have been considering this for many years, and finally arrived at the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

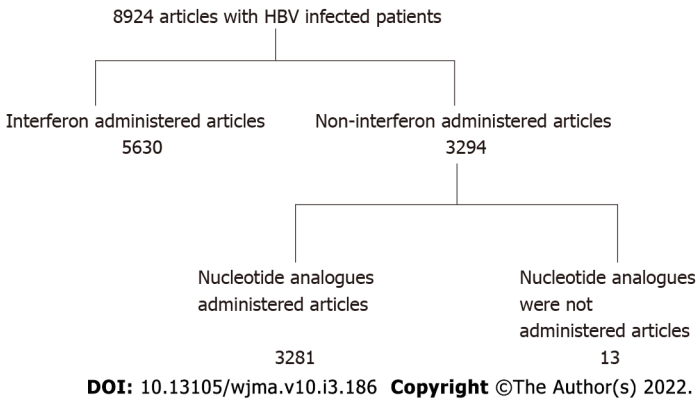

Figure 1 Flow diagram of articles with hepatitis B virus infected patients. HBV: Hepatitis B virus.

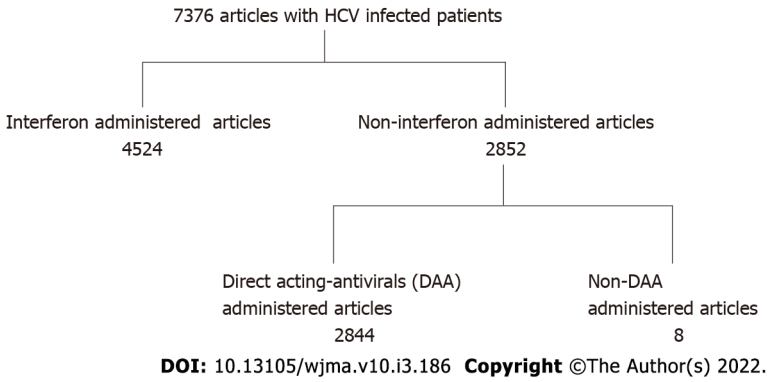

Figure 2 Flow diagram of articles with hepatitis C virus infected patients. HCV: Hepatitis C virus; DAA: Direct acting antivirals.

To investigate this, we surveyed the hazard ratio (HR) of inflammation which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

Why ALT, not AST was adopted in this study was as follows: We previously demonstrated[2] the strong association between sustained high serum ALT levels (≥ 80 international units (INU) annual average) and the development of HCC in patients with HCV-LC (Child Stage A) by long-term observation lasting about 7 years, (Cancer 1999; 86: 589-595). In this series of the study, we also investigated the association between sustained high serum AST levels (≥ 80 INU) and development, but the association was not so strong as ALT. Moreover, many studies have demonstrated a close association between severe inflammation as estimated by higher serum ALT level and initiation of HCC development (Veldt *et al*[3]; Miyakawa *et al*[4]).

MATERIALS AND METHODS

Search strategy

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC in HBV or HCV infected patients. There were 8924 studies involving HBV patients, and 7376 studies of HCV patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those who were administered nucleos(t)ide analogues were excluded, and HCV patients administered direct acting antivirals were also excluded. We also excluded articles which include co-existing liver disease such as alcoholic liver diseases and/or fatty liver diseases. Then, studies which dealt with the HR of HCC regarding inflammation (serum elevated ALT levels) were selected. Finally, there were 13 studies of HBV-infected patients[5-17], and 8 studies of HCV-infected patients[13,18-24] (Figures 1 and 2). In these selected papers, the HR of patients in a non-inflammatory state (serum ALT levels within normal range) was set as 1. We then calculated the HR in patients in an inflammatory state (serum ALT levels were above normal range).

Furthermore, for the purpose of comparing elevated ALT levels between hepatitis B and C patients, we examined the actual ALT levels cited in patients with chronic hepatitis B and hepatitis C included in this series (Tables 1 and 2) .

Table 1 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis B

Ref.	Actual elevated ALT levels
Kim *et al*[5]	Above normal levels
Du *et al*[6]	Above normal levels
Choi *et al*[7]	Above normal levels
Wen *et al*[8]	≥ 25 IU/L
Hann *et al*[11]	Elevated
Chen *et al*[12]	≥ 45 IU/L
Kumada *et al*[13]	Absence of persistently normal ALT levels
Chen *et al*[14]	Above normal levels
Ishiguro *et al*[15]	≥ 30 IU/L
Ando *et al*[16]	≥ 23 IU/L
Yamada *et al*[17]	≥ 40 IU/L

ALT: Alanine aminotransferase.

Table 2 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis C

Ref.	Actual elevated ALT levels
Ishiguro *et al*[15]	≥ 30 IU/L
Chen *et al*[18]	≥ 45 IU/L
Sun *et al*[19]	Elevated
Tanaka *et al*[20]	Elevated
Kumada *et al*[21]	> 20 IU/L
Ito *et al*[22]	> 35 IU/L
Suruki *et al*[23]	> 35 IU/L
Lee *et al*[24]	Always ≥ 45 IU/L

ALT: Alanine aminotransferase.

Statistical analysis

To compare HR of ALT for HCC between HBV and HCV patients, we calculated the weighted mean of HR for each type using the random effect model (Ref.: Dersimonian R, Laird N. Meta-analysis in Clinical trials. Controlled Clinic Trials 1986; 7: 177-188). To assess whether the mean HR among HBV patients was lower than that among HCV patients, we calculated the *P* value using a *Z* test. All reported p- values correspond to two-sided tests, and those $P < 0.05$ were considered significant. All analyses were performed using R (version 4.1.2) and R Studio (version 1.4) software.

RESULTS

In the 14 studies of HBV patients[5-17], the average HR of elevated ALT for developing HCC was 2.74 [1.98-3.77] (Figure 3), and that in 8 studies of HCV-infected patients[12,15-21] was 5.51 [3.08-9.83] (Figure 4). It was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. The HR in HCV-infected patients was significantly ($P = 0.0391$) higher than that in HBV-infected patients.

In hepatitis B patients, the abnormal range adopted was 28-45 IU/L (Table 1), and in hepatitis C patients, it was 20-50 IU/L (Table 2). It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

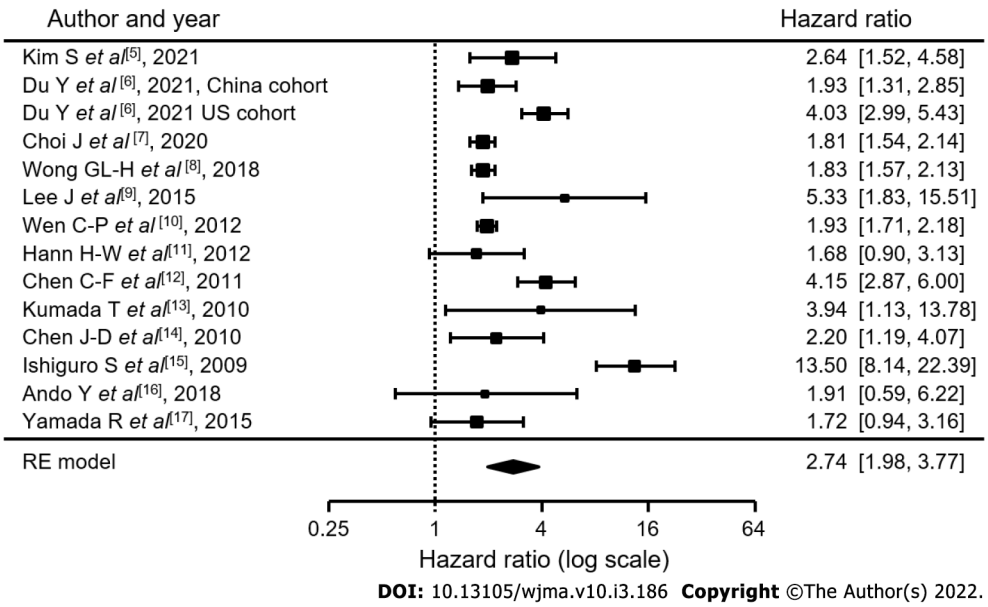

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Figure 3 In hepatitis B virus patients, a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.

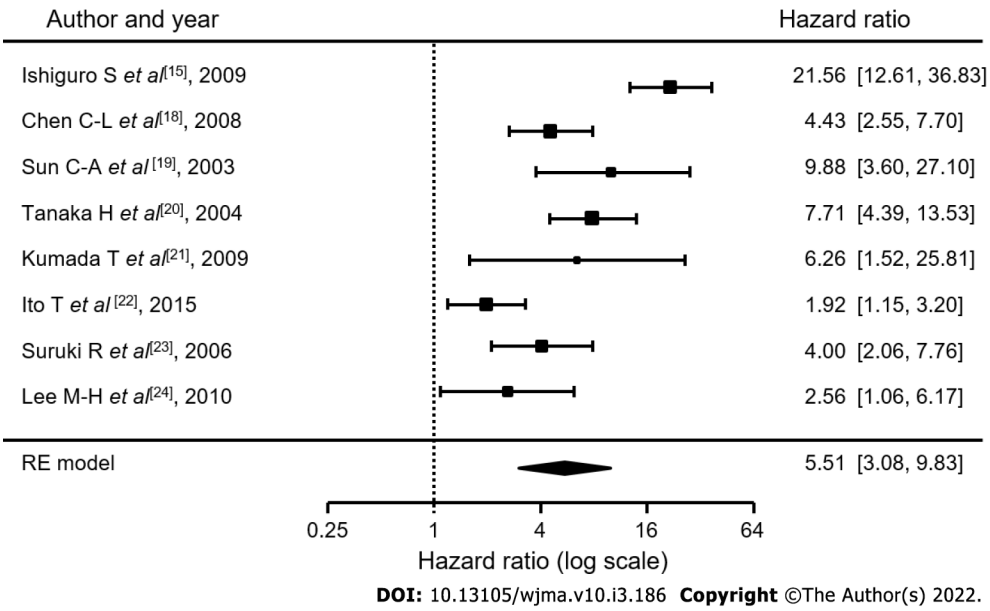

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Figure 4 In hepatitis C virus patients, Hazard ratios of patients in a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.

DISCUSSION

There are many risk factors for developing HCC: Sex, age, ALT, α-fetoprotein, presence of cirrhosis, habitual alcohol consumption, tabaco, and diabetes mellitus are typically cited, and HBV-DNA[1,3,6-8, 10] and the HBV genotype[9] are added for chronic HBV infection. The HCV genotype is also cited for HCV infection[21]. To study the impact of ALT on HCC development in chronic hepatitis B and chronic hepatitis C virus infections, we initially surveyed risk factors for HCC that are strongly associated with its development.

As shown in Table 3, the HR for developing HCC for each item in patients with chronic hepatitis B virus infection was 2.52 for sex, 3.15 for age, 2.212 for HBV-DNA, 3.37 for ALT, and 6.42 for presence of cirrhosis. Except for the presence of cirrhosis, ALT shows the highest risk ratio for HCC development.

As shown in Table 4, in patients with chronic hepatitis C virus infection, it was 5.486 for age and 5.877 for ALT. The value for ALT was higher than that for age. In HBV infection, ALT is the second-highest

Table 3 Hazard ratio for developing hepatocellular carcinoma for each item in various reports of patients with chronic hepatitis B virus infection

Ref.	Sex	Age	HBV-DNA	ALT	AFP	Presence of cirrhosis	HBV genotype	Alcohol use	Tabaco	DM
Kim *et al*[5]	2.782	1.080	0.986	2.641		2.955		2.105		2.00
Du *et al*[6]	2.94	3.30		2.55		2.45				
Choi *et al*[7]	1.67	1.05	1.02	1.54	1.21	1.54				
Wen *et al*[10]	1.93	5.34		1.93						
Hann *et al*[11]				1.21						2.60
Chen *et al*[12]			3.12	5.75		7.961	2.05 (Type C)			
Kumada *et al*[13]	6.011		5.125	3.939	6.779	18.033				
Chen *et al*[14]	1.2	2.0	1.6	1.7				2.3	1.9	
Ishiguro *et al*[15]				10.5	2.183					
Ando *et al*[16]	2.200	3.395	1.442	1.914	1.967					
Yamada *et al*[17]	1.44	5.867				5.59				
Average	2.52	3.15	2.212	3.37		6.42				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HBV: Hepatitis B virus.

Table 4 Hazard ratio for developing hepatocellular carcinoma in each item in various reports of patients with chronic hepatitis C virus infection

Ref.	Sex	Age	ALT	AFP	Presence of cirrhosis	DM	HCV-genotype
Ishiguro *et al*[15]		11.4	10.5				
Chen *et al*[18]	1.65	5.83	4.43			3.46	
Sun *et al*[19]		6.5	7.7				
Tanaka *et al*[20]	2.63	4.47	6.23				
Kumada *et al*[21]		2.42	6.263		10.003		
Ito *et al*[22]	1.448	2.187	1.916	6.5			
Suruki *et al*[23]							
Lee *et al*[24]							2.8 (HCV-1)
Average		5.486	5.877				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HCV: Hepatitis C virus.

risk factor, and in HCV infection, ALT is the higher risk factor.

In support of our findings, Benvegnù *et al*[25] demonstrated that patients with HCV infection with persistently elevated or fluctuating ALT levels during the observation period demonstrated a significantly higher rate of HCC development compared with patients in whom ALT remained or became normal during follow-up. This observation confirms that the activity of liver disease, which is characterized by inflammation, necrosis, and regeneration, plays an important role in promoting HCC development and suggests that medical interventions that limit disease activity may prevent or delay neoplastic transformation and tumor growth.

Furthermore, we demonstrated that the average HR of ALT for HCC development in HCV patients is about twice that in HBV patients ($P < 0.05$).

CONCLUSION

In conclusion, the difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

ARTICLE HIGHLIGHTS

Research background

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers.

Research motivation

The reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unknown. We considered the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

Research objectives

To investigate this, we surveyed the hazard ratio of inflammation for HCC development, which was identified by serum alanine aminotransferase levels between patients with HBV and HCV infections.

Research methods

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC, identifying 8924 HBV-and7376 HCV-infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV-infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

Research results

In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77], and that in the 8 studies on HCV-infected patients was 5.51 [3.08-9.83]. HR in HCV-infected patients was about twice that in HBV-infected patient, and was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

Research conclusions

The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

Research perspectives

In this study, it was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. So, we must optimally suppress inflammation in patients with HCV-associated liver diseases to prevent HCC development.

FOOTNOTES

Author contributions: Tarao K summarized the data and wrote the paper; Nozaki A, Komatsu H, Ideno N, Komatsu T, Ikeda T, Maeda S were involved in the interpretation of data, and the development and critical revision of the manuscript for important intellectual content; Taguri M conducted statistical analysis.

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MINIREVIEWS

SARS-CoV-2 viral load in the upper respiratory tract and disease severity in COVID-19 patients

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Abstract

Due to the disease's broad clinical spectrum, it is currently unclear how to predict the future prognosis of patients at the time of diagnosis of coronavirus disease 2019 (COVID-19). Real-time reverse transcription-polymerase chain reaction (RT-PCR) is the gold standard molecular technique for diagnosing COVID-19. The number of amplification cycles necessary for the target genes to surpass a threshold level is represented by the RT-PCR cycle threshold (Ct) values. Ct values were thought to be an adequate proxy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load. A body of evidence suggests that SARS-CoV-2 viral load is a possible predictor of COVID-19 severity. The link between SARS-CoV-2 viral load and the likelihood of severe disease development in COVID-19 patients is not clearly elucidated. In this review, we describe the scientific data as well as the important findings from many clinical studies globally, emphasizing how viral load may be related to disease severity in COVID-19 patients. Most of the evidence points to the association of SARS-CoV-2 viral load and disease severity in these patients, and early anti-viral treatment will reduce the severe clinical outcomes.

Key Words: Severe acute respiratory syndrome coronavirus-2; Viral load; Upper respiratory tract; Coronavirus disease 2019 patients; Disease severity; Clinical outcome

Core Tip: Real-time reverse transcription-polymerase chain reaction is regarded as the gold standard confirmatory test for coronavirus disease 2019 (COVID-19). Cycle threshold (Ct) values can be used to diagnose or forecast severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection since they are associated with virus load. Numerous differences exist in several clinical trials with small or large sample sizes, indicating a substantial positive correlation between the Ct value and disease severity in COVID-19. In this context, a literature review was conducted to address information gaps about the relationship between Ct levels and disease severity in COVID-19 patients globally. The majority of the data indicated a link between SARS-CoV-2 viral load and disease severity in these patients, and early antiviral therapy will minimize the severity of the clinical outcomes.

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INTRODUCTION

Prior to November 2019, six coronaviruses (CoVs) were known to infect humans and cause respiratory disease: OC43, 229E, HKU1, and NL63, four community-acquired CoVs that are endemic in humans, as well as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), two highly pathogenic CoVs that have zoonotic transmission followed by variable transmission between humans[1-5]. A new CoV discovered in late 2019 in Wuhan, Hubei Province, China has recently spread worldwide, causing a serious pandemic. SARS-CoV-2 was the name given to the new CoV, and the condition was dubbed coronavirus disease 2019 (COVID-19). SARS-CoV-2 spread rapidly from person to person, resulting in a pandemic that affected every province in China and eventually more than 203 nations and territories around the globe[6-7]. As of March 22, 2022, the World Health Organization has received reports of nearly 459 million cases of COVID-19, including more than 6 million deaths[8].

Viral load is used to diagnose severe viral infections of the respiratory system, as well as to track disease progression and treatment. By evaluating the value of the cycle threshold (Ct) of reverse transcription-polymerase chain reaction (RT-PCR), the SARS-CoV-2 viral load may be determined from the patient's viral RNA at a certain concentration. The lower the Ct values, the greater the viral load[9]. In contrast to other viral infections, no pathogen-specific prognostic indicators for SARS-CoV-2 are readily accessible. The first prognostic evaluation of individuals infected with SARS-CoV-2 may benefit from viral biomarkers capable of forecasting COVID-19 development in addition to the existing risk factors for severity. It is presently disputed whether the SARS-CoV-2 viral load affects the severity and course of the disease in this regard[10-13]. According to recent research, there may be a correlation between viral load and the severity of SARS-CoV-2 pneumonia, the degree of hypoxemia, the risk of mortality, as well as hematological, biochemical, and inflammatory alterations. However, diverse recruiting criteria have made it difficult to obtain a final, definite conclusion on the association between early nasopharyngeal viral load and individual outcomes[14-16]. The goal of this review is to ascertain if the SARS-CoV-2 Ct at diagnosis could anticipate the severity of COVID-19 and the outcomes of these patients.

SARS-COV-2 VIRAL LOAD IS ASSOCIATED WITH DISEASE SEVERITY

Knudtzen *et al*[17] conducted a prospective cohort study of adult COVID-19 patients with PCR-positive SARS-CoV-2 airway samples to determine the association between cycle quantification (Cq)-values, hospitalization, and disease severity in 87 outpatients and 82 inpatients. The findings revealed that 31 of the 82 hospitalized patients (38.0%) had severe COVID-19 disease and had considerably lower baseline Cq-values than patients with moderate disease severity (median Cq-values = 24.8 *vs* 28.1, $P = 0.01$). They also discovered a statistically significant link between lower Cq-values and a higher risk of severe disease outcome (odds ratio [OR] = 0.89, 95% confidence interval (CI): 0.81-0.98, $P = 0.018$), which was independent of the timing of the test in relation to symptom onset and the presence of confounding factors such as airway sample type. When the date of the test and confounding variables were controlled for, they observed no relationship between lower baseline Cq-values in outpatients infected with SARS-CoV-2 and a greater likelihood of hospitalization. They concluded that SARS-CoV-2 PCR Cq-values were correlated with the time since symptoms began. Early in the clinical course, Cq-values were low as a sign of high viral loads, but Cq-values were not shown to be a predictor of hospitalization. On the other hand, lower Cq-values were found to be indicative of more disease severity in

hospitalized patients.

Kawasuji *et al*[18] performed a retrospective cohort study to investigate the concentrations of SARS-CoV-2 RNA in the blood (RNAemia) and in the nasopharyngeal cavity, as well as their relationship with clinical severity in 56 COVID-19 patients. On admission, 19.6% (11/56) of patients had RNAemia, followed by 1.0% (1/25), 50.0% (6/12), and 100.0% (4/4) of intermediate, severe, and critically ill patients, respectively. Patients with RNAemia required more frequent oxygen supplementation (90.0% *vs* 13.3%), intensive care unit (ICU) admission (81.8% *vs* 6.7%), and invasive mechanical ventilation (27.3% *vs* 0.0%). The median viral load of nasopharyngeal swabs in patients with RNAemia was significantly higher in critically ill patients (5.4 Log_{10} copies/μL) than in moderate-severe cases (2.6 Log_{10} copies/μL), and significantly higher in non-survivors (6.2 Log_{10} copies/μL) than in survivors (3.9 Log_{10} copies/μL). They discovered a significant percentage of patients with SARS-CoV-2 RNAemia and a relationship between RNAemia and disease severity. Furthermore, among RNAemia patients, the viral loads of nasopharyngeal swabs were correlated with disease severity and death, suggesting the possibility of combining serum testing with nasopharyngeal tests as a prognostic indicator for COVID-19, with better quality than each test.

The connection between nasopharyngeal viral loads, host variables, and illness severity in 1122 SARS-CoV-2-infected patients was examined by Maltezou *et al*[19]. There were 309 (27.5%) patients with a high viral load, 316 (28.2%) with a moderate viral load, and 497 (44.3%) with a low viral load. In univariate analysis, individuals with high viral loads were older, had more comorbid diseases, required intubation for symptomatic disorders, and eventually passed away. Patients with a high viral load spent more time in the critical care unit and required more intubation than patients with a low viral load. Furthermore, individuals with chronic cardiovascular disease, hypertension, chronic lung disease, immunosuppression, obesity, and chronic neurological disease were more likely to have high viral loads. They concluded that viral load in the nasopharynx may be used to identify patients at high risk of morbidity or poor outcome.

Zheng *et al*[20] conducted a retrospective cohort study on 96 consecutively hospitalized COVID-19 patients, including 22 with moderate disease and 74 with severe disease, to assess viral loads at various phases of disease progression. After admission, 3497 respiratory, stool, serum, and urine samples were obtained from patients and tested for SARS-CoV-2 RNA viral load. RNA was also found in the feces of 55 (59%) of the patients and the serum of 39 (41%) of the patients. One patient's urine sample tested positive for SARS-CoV-2. The median duration of the virus in feces (22 d) was substantially longer than that in respiratory (18 d) and serum samples (16 d). Furthermore, the median duration of the virus in patients with severe disease (21 d) was substantially longer than that in patients with moderate disease (14 d). In the moderate group, viral loads peaked in respiratory samples in the second week after the illness started, but in the severe group, viral loads remained high throughout the third week. Virus duration was greater in individuals over the age of 60 and in men. They proposed that the duration of SARS-CoV-2 RNA in stool samples is significantly longer than that in respiratory and serum samples, emphasizing the importance of improving stool sample management in epidemic prevention and control and that the virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease.

Aydin *et al*[21] investigated the predictive significance of viral load identified in the saliva of 300 COVID-19 patients in the early stages of illness. The results showed a mean Ct-value of 25.30 in the mild illness group, 19.85 in the intermediate disease group, 16.75 in the severe disease group, and 15.48 in the critical disease group. The pattern of the mean Ct-value of the oro-nasopharyngeal swab was similar to that of saliva. The authors concluded that the Ct-value of saliva and oro-nasopharyngeal swab might be used to predict disease severity.

de la Calle *et al*[14] performed a retrospective study of 455 hospitalized patients with a confirmed diagnosis of SARS-CoV-2 infection using prospective computerized medical data. The study population was separated into three groups based on the Ct value obtained upon admission: Patients with high viral load (Ct < 25), those with intermediate viral load (Ct 25-30), and those with low viral load (Ct > 30). The researchers discovered that 130 (28.6%) patients had a high viral load, 175 (38.5%) had an intermediate viral load, and 150 (33%) had a low viral load. They discovered that 120 (26.4%) patients died while they were in the hospital, and that 161 (35.4%) patients experienced respiratory failure after spending a median of 9 d there. High viral loads were associated with increased respiratory failure and a higher mortality rate at 30 d following admission in these patients. However, the risk of ICU admission was greater among patients with low and intermediate viral loads (12.3% *vs* 6.2%, $P = 0.054$). Septic shock, acute renal damage, venous thrombosis, hepatitis, or major adverse cardiovascular events were not different across groups. According to the authors, a useful prognostic indicator for the beginning of respiratory failure is the Ct value of RT-PCR in nasopharyngeal swabs at the time of admission.

Kwon *et al*[22] conducted a study on 31 hospitalized COVID-19 patients to investigate viral load, antibody responses to SARS-CoV-2, and cytokines/chemokines along the illness course, as well as to find parameters linked to disease severity. Asymptomatic and moderate patients had lower viral loads and longer viral shed than severe and critical cases. Unlike plasma IgG, which grew gradually and remained stable during hospitalization, plasma IgM peaked 3 wk after symptoms started and then declined. The antibody response was somewhat delayed but greater in severe and critical cases than in

others. High levels of interferon (IFN)-α, IFN-γ induced protein-10, chemokine generated by IFN-γ, and interleukin-6 were linked with the severity of COVID-19 5-10 d after symptom onset. The authors hypothesized that a high viral load in the respiratory tract, as well as excessive cytokine and chemokine production between 1 and 2 wk after the onset of symptoms, was substantially linked with the severity of COVID-19.

Piubelli *et al*[23] conducted a retrospective analysis to assess the viral load of 373 confirmed COVID-19 patients seen in the emergency department between March 1, 2020 and May 31, 2020. According to the authors, 281 COVID-19 individuals were identified in March, 86 in April, and 6 in May. Along with a decline in the number of cases, they observed a considerable fall in the proportion of patients requiring critical care, which fell from 6.7% (19/281) in March to 1.1% (1/86) in April, and to none in May. In terms of viral load, they noticed a tendency for Ct to rise from a median of 24 to 34 between March and May, particularly in non-ICU patients. They concluded that throughout the pandemic, they saw a dramatic decline in severe COVID-19 patients that required critical care in addition to the declining viral load.

Shlomai *et al*[13] studied 170 hospitalized COVID-19 patients to see if there was a link between viral load at the time of admission, lung inflammation, and disease prognosis. The authors discovered that non-survivors and mechanically ventilated patients (n = 21) had a considerably greater virus load (8-fold, Ct = 23.43, P = 0.0001) than surviving non-intubated patients (n = 149, Ct = 29.55, P = 0.0001). Furthermore, a multivariate study adjusted for age, gender, and blood oxygen saturation $(BOS)_{min}$ found that low viral load was linked with a lower risk of mechanical ventilation and death (OR = 0.90, 95%CI: 0.81-0.99, P = 0.046). Furthermore, both BOS and patient age were independently related to mechanical ventilation and mortality (OR = 0.91, 95%CI: 0.84-0.98, P = 0.009 for BOS and OR = 1.05, 95%CI: 1.004-1.097 for patient age). They concluded that their data indicated a strong link between nasopharyngeal viral load and hypoxemia, as well as worse clinical outcomes in COVID-19 patients hospitalized.

In a study of 448 COVID-19 patients, Soria *et al*[24] looked at the relationship between viral load, as measured using nasopharyngeal swabs, and the severity of the illness. They clinically categorized individuals as having mild, moderate, or severe COVID-19 based on a variety of clinical characteristics such as the need for hospitalization, the necessity for oxygen treatment, admission to critical care units, and/or mortality. The authors discovered a statistically significant relationship between viral load and disease severity, with higher viral load associated with a worse clinical prognosis, independent of several previously identified risk factors such as age, gender, hypertension, cardiovascular diseases, diabetes, obesity, and pulmonary diseases.

Trunfio *et al*[25] conducted a study on 200 confirmed COVID-19 patients to see if the SARS-CoV-2 Ct value at diagnosis might predict COVID-19 disease severity, clinical symptoms, and 6-mo sequelae. Patients were divided into three groups based on diagnostic Ct values discovered from the initial swab: Ct 20, Group A; Ct = 20 - 28, Group B; and Ct > 28, Group C. The severity of the disease was graded on a six-point scale: Death, hospitalization with intubation, hospitalization needing continuous positive airway pressure support, hospitalization requiring low-flow wall oxygen to reservoir mask assistance, hospitalization without oxygen support, and no hospitalization. There were 168 survivors and 32 deaths among the 200 individuals. The range for the median age was 43-69. There were 116 (58.0%) men, and 188 of them were of European descent (94.0%). Patients with SARS-CoV-2 Ct were distributed as follows: 55 in Group A (27.5%), 55 in Group B (27.5%), and 90 in Group C (45.0%). Even after controlling for the time from COVID-19 onset to swab collection, the linear Ct values were negatively associated with the number of comorbidities per patient. Hospitalization-related patients were seen in Group A more frequently than in Group C (74.5% *vs* 56.7%). The severity of COVID-19 was substantially higher in Group A than in Groups B and C. With respect to Ct, there was an inverse distribution in the five categories of illness severity. Finally, 6-mo results for COVID-19 were worse in Group A than in the other groups; only 29.1% of patients in Group A had fully recovered at this point, compared to 70.9% and 80.0% in Groups B and C, respectively. Furthermore, Group A had a greater fatality rate (36.4%) than the other groups (Group B had a 12.7% lethality rate and Group C had a 5.6% lethality rate). After controlling for confounding variables, in multivariate analysis, lower SARS-CoV-2 Ct levels were independently associated with a greater risk of COVID-19-related death, along with older age and more comorbidities. The authors showed a correlation between COVID-19-related deaths, disease severity, the number of signs and symptoms at diagnosis, and the persistence of sequelae at 6 mo in symptomatic hospitalized and non-hospitalized patients, and the Ct value detected in nasopharyngeal swabs collected within the first week of COVID-19 onset.

Tsukagoshi *et al*[26] conducted a study on 286 confirmed COVID-19 patients to assess the links between epidemiological data, viral load, and disease severity (15 fatal cases, 133 symptomatic cases, and 138 asymptomatic cases). Compared to the number of viral copies at the time of sample collection, fatal cases had 3.57 ± 4.70 × 10^9 copies/mL, symptomatic cases had 3.92 ± 1.60 × 10^8 copies/mL, and asymptomatic cases had 4.92 ± 1.48 × 10^7 copies/mL. These findings imply that the viral loads of fatal and symptomatic patients were greater than those of asymptomatic cases. According to the authors, a high viral load of SARS-CoV-2 in elderly patients at an early stage of the disease, particularly those with pneumonia symptoms, results in a bad prognosis. Therefore, in such circumstances, we should intervene early to avoid the condition's progressing to a severe degree.

Wang *et al*[27] conducted a study on 12 seriously ill and 11 slightly ill COVID-19 patients to explore the immune response and its link with clinical outcomes. The rates of viral replication, neutralizing antibody responses, and cross-reactivity with other human respiratory CoVs were also examined for use in the diagnosis, prognosis, and epidemiological studies. All 23 patients provided 461 clinical samples (84 nasal swabs, 59 throat swabs, 36 sputum samples, 90 fecal samples, 79 urine tests, and 113 plasma samples), including 1 stomach biopsy. They discovered that the majority of patients with severe illness shed viral loads for up to 30-40 d after beginning, but the majority of slightly unwell individuals had no detectable viral loads 15 d after onset. The peak viral load differed significantly between severe and moderate patients. The viral loads in the respiratory samples were larger in the severe group than in the mild group, and they gradually decreased with time. The SARS-CoV-2 was mostly found in respiratory samples. However, in the majority of critically ill patients, feces remained positive for viral RNA for an extended period of time. IgM responses in patients with severe disease increased within 1 to 2 wk after beginning and were progressively reduced after 4 wk, but IgM responses in patients with moderate disease were substantially lower. The majority of the mildly unwell patients (8/11) did not develop substantial IgM antibodies throughout the disease course, demonstrating that the IgM diagnosis was not sensitive for mildly ill individuals. IgG responses appeared 10-15 d after the initiation. The majority of patients had high levels of IgG antibodies that lasted at least 6 wk.

Faíco-Filho *et al*[28] conducted a retrospective cohort analysis on 875 confirmed COVID-19 patients to assess the relationship between SARS-CoV viral load and mortality. Fifty percent (439/875) of these patients had mild disease, 30.4% (266/875) had moderate disease, and 19.5% (170/875) had severe disease. In these COVID-19 individuals, a Ct value of 25 indicated a high viral load, which was independently related to death. They concluded that the SARS-CoV-2 virus load at admission was independently linked with death among hospitalized COVID-19 patients.

Pérez-García *et al*[29] conducted a retrospective study of 255 SARS-CoV-2–infected patients to determine the viral RNA content and expression of selected immune genes in the upper respiratory tract (nasopharynx), as well as their correlation with severe COVID-19. In the beginning, patients were split into three groups based on severity: 85 outpatients who underwent emergency room examinations and were discharged within the first 24 h (mild cases), 87 inpatients in medicine wards who did not require critical care (moderate cases), and 83 critical patients who were admitted to the ICU, or who passed away within 28 d of hospital admission (severe cases), and 30 healthy individuals were used as the control group. Interferon-stimulated gene 15 (ISG15), interferon-β (IFN-β), interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), retinoic acid-inducible gene I (RIGI), tumor necrosis factor (TNF-β), interleukin 6 (IL-6), and chemokine (C-C motif) ligand 5 (CCL5) were all expressed at higher levels in COVID-19 patients. Individuals with severe COVID-19 had considerably greater SARS-CoV-2 viral load, IFN-β, IFIT1, IL-6, and IL-8 levels than patients with mild or moderate illness, although CCL5 values were significantly lower. They also found that ISG15, RIGI, TNF-β, IL-6, and CXCL10 strongly correlated with SARS-CoV-2 virus load. In adjusted regression models, SARS-CoV-2 viral load was a risk factor, but CCL5 was a protective factor for ICU admission or mortality during hospitalization. They also discovered significant relationships between the SARS-CoV-2 viral load and CCL5 in both cohorts when the entire cohort was divided in half, demonstrating a strong correlation between the severity of COVID-19 and both high levels of SARS-CoV-2 virus load and low levels of CCL5 expression. They concluded that a number of innate immune genes are stimulated by SARS-CoV-2 replication in the nasopharyngeal mucosa. Low CCL5 expression levels and high SARS-CoV-2 viral loads were associated with ICU admission or fatality, despite the fact that CCL5 was the best predictor of COVID-19 severity.

Guo *et al*[30] studied the relationship between SARS-CoV-2 viral load and disease severity in 195 hospitalized COVID-19 patients. The differences in clinical characteristics across four groups (mild, moderate, severe, and critical) and two groups (severe *vs* non-severe) were analyzed using one-way ANOVA and the student's *t*-test, respectively. More severe patients appear to have the following characteristics: Older age, underlying diseases, higher maximum body temperature within 24 h of hospitalization, longer time for virus clearance, longer duration of fever, higher levels of plasma C-reactive protein, D-dimer, procalcitonin, and aspartate aminotransferase, increased white blood cell count, particularly neutrophils, lower lymphocyte count, and higher initial viral load.

Tanner *et al*[31] performed a study on 185 hospitalized COVID-19 patients to assess the relationship between Ct value at admission and patient outcome while carefully controlling for confounders. On univariate analysis, the authors discovered that the Ct value at presentation was related to the likelihood of both ICU admission and mortality. Furthermore, Ct values changed considerably by age, length of illness at presentation, and antibody status. In a multivariate analysis, the Ct value was associated with the likelihood of death but not ICU admission. The presence of neutralizing antibodies at the time of presentation was not linked with death or ICU admission. They concluded that the SARS-CoV-2 Ct value at admission was independently related to mortality when other characteristics were controlled for and that it may be utilized for risk stratification.

SARS-COV-2 VIRAL LOAD IS NOT ASSOCIATED WITH DISEASE SEVERITY

Berastegui-Cabrera *et al*[32] conducted a prospective multicenter cohort study in 72 COVID-19 patients to assess the relationship between SARS-CoV-2 RNAemia, and viral load in the nasopharyngeal swab, and an unfavorable outcome, defined as ICU admission and/or death. Nine (12.5%) patients were treated as outpatients following an evaluation in the emergency room, whereas 63 (87.5%) patients were admitted to the hospital. Eleven (15.3%) of the patients were found to have SARS-CoV-2 RNAemia, with ten of them being hospitalized. The median viral load in plasma for the 11 SARS-CoV-2 RNAemia patients was 2.88 $\log_{10}$ copies/mL, while the median viral load in nasopharyngeal swabs for the 72 patients was 6.98 $\log_{10}$ copies/mL. Additionally, patients with SARS-CoV-2 RNAemia required more invasive mechanical ventilation (36.4% *vs* 6.6%) and had higher ICU admission rates (45.50% *vs* 8.2%) and ARDS (54.5% *vs* 9.8%). SARS-CoV-2 RNAemia patients exhibited a greater death rate (36.4% *vs* 4.9%) and a poorer prognosis (63.6% *vs* 13.1%). The authors concluded that patients with severe chronic liver disease and solid organ transplantation are more likely to have SARS-CoV-2 RNAemia at the time of the initial emergency room evaluation. They also noted that this condition is not predicted by a viral load in the upper respiratory airways and is linked to a poor prognosis.

Karahasan Yagci *et al*[33] conducted a study on 730 RT-PCR-positive patients to assess the severity of chest computed tomography (CT). Of the 284 patients admitted to the hospital, 27 (9.5%) died. There were no Ct results in 236 (32.3%) of the patients, and 216 (91.5%) of them were outpatients. In hospitalized patients, the total severity score (TSS) was much greater; 5.3% experienced severe alterations. Outpatients had lower Ct values, indicating a greater viral load. In both groups, an inverse relationship between viral load and TSS was seen. The severity of Ct was associated with age, with older individuals having a greater TSS. The authors concluded that viral load was not a significant risk factor for hospitalization or fatality. Outpatients exhibited high levels of viruses in their nasopharynx, making them infectious to their contacts. The viral load is critical in diagnosing the early stages of COVID-19 in order to limit potential transmission, whereas chest CT can assist in identifying patients that require significant medical treatment.

Le Borgne *et al*[34] conducted a retrospective study on 287 individuals with a confirmed diagnosis of COVID-19 to evaluate the association between SARS-CoV-2 viral load and disease severity. Nearly half of them (50.5%) had a moderate form, while the remaining half (49.5%) had a severe form that required mechanical ventilators. At admission, the median (interquartile range) viral load in the first upper respiratory swab was 4.76 (3.29-6.06) $\log_{10}$ copies/mL. This viral load measurement did not differ by subgroup when comparing survivors and non-survivors. Furthermore, the authors discovered that measuring respiratory viral load did not predict in-hospital mortality or disease severity. They claimed that the respiratory viral load in the first nasopharyngeal swab obtained during emergency department care is neither a predictor of the severity of the infection nor of death from SARS-CoV-2. The number of underlying comorbidities, as well as the host response to this viral infection, may be more predictive of disease severity than the virus itself.

Hasanoglu *et al*[35] studied the viral loads in six different sample types (nasopharyngeal, oral cavity, saliva, rectal, urine, and blood) from 60 patients to determine the relationship between disease severity and SARS-CoV-2 viral load, as well as differences in viral loads between asymptomatic and symptomatic patients. The authors discovered that 15 (25%) of the patients were asymptomatic, whereas 45 (75%) were symptomatic. There was a substantial difference in the mean ages of asymptomatic and symptomatic individuals (26.4 and 36.4, respectively). Asymptomatic individuals' viral loads were found to be substantially greater than symptomatic patients'. With increasing age, viral load has demonstrated a substantial negative tendency. With increasing disease severity, there was a considerable drop in viral load.

Bakir *et al*[36] conducted a study on 158 confirmed COVID-19 patients to evaluate the link between SARS-CoV-2 viral load Ct values and pneumonia. The authors discovered pneumonia in 40.5% of the individuals who underwent chest CT. SARS-CoV-2 Ct value and nasopharyngeal samples were shown to have a poor but significant connection with chest CT score. There was no link identified between viral load Ct value and age, gender, or death. There was no statistically significant relationship between chest CT score and death. The authors noted that the quantity of SARS-CoV-2 viral load did not correlate with the severity of the pulmonary lesions shown on chest CT.

Ng *et al*[37] studied 351 people (138 confirmed COVID-19 patients and 213 SARS-CoV-2-negative patients) to see if there is a link between SARS-CoV-2 viral load and disease severity. They discovered that viral loads in more seriously ill hospitalized patients, including those in the intensive care unit, were not significantly different from those in outpatient clinics. According to the authors, there is no clear association between viral load and disease severity, and a suitable biomarker for disease severity is currently unavailable in clinical settings.

DISCUSSION

Although qualitative SARS-CoV-2 RT-PCR tests are routinely used to diagnose COVID-19, the

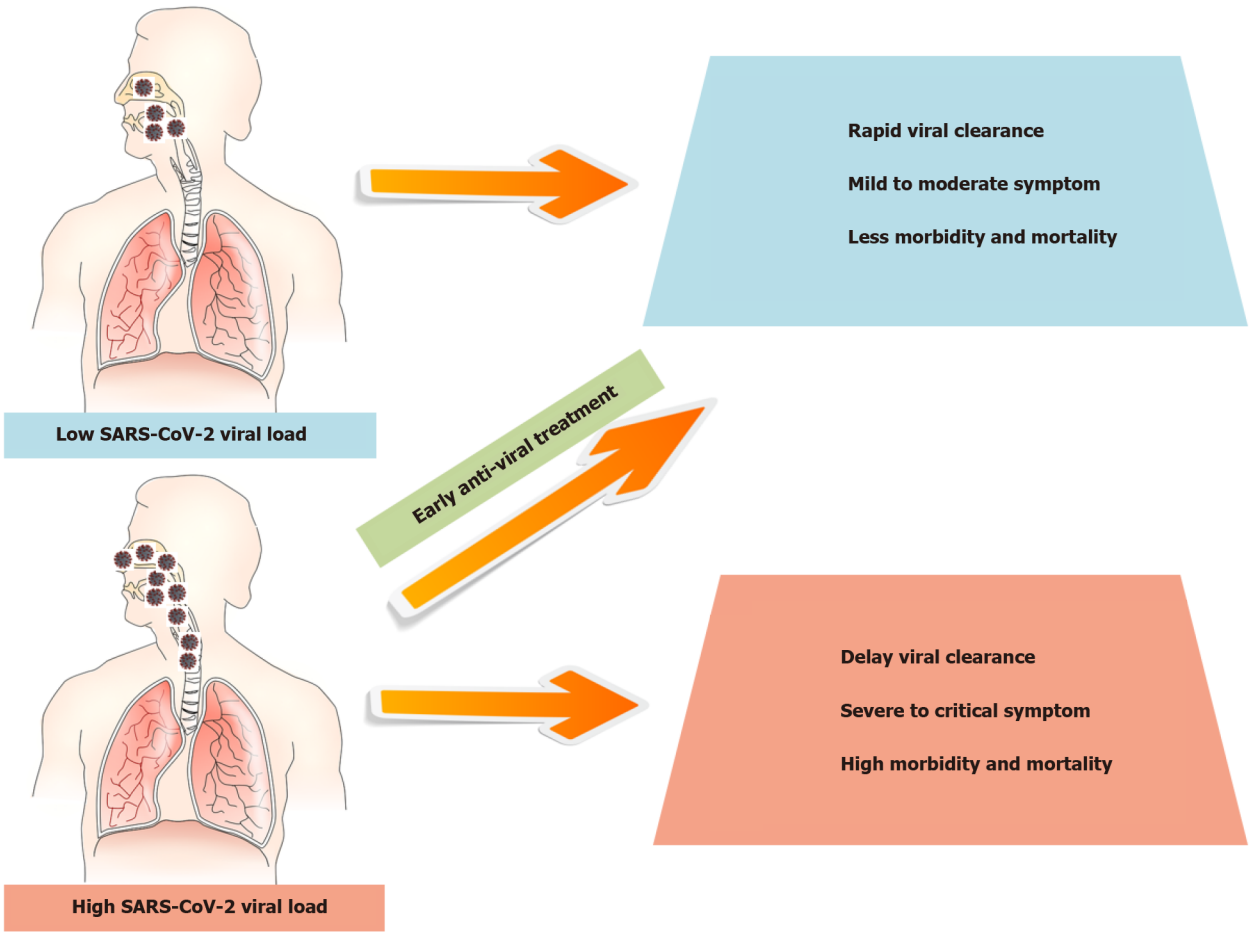

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Figure 1 High and low severe acute respiratory syndrome coronavirus 2 viral load and clinical outcomes in coronavirus disease 2019 patients. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

therapeutic significance of quantitative information on Ct values being negatively associated with SARS-CoV-2 viral load for identifying viral copies must be understood. So far, several studies have shown inconsistent findings of the viral shedding kinetics in moderate and severe COVID-19 patients with an association or no association with disease severity. Table 1 summarizes the information regarding the countries of origin, study design, number of COVID-19 patients, mean or median Ct value, association of disease severity, and conclusions. The majority of the evidence suggests that a high SARS-CoV-2 viral load is associated with a severe clinical outcome. Along with this data, several studies found that patients admitted to the hospital with high SARS-CoV-2 virus loads, as determined by Ct values of nasopharyngeal swab samples, were more likely to be intubated or die during their hospitalization[11,16,38,39]. Furthermore, many researchers demonstrated that early antiviral treatment could effectively reduce virus load, shorten virus clearance time, and prevent COVID-19 from rapidly progressing to a severe disease outcome (Figure 1)[40-44].

CONCLUSION

This review demonstrates an association between the Ct value discovered in nasopharyngeal swabs, which represented the quantitative SARS-CoV-2 viral load, and COVID-19-related fatalities and disease severity in both symptomatic hospitalized and non-hospitalized patients. These findings imply that the Ct value might be utilized as a tool to aid in the identification of individuals who are at a higher risk of having a catastrophic outcome. Early antiviral medication may successfully reduce viral load, decrease virus clearance time, and prevent the fast progression of COVID-19 to severe disease outcomes in this situation.

Table 1 Severe acute respiratory syndrome coronavirus 2 viral load and disease severity in coronavirus disease 2019 patients

Ref.	Study design	No. of COVID-19 cases	Median/mean viral load (Ct or Cq) (log_{10} copies/mL)	Association with disease severity	Conclusion
Knudtzen *et al* [17], Denmark	Prospective cohort	169 (87 OP/82 IP)	24.8 *vs* 28.1 (Severe *vs* Moderate)	Yes	Lower Cq-values were found to be indicative of more disease severity in hospitalized patients
Kawasuji *et al* [18], Japan	Retrospective cohort	56 (56 IP)	5.4 *vs* 2.6 (Critical/Moderate-Severe)	Yes	The viral loads of NP swabs were correlated with disease severity and death
Maltezou *et al* [19], Greece	Prospective cohort	1122 (274 OP/848 IP)	N/A	Yes	The viral load in the nasopharynx might be utilized to identify patients at increased risk for morbidity or poor outcome
Zheng *et al*[20], China	Retrospective cohort	96 (96 IP)	N/A	Yes	The virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease
Aydin *et al*[21], Turkey	Prospective cohort	300 (168/79/29/24)(M/I/S/C)	25.30/19.85/16.75/15.48 (M/I/S/C)	Yes	The Ct-values of saliva and oro-nasopharyngeal swab were useful in predicting disease severity
de la Calle *et al* [14], Spain	Retrospective cohort	455 (455 IP)	N/A	Yes	The Ct value of RT-PCR in nasopharyngeal swabs on admission is a useful predictive marker for the development of respiratory failure
Kwon *et al*[22], Korea	Prospective cohort	31 (31 IP)	35.2/27.9/26.7 (M/I/S+C)	Yes	High viral load in the respiratory tract and excessive cytokines and chemokines were substantially linked with the severity of COVID-19
Piubelli *et al* [23], Italy	Retrospective study	373 (373 OP)	N/A	Yes	The decreasing viral load that they observed during March to May 2020 was associated with a significant reduction in severe COVID-19 cases that needed intensive care
Shlomai *et al* [13], Israel	Retrospective cohort	170 (149 NS/21 SV)	23.43 *vs* 29.55 (NS *vs* SV)	Yes	There was a clear relationship between nasopharyngeal viral load and hypoxemia, as well as worse clinical outcomes in hospitalized COVID-19 patients
Soria *et al*[24], Spain	Prospective cohort	448 (110/236/102) (M/I/S)	35.75/32.69/29.58 (M/I/S)	Yes	The link between viral load and disease severity was shown in COVID-19 patients
Trunfio *et al* [25], Italy	Retrospective cohort	200 (32 NS/168 SV)	N/A	Yes	The Ct value detected within the first week of COVID-19 onset was associated with deaths and disease severity
Tsukagoshi *et al*[26], Japan	Retrospective study	286 (138 AS/133 SM/15 FT)	N/A	Yes	The high viral load in elderly patients at an early stage of the disease results in a bad prognosis
Wang *et al*[27], China	Prospective cohort	23 (11/12)(M/S)	N/A	Yes	The viral loads in the respiratory samples were larger in the severe group than in the mild group, and they gradually decreased with time
Faíco-Filho *et al* [28], Brazil	Retrospective cohort	875 (439/266/170)(M/I/S)	22/27/21.5 (M/I/S)	Yes	The SARS-CoV-2 virus load at admission was independently linked with death among hospitalized COVID-19 patients
Pérez-García *et al*[29], Spain	Retrospective study	255 (85/87/83) (M/I/S)	N/A	Yes	The SARS-CoV-2 viral load was a risk factor, but CCL5 was a protective factor for ICU admission or mortality during hospitalization
Guo *et al*[30],	Prospective	195 (16/132/41/6)	33.74/33.59/32.10/27.53	Yes	The higher initial viral load was

China	cohort	(M/I/S/C)	(M/I/S/C)		associated with disease severity in COVID-19 patients
Tanner *et al* [31], United Kingdom	Prospective cohort	185 (IP)	N/A	Yes	The SARS-CoV-2 Ct value at admission was independently related with mortality
Berastegui-Cabrera *et al* [32], Spain	Prospective cohort	72 (9 OP/63 IP)	N/A	No	The viral load in the upper respiratory airways was associated with poor outcome
Karahasan Yagci *et al*[33], Turkey	Retrospective study	730 (446 OP/284 IP)	(27.8/29.4/27.9) (M/I/S)	No	The viral load was not a significant risk factor for hospitalization or fatality
Le Borgne *et al* [34], France	Retrospective study	287 (42 NS/245 SV)	4.99 *vs* 4.76 (NS *vs* SV)	No	The viral load in the first nasopharyngeal swab was neither a predictor of severity nor of death in SARS-CoV-2 infection
Hasanoglu *et al* [35], Turkey	Prospective cohort	60 (15 AS/45 SM)	N/A	No	Asymptomatic individuals' viral loads were found to be substantially greater than symptomatic patients'
Bakir *et al*[36], Turkey	Retrospective study	158 (45 OP/113 IP)	26.76 *vs* 27.53 (OP *vs* IP)	No	The quantity of SARS-CoV-2 viral load did not correlate with the severity of the pulmonary lesions shown on chest CT
Ng *et al*[37], USA	Retrospective study	133	N/A	No	The viral loads in more seriously ill hospitalized patients were not significantly different from those in outpatient clinics

AS: Asymptomatic; C: Critical; CCL5: Chemokine (C-C motif) ligand 5; Cq: Cycle quantification; Ct: Cycle threshold; CT: Computerized tomography; FT: Fatality; I: Intermediate; IP: Inpatient; M: Mild; N/A: Not applicable; NP: Nasopharyngeal; NS: Non-survivor; OP: Outpatient; RT-PCR: Reverse transcription polymerase chain reaction; S: Severe; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SM: Symptomatic; SV: Survivor.

FOOTNOTES

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META-ANALYSIS

No increase in burnout in health care workers during the initial COVID-19 outbreak: Systematic review and meta-analysis

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Abstract

BACKGROUND

For decades and before the coronavirus disease 2019 (COVID-19) pandemic, for health care workers (HCWs) burnout can be experienced as an upsetting confrontation with their self and the result of a complex a multifactorial process interacting with environmental and personal features.

AIM

To literature review and meta-analysis was to obtain a comprehensive understanding of burnout and work-related stress in health care workers around the world during the first outbreak of the COVID-19 pandemic.

METHODS

We performed a database search of Embase, Google Scholar and PubMed from June to October 2020. We analysed burnout risk factors and protective factors in included studies published in peer-reviewed journals as of January 2020, studying a HCW population during the first COVID-19 wave without any geographic restrictions. Furthermore, we performed a meta-analysis to determine overall burnout levels. We studied the main risk factors and protective factors related to burnout and stress at the individual, institutional and regional levels.

RESULTS

Forty-one studies were included in our final review sample. Most were cross-sectional, observational studies with data collection windows during the first wave of the COVID-19 surge. Of those forty-one, twelve studies were included in the meta-analysis. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards (intensive care unit, emergency room and dedicated

internal medicine wards). Indeed, exposure to the virus was not a leading factor for burnout. Our meta-analytic estimate of burnout prevalence in the HCW population for a sample of 6784 individuals was 30.05%.

CONCLUSION

There was a significant prevalence of burnout in HCWs during the COVID-19 pandemic, and some of the associated risk factors could be targeted for intervention, both at the individual and organizational levels. Nevertheless, COVID-19 exposure was not a leading factor for burnout, as burnout levels were not notably higher than pre-COVID-19 levels.

Key Words: Burnout; Initial COVID-19 outbreak; SARS-CoV-2 pandemic; Healthcare workers; Mental health services; Maslach burnout inventory

Core Tip: We performed a database search from June to October 2020. We analysed burnout risk factors and protective factors in retained studies and performed a meta-analysis to determine overall burnout levels during the initial coronavirus disease 2019 (COVID-19) outbreak. We found a significant prevalence of burnout in health care workers during the COVID-19 pandemic and some of the associated risk factors could be targeted for intervention, both at the individual and organizational level. Nevertheless, COVID-19 exposure was not a leading factor for burnout, as burnout levels were not notably higher than pre-COVID-19.

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INTRODUCTION

Burnout is an occupational phenomenon defined as a syndrome of emotional exhaustion, depersonalization of others, and a feeling of reduced personal accomplishment[1,2]. It is the result of a complex and multifactorial process, with interacting environmental features and personal frailties[3-6], in a process that juxtaposes personal needs and expectations on one hand, and the institution's demands, (in)equalities and (in)justices on the other. For health care workers (HCWs), burnout can be experienced as an upsetting personal confrontation, as the progressive lack of compassion and diminished effectiveness has a distressing impact on their professional identity[4]. The scientific literature on HCW burnout is vast, as decades before the coronavirus disease 2019 (COVID-19) pandemic, burnout was recognized as a significant problem both in terms of magnitude and impact. A recent systematic review over a period of 25 years showed burnout levels of 25% among nurses[7]. Another recent meta-analysis studying physicians reported a combined prevalence of 21%, although with substantial variability due to uneven definitions, assessment methods, and study quality[8]. In the past decade, an increasing number of respiratory virus epidemics have placed additional pressure on the health care system and its workers through various mechanisms. During the 2003 severe acute respiratory syndrome (SARS) outbreak, some HCWs isolated themselves out of fear of infecting their friends and families[9], and lack of training, protection and hospital support was associated with higher burnout[10]. The novel influenza A virus (H1N1) outbreak in 2009 highlighted HCWs' concern for infection of family and friends and fears about consequences for their own health[11]. Other authors showed an increase in the stress and psychological burden of HCWs during the 2012 Middle East Respiratory Syndrome outbreak, due to infectious disease-related stigma, such as social rejection or discrimination[12], or increased burnout levels due to poor hospital resources[13].

Early 2020, economic uncertainty and societal anxiety reached unseen levels, as the COVID-19 pandemic profoundly changed our view of health, work and social interactions. As the UN put it, we are facing a global health crisis […], one that is killing people, spreading human suffering, and upending people's lives. However, this is much more than a health crisis. It is a human, economic and social crisis[14]. For most workers, the pandemic has accelerated a change in workplace habits and a shift from office work towards teleworking. HCWs, however, were subject to sudden and dramatic transformation of the health care institutions and were faced with unseen numbers of critically ill patients and casualties. In many countries, the pandemic was source of a tremendous increase in workload and significant levels of stress and fear regarding physical integrity. Most countries were

faced with an ominous atmosphere of fear of the unknown and a staggering shortage of means, including personal protective equipment (PPE). Particularly in the early days of the pandemic, HCWs were facing uncertainty about the virus's modes of transmission, questions about levels of contagiousness, and hence about the risk of self-infection and of infecting family members and friends.

Burnout in HCWs has been associated with poor patient safety outcomes, medical errors and adverse outcomes on the health care system as a whole[15,16]. In this review, we explore the main contributors to burnout in health care providers, specifically within the scope of the COVID-19 pandemic in early 2020. Despite the great variability in burnout measuring instruments, subscales, and cut-off levels therein, we endeavour to provide a meta-analytic estimate of burnout levels during the initial COVID-19 outbreak.

MATERIALS AND METHODS

Database search and initial study selection

We conducted a literature search in PubMed, Embase and Google Scholar from 1st of June to 10th of October 2020, following the PRISMA 2020 recommendations (unregistered). The search terms were associated with Boolean operators as detailed in Supplementary Table 1. Some additional relevant articles were included from the references sections of the articles found in the initial search.

Study eligibility criteria

We included original studies published in peer-reviewed journals as of January 2020, studying an HCW population during the first COVID-19 wave without any geographic restrictions. The exclusion criteria are detailed in Table 1. Initially, assessed studies comprised several randomized controlled trials (RCTs), mostly cross-sectional and some interventional studies. From those, RCTs and interventional studies were excluded during the screening phase, as they were not within the burnout or stress scope of this review.

Independent variables

The main independent variable was burnout and its prevalence during the COVID-19 pandemic in the first half of 2020 as measured with a recognized instrument or validated custom instrument. High levels of chronic work-related stress are generally accepted as a precipitator of burnout, and a recent study showed that high stress levels interfere with sound sleep[17], which in turn can precipitate burnout. Taking this into consideration, we included (perceived) stress as an independent variable in our analysis.

The main instrument used is the Maslach Burnout Inventory (MBI), a scale measuring burnout through three dimensions: emotional exhaustion (EE), depersonalization (DP) and decreased personal achievement (PA)[18,19]. EE refers to feelings of being overextended and depletion of one's resources [6]. Conceptually, it incorporates traditional stress reactions, such as job-related depression, psychosomatic complaints and anxiety[20,21], and has been related to similar behavioural outcomes, such as intention to quit and absenteeism[22]. HCWs experiencing EE feel apathetic and indifferent about their work and patients and no feel longer invested in situations arising during their workday[23]. DP refers to a cynical, insensitive, or disproportionately detached response to other people as EE becomes more severe. It can be perceived as withdrawal or mental distancing from care recipients[24], which are distancing techniques used to reduce the intensity of arousal and prevent the worker from disruption in critical and chaotic situations requiring calm and efficient functioning[25]. PA refers to a decline in one's feelings of competence and successful achievement at work, reduced productivity, low morale and inability to cope[26]. One can appreciate how reduced performance and productivity among HCWs lead to poor clinical decision-making and medical errors[23]. The questions used in the MBI are detailed in Supplementary Table 2. Other instruments used are detailed in Supplementary Table 3.

Dependent variables

The dependent variables were sociodemographic variables, personality traits, psychological and physical health status, occupational role, ward, organizational and geographic variables. Physical symptoms were described in certain studies, but they were not the focus of this review. The detailed study selection process is outlined in the flow chart in Figure 1.

Statistical analysis and meta-analysis

Units were unified for aggregation of dependent variables. When only median age and standard deviation were available, we used normal distribution inference to categorize the respondents into age categories. For other studies, we forced study age groups in the closest comparable group of our review. These adaptations may report inaccurate age distributions at the individual study level, but we believe that the aggregated data benefit from this approach. Meta-analysis was performed in MedCalc Version 19.5.3. Proportions with random effects models were studied, and we calculated the I^2 statistic of hetero-

Table 1 Exclusion criteria for the qualitative review

Studies that did not unambiguously study burnout and/or stress at work
Studies that did not focus on HCWs or a subpopulation thereof
Literature reviews, meta-analyses and systematic reviews
Full English text not available
Preprints, unreviewed articles
Short communications, editorials, *etc.* (not sufficient data)

HCWs: Health care workers.

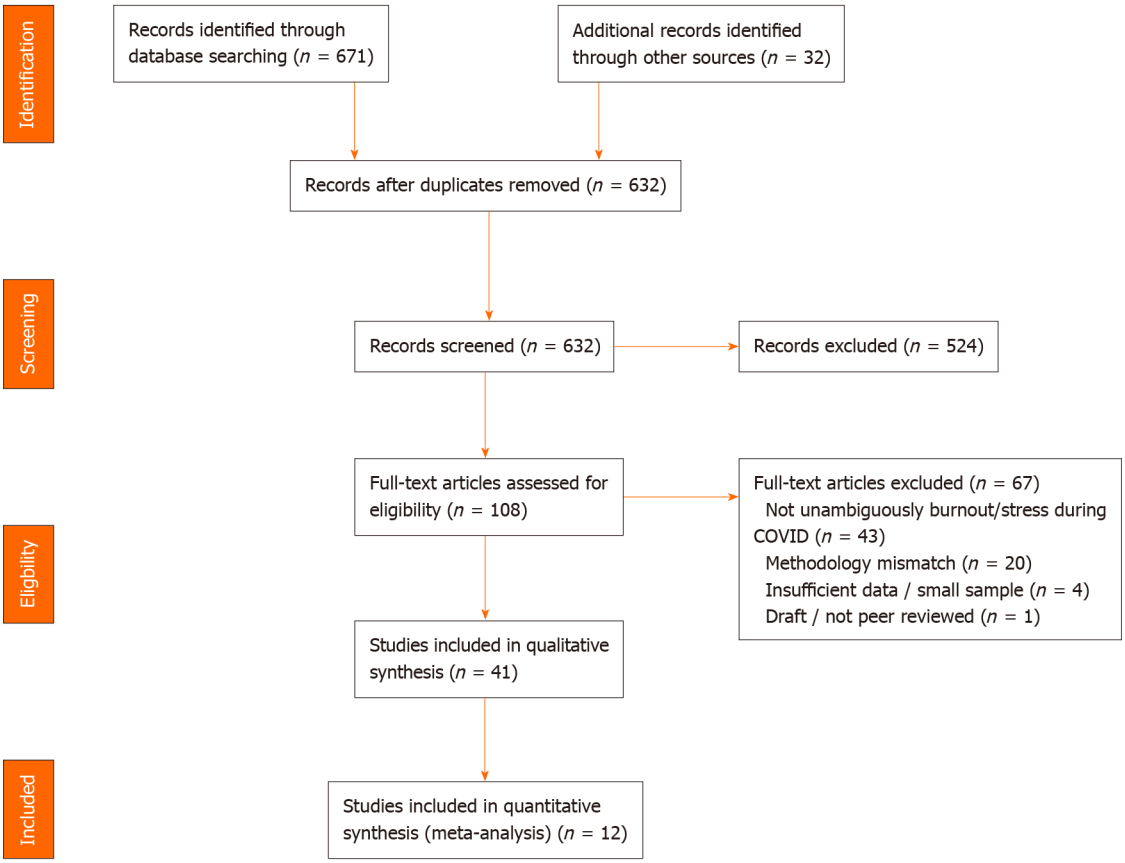

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Figure 1 Flow chart of the selection process.

geneity and publication bias through Egger's and Begg's tests, respectively.

Review outcomes

From the final list of retained studies, we selected those that had sufficient numeric data to perform a meta-analysis. These studies used validated burnout measuring instruments and reported either burnout prevalence or scores that permitted deducing HCW burnout prevalence. Descriptive analysis was performed using statistically significant data from the studies retained. For some studies, the conclusions retained in our review may not have been the most striking outcomes from their perspective. We focused mainly on burnout, stress, and related dependent variables.

RESULTS

Features of the included studies and sociodemographic data

Through screening, 39 cross-sectional, one longitudinal and one prospective cohort study were retained.

Of the 41 studies, all from 2020, 12 were included in the meta-analysis. Table 2 details the main features of the studies.

Of the studies retained, 44% were European studies, and 28% studied Asian-Pacific countries. After China, the pandemic hit hardest in European countries, such as Italy and Spain, in the first quarter of 2020. These two countries represented 21% and 19% of the respondents of European studies, respectively. Among the latter, Germany represented 39%. Table 3 shows a sociodemographic overview of respondents in the 41 studies. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards [intensive care unit (ICU), emergency room (ER) and dedicated internal medicine wards]. Supplementary Table 4 displays the complete list of studies and, for each study, a short description summarizing the main conclusions relevant for our review.

Burnout prevalence and meta-analytic estimate

Twelve studies were included in our meta-analysis (Figure 2). Egger's test result was -3.7859 (95%CI: -11.79–4.22 and $P = 0.3169$), and Begg's test rendered a Kendall's Tau of -0.1818 ($P = 0.4106$), showing no significant asymmetry or publication bias. The test for heterogeneity, however, showed a high level of inconsistency (I^2: 96.66%, $P < 0.0001$), prompting the use of the random effects model in estimating the meta-analytic effect. The meta-analytic estimate of burnout prevalence in HCWs was 30.05% (95%CI: 23.91%–36.5%), with a sample size of 6784.

DISCUSSION

The typical profile of an HCW with high levels of burnout was a single female nurse or resident physician under 30 years of age in an institution perceived as poorly prepared for the COVID-19 pandemic. This HCW experienced anxiety regarding infection with COVID-19 or infecting their friends and family and might have had a history of prior psychiatric conditions and low levels of resilience.

Age, sex, marital status

A recurring risk factor associated with burnout was female sex[27-34]. Female sex was correlated with higher perceived stress[17,35-38], despite one study showing identical cortisol levels as in males. This is consistent with males being less likely to report symptoms, even if they were experiencing them[29,30], and with females having a higher tendency to somatise[34].

Early residency years and younger age were associated with higher stress levels, burnout and associated negative symptoms[17,29-31,35,40-42]. Younger physicians are more likely to have young children, which may explain the increased stress of infecting families. Accordingly, one study found higher perceived stress levels in HCWs with small children[43]. In nurses, the number of children and parenting stress were positively correlated with burnout[44]. Some authors stated that senior residents experienced more stress because of the inability to quickly adapt to a new subject they never learned in medical school[45]. Among nonphysicians, younger HCWs had lower levels of burnout than middle-aged groups[46], although other authors found that more experience comes with less burnout[47].

Single respondents experienced higher burnout than those who were married or in a relationship[36,44]. Respondents with support from family and friends scored lower on stress and burnout[34-36,48], whereas living alone predicted increased stress[49]. We believe that social support could be considered an external resource that alleviates burnout, fitting the Job Demands-Resources (JD-R) burnout model [24].

Health status, coping strategies, resilience

Prior psychiatric conditions were strongly correlated with high levels of burnout and distress[29,48]. Higher levels on the EE and DP subscales were linked with more negative symptoms[28,42], including irritability, change in food habits, insomnia, depression and muscle tension[50]. Similarly, reporting physical symptoms was associated with higher stress levels[51], although this association may be bidirectional[52]. Additionally, an association was found between EE and the perception of needing psychiatric treatment in the future[53].

A positive attitude was strongly protective against stress, whereas avoidance constituted a risk factor [36,49]. Stigma (discrimination, fear of COVID-19) was an important predictor of burnout[33]. Resilience was associated with lower levels of stress, anxiety, fatigue, and sleep disturbances[54], as well as less COVID-19-related anxiety[55], symptoms of posttraumatic stress and depression[42] and burnout[44]. Resilience is a complex coping mechanism in which individuals can function in difficult environments. Focusing on solutions rather than on difficulties puts the individual in a position that favours the development of new skills[56,57].

Table 2 Main features of the studies selected (N = 41)

	N	%		N	%
Publication month (2020)			**Region**		
March	1	2	Asia & Pacific	12	29
April	3	7	Europe	18	44
May	3	7	Global	2	5
June	5	12	Middle east	3	7
July	3	7	North America	4	10
August	15	37	South/Latin America	2	5
September	6	15			
October	5	12	**Population**		
			Physicians	36	88
Type of work			Nurses	27	66
Cross-sectional survey	39	95	Other HCWs	17	41
Longitudinal study	1	2			
Longitudinal cohort study	1	2	**Measuring scale**		
			Validated burnout scale	18	44
			Validated stress scale	18	44

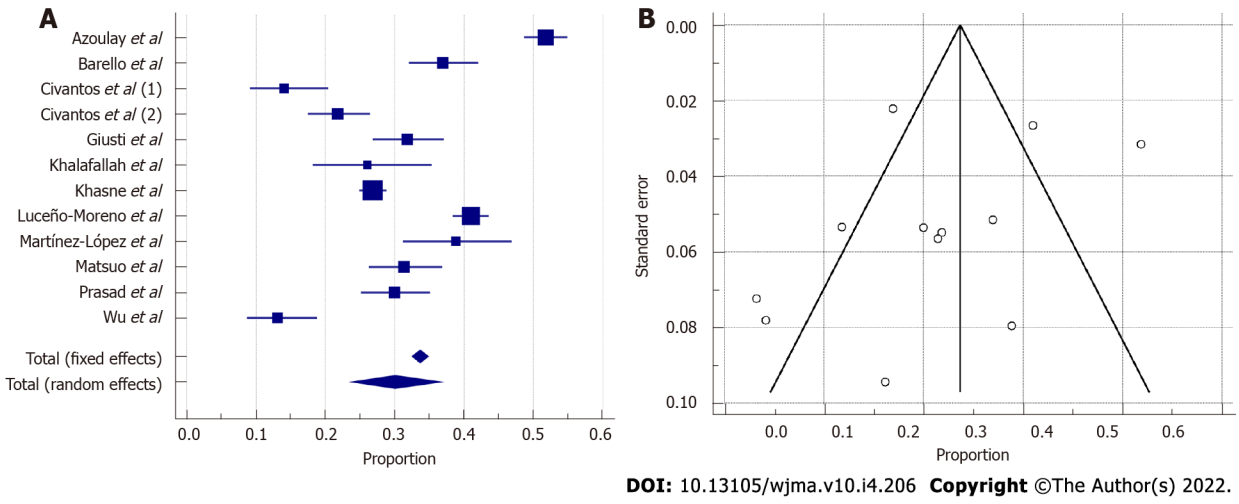

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Figure 2 Studies included in meta-analysis. A: Forest plot of studies; B: Funnel plot of studies.

Occupational role, ward, contact with COVID-19 patients

Several authors reported higher levels of stress or burnout in nurses than in physicians or other HCWs [38,41,43,46,51,58]. Several authors who studied the nurse population highlighted the importance of organizational support, safety guidelines, and PPE as protective from burnout related to anxiety about self-infection or infection of friends and families[32,34,55,59]. Some authors found that nurses had high morale, enthusiasm and empathy, which could partially set off burnout along the DP axis[47]. Despite having similar stress levels to physicians and working in equally difficult situations in terms of the availability of resources, nurses scored higher compassion satisfaction (CS), which protects against burnout[60].

There is an important intersection between nurses and the female population; women accounted for 93.2% among four studies studying only nurses, making female sex an important confounding factor. In many cultures, women are still in charge of the household and the children, often causing a surplus in workload and obligations. The nursing population had to deal with increased workload at work and locked-down children who needed to be fed and protected from infection. Additionally, nurses spending the most time with patients are most vulnerable to the risk of infection if PPE is lacking.

Table 3 Sociodemographic data of the respondents of studies reviewed

	N							%
Region	**Asia & Pacific**	**Europe**	**Middle east**	**North America**	**South/Latin America**	**Multi-country**	**Total**	
Studies	12	18	3	4	2	2	41	
Respondents	12587	9754	1774	1546	512	1734	27907	
%	45.1	35.0	6.4	5.5	1.8	6.2		
Gender[a]								
Female	9775	6590	1176	544	179	342	18606	70.4
Male	2695	3'073	598	339	333	659	7697	29.1
Non-binary/other	37	91	0	1	0	0	129	0.5
Age category[b]								
18-30	5344	1767	430	407	94	397	8439	30.7
31-45	5134	3543	1157	676	249	639	11398	41.5
> 45	2078	4019	187	460	169	699	7612	27.7
Occupational role								
Physician	3308	3780	799	1134	512	1734	11267	40.4
Nurse	7996	4499	552	248	0	0	13295	47.6
Other	1283	1475	423	164	0	0	3345	12.0
Ward[a]								
Front line	5336	2931	860	947	0	1001	11075	44.4
Usual ward	7251	4212	914	252	512	733	13874	55.6
Married/concubine[a]								
Yes	5704	2624	987	92	-	831	10238	66.2
No	3691	1204	149	19	-	170	5233	33.8
Children[a]								
Yes	515	1086	277	185	-	0	2063	48.6
No	905	778	149	352	-	0	2184	51.4
Psychological comorbidities[a]								
Yes	-	45	122	-	18	0	185	9.2
No	-	675	1013	-	145	0	1833	90.8

[a]Not all studies delivered this information.
[b]Some respondents were forced in these categories based on normal distributions.

Interestingly, a few studies found that whether HCWs dealt directly with COVID-19 patients did not correlate with burnout or stress[51,61], possibly because it was counterbalanced by higher CS[62]. For others, the actual duration of interactions with COVID patients was associated with a higher risk of burnout[17,48,61]. In ICUs around the world, direct COVID-19 exposure was not a leading factor for burnout[27]. Some authors found that working with COVID-19 patients increased stress[31,36-38,54,63,64]. Others found the opposite: lower burnout levels in front-line wards (FL) compared to usual wards (UW)[65,66]. The number of positive cases in the country was not associated with burnout or stress[46,67]. Some authors stated that redeployed staff had a higher risk of burnout, possibly related to increased demands, limited resources, and psychological stress of dealing with an unfamiliar disease in an unfamiliar environment[40]. Others found that redeployment had no impact on perceived stress[59]. One study found that surgical residents had a decrease in routine surgical activities along with a decrease in burnout[68].

The predominant theory appears to be that FL workers were subject to less burnout than UW workers. We postulate that FL had more opportunity to exercise competencies and judgement, thereby increasing their sense of control. From the Job Strain-Job Decision model perspective, this put these

workers in active jobs, with higher job satisfaction and actual development of competencies, setting off part of the higher stress (*vs* UW) and generating new behaviour patterns[69]. Accordingly, Dinibutun [70] found a high sense of PA among physicians in FL. We also suggest that FL workers experienced increased attention from hospital management, with more communication and updated policies. FL workers received public and media recognition, increasing their sense of worth, experienced by some as justice, at last. Several burnout models appreciate that recognition and sense of worth act as enhancers of rewards, alleviating high efforts[71,72] as somehow protective from burnout.

In primary care, some authors measured lower levels of psychological distress, possibly explained by the use of telemedicine, alleviating the risk of infection[73]. We believe, however, that unprepared implementation of technological diagnostic tools can also lead to technostress. This is suitably illustrated by a global study amongst dermatologists who started using telemedicine during the COVID-19 pandemic[50].

Organizational and geographic factors

Higher actual or perceived preparedness at the hospital or country level was associated with lower stress or burnout[27,43,50,53,58,59]. Underlying features of preparedness included availability of PPE, training, communication, and protocols; improving these could alleviate perceived stress[58,74,75]. Increased stress and burnout related to preparedness was partially mediated by fear of self-infection and infection of others[32,48,50,52,59]. Increased appreciation and communication from hospital management was correlated with less burnout[74], whereas institutional failure to triage appropriately, or a lack of ethical climate increased stress and burnout[27]. Having been tested for COVID-19 or sufficient and discretionary access to testing for patients seemed protective from burnout[74]. Conversely, having infected relatives could significantly increase stress[34].

Preparedness is a textbook illustration of burnout models in action. The unavailability of resources (such as PPE) to accomplish one's job in the best possible conditions increases disengagement and DP, as postulated in the JD-R model[24,53], increases strain through anxiety of transmitting the virus[69] and decreases resources through social isolation (to avoid transmission)[24]. Lack of institutional communication and protocols are decreased reward components in the Effort-Reward Imbalance model: they create job and institutional uncertainty[71] and might be perceived as unjust by the worker[72].

Burnout prevalence

According to several pre-COVID-19 meta-analyses, burnout prevalence among residents was 35.7%[76] or above 60%[77]. Among nurses, burnout prevalence was between 15% and 28%[78], between 29% and 36%[79] and between 15% and 35%[80]. The pooled prevalence of a 2020 meta-analysis among 1943 emergency physicians was between 35% and 41%[81]. Our own meta-analytic estimate of burnout during the first wave of the COVID-19 pandemic was approximately 30%, *i.e.*, less than most studies pre-COVID-19. We hypothesize that, although HCWs were put under enormous strain during this period, they were also rewarded by a considerable increase in attention and had the opportunity to give actual sense to their profession, albeit in very difficult circumstances. Additionally, we must put this number in perspective, as it is based on very different studies in terms of duration, methodology and geography.

Limitations

The short time span of a pandemic does not necessarily allow for the time and preparation needed to set up a well-structured randomized controlled trial. This may explain the lack of many such studies and their subsequent absence in our review. Cross-sectional studies, in contrast, do not admit explanation by causality. The absence of a control group in cross-sectional studies does not allow us to determine if findings are reflective of the general population or only of considered HCWs.

Responder bias and auto-questionnaires are important limitations of cross-sectional studies. Certain topics, such as a prior history of psychiatric conditions, are particularly at risk of response bias given the possible stigma. Additionally, at the time of the survey, HCWs might not have been interested due to a lack of any personal (mental) health concerns, or conversely, they could have been suffering from a crushing burden of either stress, burnout, or physical symptoms, preventing them from responding to the survey.

Another limitation of this review is that, during this pandemic, we must consider that occupational burnout could have been caused by the interaction between environmental-related (such as workplace-related events) and individual-related factors (such as disruption of work–life balance and personality traits)[81].

Limitations specific to our review and meta-analysis are the heterogeneity of studies in terms of measurement instruments, scales and subscales, and cut-off scores used to determine overall burnout prevalence. There was also geographic diversity and heterogeneity of the populations studied, as our intention was not to focus on one part of the workforce or region but to highlight burnout and its influencing factors in the specific context of the COVID-19 pandemic. As a result, we cannot compare the prevalence of our study with the prevalence found in earlier, pre-COVID-19 studies.

Relevance to clinical practice

It is critical that countries and institutions understand and acknowledge the nature, risk factors and protective factors of stress and burnout in their health care workforce. Awareness lies at the basis of preventive interventions, which can happen both at the individual and institutional levels.

In a pandemic context such as COVID-19, specific interventions could probably yield immediate results, benefiting HCWs and patients in very direct ways. We have highlighted how institutional preparedness has a clear correlation with stress and burnout. PPE, up to date protocols, and regular communication from hospital management are low hanging fruit, as they would both reduce actual infection rates amongst staff and alleviate fear of infection and transmission. Workload and stress about childcare are recurring subjects, and if the former is a challenge during a pandemic, it should be feasible for institutions to help organise childcare for single workers who are more at risk for burnout.

Commonly studied burnout interventions in HCWs are mindfulness, stress management and small-group discussions. The results suggest that these factors could have positive effects on burnout, although more research is needed[82]. A recent mapping by Hilton *et al*[83] of RCTs conducted in health care providers and medical students returned promising results on the use of mindfulness in the workplace but highlighted the need for more definitive evidence of benefits on burnout. Other interventions focus on leadership skills, community and institutional culture, which have been largely studied[84,85].

Where prevention fails, institutions must deal with existing stress and burnout resulting from both ordinary and extraordinary circumstances. Some institutions implemented telephone helplines for HCWs with difficulties coping with grief, death, high workloads, and burnout, the use of which was perceived as useful and appropriate[86,87]. A culture promoting acknowledgement, communication and peer support programs, employee assistance programs and structured health response programs are many other exploration options.

CONCLUSIONS

During the COVID-19 pandemic, HCWs have been under high levels of stress and have suffered considerable burnout, putting quality of care at risk. We reviewed 41 studies and highlighted personal and sociodemographic features strongly associated with higher perceived stress and burnout. Female sex, younger age, low resilience, nurse occupational role and lack of preparedness were associated with higher burnout, but actual COVID-19 exposure was not a leading factor. Prevalence pre-COVID-19 was either lower or in the same ballpark as during COVID-19; our meta-analytic estimate based on 12 studies and approximately 6800 respondents returned a burnout prevalence of 30%, with important geographical variations. Both the individual and macro levels offer opportunities for intervention, as primary and secondary prevention, but the identification of early signs could also inform a reduction in burnout levels in our health care workforce. Further research is needed to evaluate the mid- and long-term impacts of the COVID-19 outbreak on HCWs.

ARTICLE HIGHLIGHTS

Research background

For decades and before the coronavirus disease 2019 (COVID-19) pandemic, for health care workers, (HCWs) burnout can be experienced as an upsetting confrontation with their self and the result of a complex a multifactorial process interacting with environmental and personal features.

Research motivation

During these century previous outbreak, some HCWs isolated themselves out of fear of infecting their friends and families, and lack of training, protection and hospital support was associated with higher burnout.

Research objectives

The objective of this literature review and meta-analysis was to obtain a comprehensive understanding of burnout and work-related stress in health care workers around the world during the first outbreak of the COVID-19 pandemic.

Research methods

We analysed burnout risk factors and protective factors in included studies published from June 1, 2020 to October 10, 2020, studying an HCW population during the first COVID-19 wave. The typical profile of an HCW with high levels of burnout was a young, single, female nurse or resident physician in an institution perceived as poorly prepared for the COVID-19 pandemic. This HCW experienced anxiety

related to infection with COVID-19 or infecting her friends and family and possibly had a history of prior psychiatric conditions and low levels of resilience. Nevertheless, COVID-19 exposure was not a leading factor in burnout, as burnout levels were not notably higher than those before the COVID-19 pandemic. We included original studies published in peer-reviewed journals as of January 2020, studying an HCW population during the first COVID-19 wave without any geographic restrictions

Research results

Through screening, 39 cross-sectional, one longitudinal and one prospective cohort study were retained. Of the 41 studies, all from 2020, 12 were included in the meta-analysis. Table 2 details the main features of the studies. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards (intensive care unit, emergency room and dedicated internal medicine wards). The meta-analytic estimate of burnout prevalence in HCWs was 30.05% (95%CI: 23.91%–36.5%), with a sample size of 6784.

Research conclusions

During the COVID-19 pandemic, HCWs have been under high levels of stress and have suffered considerable burnout, putting quality of care at risk. We reviewed 41 studies and highlighted personal and sociodemographic features strongly associated with higher perceived stress and burnout. Female sex, younger age, low resilience, nurse occupational role and lack of preparedness were associated with higher burnout, but actual COVID-19 exposure was not a leading factor. Prevalence pre-COVID-19 was either lower or in the same ballpark as during COVID-19; our meta-analytic estimate based on 12 studies and approximately 6800 respondents returned a burnout prevalence of 30%, with important geographical variation

Research perspectives

In a pandemic context such as COVID-19, specific interventions could probably yield immediate results, benefiting HCWs and patients in very direct ways. We have highlighted how institutional preparedness has a clear correlation with stress and burnout. PPE, up-to-date protocols and regular communication from hospital management are low hanging fruit, as they would both reduce actual infection rates amongst staff and alleviate fear of infection and transmission. Workload and stress about childcare are recurring subjects, and if the former is a challenge during a pandemic, it should be feasible for institutions to help organize childcare for single workers who are more at risk for burnout. Where prevention fails, institutions must deal with existing stress and burnout resulting from both ordinary and extraordinary circumstances. Some institutions implemented telephone helplines for HCWs with difficulties coping with grief, death, high workloads, and burnout, the use of which was perceived as useful and appropriate. A culture promoting acknowledgement, communication and peer support programs, employee assistance programs and structured health response programs are many other exploration options.

FOOTNOTES

Author contributions: Kimpe V helped to develop the research question, performed the review, and wrote the main part of the manuscript; Sabe M participated in the development of the research question, helped with the meta-analysis strategy and contributed to the writing of the manuscript; Sentissi O developed the research question, oversaw the progress of the review, and contributed to the writing of the manuscript. The authors approved the manuscript.

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META-ANALYSIS

Outcomes of microwave *versus* radiofrequency ablation for hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

BACKGROUND

Studies to date comparing outcomes of microwave ablation (MWA) with radiofrequency ablation (RFA) on patients with hepatocellular carcinoma have yielded conflicting results, with no clear superiority of one technique over the other. The aim of this systematic review and meta-analysis was to compare the efficacy and safety of MWA with RFA.

AIM

To perform a systematic review and meta-analysis comparing the efficacy and safety of MWA with RFA.

METHODS

A systematic literature search was performed using Ovid Medline, Embase, PubMed, Reference Citation Analysis, Cochrane Central and Cochrane Systematic Review databases, and Web of Science. Abstracts and full manuscripts were screened for inclusion utilising predefined inclusion and exclusion criteria comparing outcomes of MWA and RFA. A random-effects model was used for

each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies. Primary outcome measures included complete ablation (CA) rate, local recurrence rate (LRR), survival [local recurrence-free survival (LRFS), overall survival (OS)] and adverse events.

RESULTS

A total of 42 published studies [34 cohort and 8 randomised controlled trials (RCT)] with 6719 patients fulfilled the selection criteria. There was no significant difference in tumour size between the treatment groups. CA rates between MWA and RFA groups were similar in prospective cohort studies [odds ratio (OR) 0.95, 95% confidence interval (CI) 0.28–3.23] and RCTs (OR 1.18, 95%CI 0.64–2.18). However, retrospective studies reported higher rates with MWA (OR 1.29, 95%CI 1.06–1.57). Retrospective cohort studies reported higher OS (OR 1.54, 95%CI 1.15–2.05 and lower LRR (OR 0.67, 95%CI 0.51–0.87). No difference in terms of LRFS or 30-d mortality was observed between both arms. MWA had an increased rate of adverse respiratory events when compared to RFA (OR 1.99, 95%CI 1.07–3.71, $P = 0.03$).

CONCLUSION

MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS compared to RFA. Apart from an increased rate of respiratory events post procedure, MWA is as safe as RFA.

Key Words: Microwave ablation; Radiofrequency ablation; Hepatocellular carcinoma; Survival; Recurrence; Meta-analysis

Core Tip: Studies to date comparing outcomes of microwave ablation with radiofrequency ablation have yielded conflicting results, with no clear superiority of one technique over the other. To our knowledge, this is the most comprehensive study on this topic. A large cohort of 6719 patients were examined, enabling us to identify outliers and provide results with a smaller margin of error. The primary outcomes of this study were complete ablation, local recurrence rate, overall and local recurrence free survival and safety.

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INTRODUCTION

Hepatocellular carcinoma (HCC) now ranks worldwide as the seventh most common cancer and the second leading cause of cancer mortality[1-3] and is rapidly increasing in incidence in several developed regions including North America, Europe, and Australasia[4-6]. Furthermore, an increasing proportion of HCC patients are being diagnosed at an early stage and are eligible for curative therapy[7,8] including local ablation which is considered standard of care for those not suitable for surgery[9-11].

Of the common modalities used to ablate HCC, radiofrequency ablation (RFA) is the most strongly recommended[12]. This is based on evidence from randomised controlled trials (RCTs)[13-16] and three meta-analyses[17-19] showing that RFA provides better local disease control and overall survival (OS) outcomes than percutaneous ethanol injection, particularly among nonsurgical candidates[20]. Recently, microwave ablation (MWA) has become a popular ablative technique because of its reduction in heat-sink effect, ability to produce wider and more predictable ablation volumes that result in high complete ablation rates, and the ability to simultaneously treat multiple and/or larger lesions more effectively and over a shorter procedural time[12,21]. Studies to date comparing outcomes of MWA with RFA have yielded conflicting results, with no clear superiority of one technique over the other[22-24]. A Cochrane review reported that there were insufficient data to recommend RFA over other thermal ablation techniques in the management of HCC[25], with the authors emphasising that only a single small RCT comparing MWA with RFA, with a total of 72 patients, had been performed[23]. Subsequently, a further six RCTs have been performed with the latest meta-analysis only including five RCTs and 21 cohort

studies[26]. In this context, additional evidence, particularly from a comprehensive meta-analysis that incorporated all RCTs, and data from large real-world observational cohort studies would provide clinicians with a better understanding of whether the comparative overall efficacy and safety of MWA over RFA supports the current preferential use of MWA for the treatment of early-stage HCC.

This study was a contemporary systematic review and meta-analysis of RCTs and cohort studies to determine whether MWA is equivalent to or more effective than RFA in relation to the primary treatment endpoints of complete ablation (CA), local recurrence rate (LRR), local recurrence-free survival (LRFS), OS, and safety including adverse events.

MATERIALS AND METHODS

Literature search

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[27] were followed and the Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool[28] was used to perform this study. A systematic electronic search was conducted independently by two authors in the Ovid Medline, Embase, PubMed, Reference Citation Analysis, Cochrane library databases, and Web of Science was performed from the inception of each until the first week of October 2021 inclusive of the database of articles that were accepted but not yet published, as well as the clinicaltrials.gov website to identify relevant articles for our review (Supplementary Tables 1–5). The search strategy used the search terms "radiofrequency ablation", "microwave ablation" and "hepatocellular carcinoma" both as exploded medical subject headings where possible, and as text words. In addition, reference lists of relevant articles including recent reviews, and systematic reviews related to locoregional therapy of HCC were searched. Studies were limited to cohort studies and RCTs using appropriate hedges for each database. A search for unpublished literature was also performed.

Eligibility criteria

Studies were included using the following criteria: (1) Patient age ≥ 18 years; (2) diagnosis of HCC by American Association for the Study of Liver Disease imaging criteria[29] or histopathology; (3) HCC of any size; and (4) no evidence of macrovascular invasion or extrahepatic spread. Studies were excluded based on the following criteria: (1) Case series; (2) studies from the same group that contain overlapping patient populations; (3) treatment with any other modality in conjunction with local ablation therapy with microwave ablation or radiofrequency ablation; (4) non-HCC liver cancer; and (5) Studies where treatment was given as a bridge to liver transplantation.

Study outcomes

The primary outcomes of this study were CA, LRR, LRFS, OS and safety including adverse events and complications. CA was defined in studies as the absence of residual HCC on follow-up imaging postablation. LRR was defined in studies as the development of HCC lesions within the same liver segment as the treated tumour on imaging after CA. LRFS was defined as the proportion of patients alive at various timepoints in the absence of any evidence of local recurrence of HCC after treatment. Included studies had to have reported at least one of the primary endpoints as part of an RCT or observational cohort study.

Selection process

The initial literature search was performed independently by two reviewers (MJT and JL) to identify relevant articles based on the above inclusion and exclusion criteria. Where a difference of opinion occurred on the inclusion of studies for the review, consensus agreement was obtained *via* formal discussion between the two reviewers.

Data collection and bias assessment

Included RCTs were assessed for methodological quality and were classified as being of low, high, or unclear risk of bias according to the Jadad scale[30]. Included cohort studies were quality assessed using the Newcastle–Ottawa Scale[31] where a value ≥ 7 qualified the study as high quality. Data were extracted from the selected studies independently using a data extraction form to collect data on the following: (1) Study details (first author, publication year, journal, country, study design, interventions used, intervention group size); (2) baseline participant characteristics (age, sex, and cirrhosis status); (3) tumour characteristics (tumour stage and staging system, largest nodule size, nodule number, alfafetoprotein level, mean-tumour size); (4) intervention details; and (5) outcome measures: (complete ablation, local recurrence rate, overall and local recurrence free survival, adverse events, 30-d mortality).

Statistical analysis

A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies.

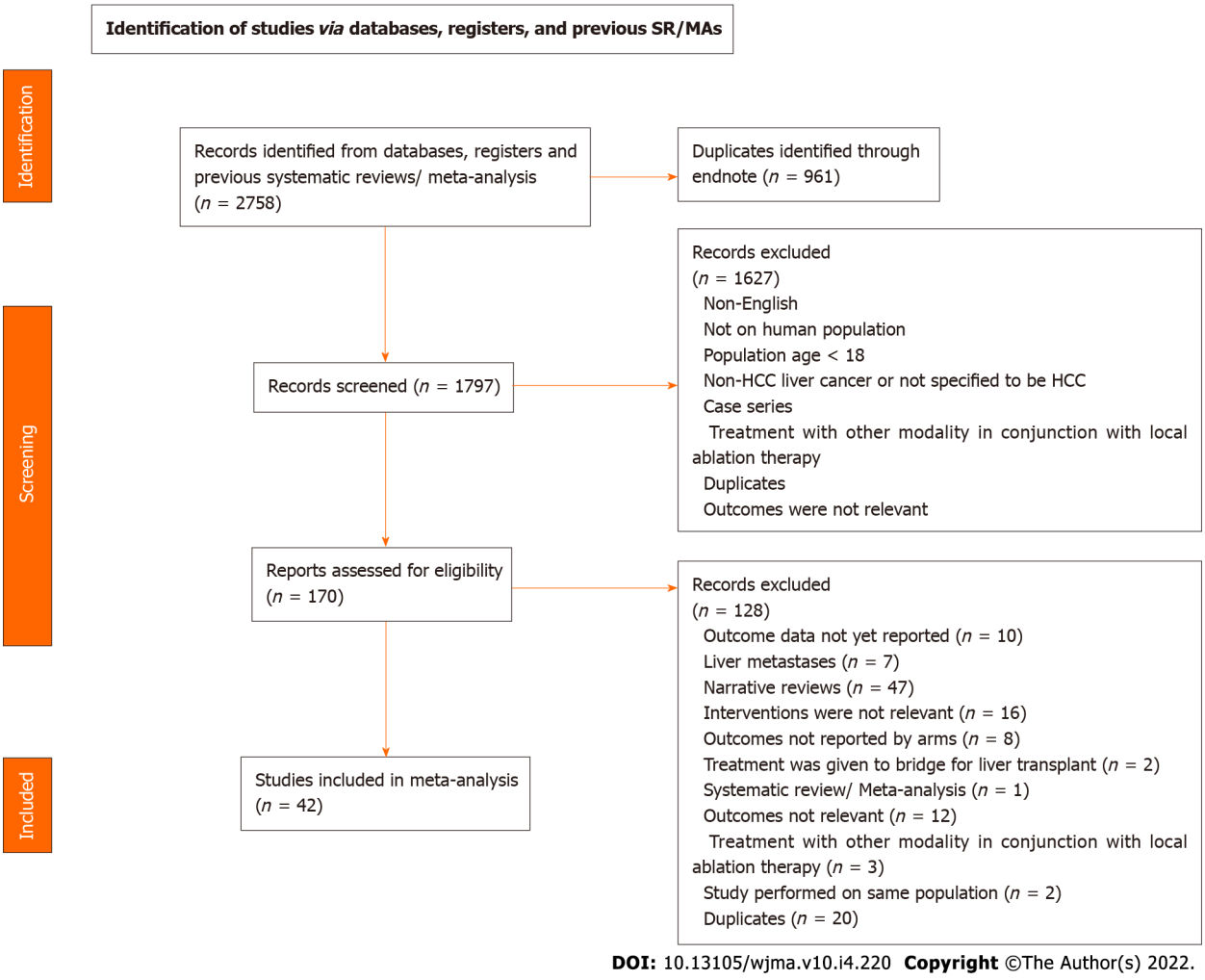

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Figure 1 Flowchart of search strategy and article screening process.

Analysis was also performed individually for RCTs, prospective and retrospective cohort studies. Heterogeneity was assessed using the I^2 statistic with results of 30%–60% (moderate), and > 50% (high) levels of heterogeneity[32]. Outcomes were reported using a pooled odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI). We assessed publication bias using the Egger's regression model only if there were > 10 studies. All analyses were performed with Comprehensive Meta-analysis (version 3.0), Biostat, Englewood, NJ (2014). The statistical methods of this study were reviewed by academic statistician Guy Eslick from Clued Ptd Ltd.

RESULTS

Study selection and characteristics of included studies

As shown in Figure 1, the search strategy utilised for this meta-analysis identified 2758 studies initially. After removing duplicates and excluding studies based on our inclusion and exclusion criteria, 170 studies were assessed for eligibility from which a total of 42 studies, eight RCTs[22,23,33-38] and 34 cohort studies[33,39-71] were finally included in the meta-analysis. The main characteristics of included studies are reported in Table 1. The sample size of included studies (eight RCTs and 34 cohort studies) ranged from 42 to 879, with males forming the majority. In total, we examined a cohort of 6719 patients. A total of 24 studies were conducted in Asia, nine in Europe, five in Egypt, two in the USA, and one each in Australia and Turkey. Study follow-up duration ranged from 3 to 126 mo and was performed through the utilisation of computed tomography or magnetic resonance imaging. Across all studies, the mean age reported was 61 years. Most studies recruited patients with Child–Pugh stage A and B liver disease with only one RCT and nine cohort studies recruiting stage C patients. Notably, all 42 studies were comparable with regards to clinical and tumoral parameters. Maximum nodule sized ranged from 9 to 55 mm in RCTs and 8 to 60 mm in cohort studies. In total, six RCTs and 18 cohort studies reported mean tumour size. There was no significant difference in tumour size treated with MWA compared to

Table 1 Summary of patient characteristics of included randomised controlled trials and cohort studies

Ref.	Design	Country	Year	Arms	NP	Age/yr	% males	NL	Tumour size, mean or median (range or SD)/mm	CPC (A/B/C)	F/U Duration/mo
Abdelaziz *et al* [72], 2014	RCT	Egypt	2009-2011	MWA	66	53.6 (48.6-58.6)	72.7	76	29 (19.3-38.7)	25/41/0	NR
				RFA	45	56.8 (49.5-64.1)	68.9	52	29.5 (19.2-39.8)	24/21/0	
Chong *et al*[34], 2020	RCT	Hong Kong	2011-2017	MWA	47	63 (50–80)	63.8	NR	31 (20–45)	39/7/1	38.3 (2.3–78.0)
				RFA	46	64.5 (42–5)	82.6		28 (20–55)	40/6/0	33.9 (4.9–72.7)
Kamal *et al*[35], 2019	RCT	Egypt	2017	MWA	28	55 (42-80)	75	34	32.5 (23.3-41.7)	22/6/0	12
				RFA	28	55 (42-80)	78.6	34	32.8 (23.7-41.9)	22/6/0	12
Qian *et al*[36], 2012	RCT	China	2009-2010	MWA	22	52 (43–75)	90.9	22	21 (17-25)	22/0/0	5.1 ± 1.3 (2.8-6.5)
				RFA	20	56 (43–76)	95	20	20 (15-25)	20/0/0	5.1 ± 1.3 (2.8-6.5)
Shibata *et al*[23], 2002	RCT	Japan	1999-2000	MWA	36	62.5 (52–74)	66.7	46	22 (9–34)	19/17/0	18 (6-27)
				RFA	36	63.6 (44–83)	72.7	48	23 (10–37)	21/15/0	18 (6-27)
Tian *et al*[37], 2014	RCT	China	2014	MWA	120	NR	NR	86	26 (13-39)	NR	NR
				RFA				79	22 (13-31)		
Vietti *et al*[38], 2018	RCT	France & Switzerland	2011-2015	MWA	76	NR	NR	98	NR	NR	26 (18-29)
				RFA	76			104			25 (18-34)
Yu *et al*[22], 2017	RCT	China	2008-2015	MWA	203	NR	NR	265	27 (7– 50)	NR	35.2 (2.0–81.9)
				RFA	200			251	26 (9–50)		35.2 (2.0–81.9)
Abdel-Samiee *et al*[33], 2020	Retro	Egypt	2020	MWA	50	NR	NR	NR	NR	NR	36
				RFA	50						36
Bouda *et al*[39], 2020	Retro	France	2008-2016	MWA	79	62.8 (52.4-73.2)	81	99	21.3 (13-29.6)	71/8/0	34 (3–65)
				RFA	43	62.2 (50.3-74.1)	76.7	52	23.0 (14.9-31.1)	39/4/0	40 (5–126)
Chinnaratha *et al* [40], 2014	Retro	Australia	2006-2012	MWA	101	62.1 (51.7-72.5)	98	NR	21.1 (10.9-31.3)	92/23/2	36
				RFA	25	62.1 (51.7-72.5)	98		21.1 (10.9-31.3)		36
Cillo *et al*[41], 2014	Pros/Retro	Italy	2004-2010	MWA	42	64 (47–81)	83	50	NR		24
				RFA	100	63 (34–81)	83	NR			24
Ciruolo *et al*[42], 2020	Retro	Italy	2013-2019	MWA	NR	64	71.7	78	NR	NR	NR
				RFA				172			

Ding *et al*[43], 2013	Retro	China	2006-2010	MWA	113	59.06 (30–86)	75.2	131	25.5 (8–50)	75/38/0	18.3 (3–51.4)
				RFA	85	58.64 (40–77)	80	98	23.8 (10–48)	49/36/0	27.7 (4–60)
Du *et al*[44], 2020	Retro	China	2014-2016	MWA	218	56.3 (46.3-66.3)	80	136	24 (13-35)	107/8/0	28 (15-51)
				RFA	234	57.5 (48-67)	76.5	137	26 (15-37)	105/10/0	
Gaia *et al*[45], 2021	Retro	Italy	2013-2019	MWA	81	67 (57–73)	76.5	77	29 (20–35)	71/10/0	20.4 (10.8-38.4)
				RFA	170	63 (56–72)	69.4	169	20 (15–25)	148/22/0	34.8 (19.2–51.6)
Ghweil *et al*[46], 2019	Pros	Egypt	2019	MWA	25	NR	NR	NR	NR	NR	NR
				RFA	30						
Iida *et al*[47], 2013	Retro	Japan	2001-2012	MWA	40	70.1 (63.5-76.7)	NR	NR	20 (11-29)	NR	NR
				RFA	18	73.5 (69.5-77.5)			21 (16-26)		
Ding *et al*[48], 2013	Retro	China	2002-2011	MWA	556	58.4 (48.1-68.7)	74.8	1090	23 (12-34)	466/167/22	(6-75)
				RFA	323	58 (47.8-68.3)	79.8	562	22.8 (11.7-33.9)	248/106/22	(6-75)
Kuang *et al*[49], 2011	Pros	China	1997-2008	MWA	19	55 (27-74)	94	NR	NR	77/4 /0	45 (24-155)
				RFA	31						
Kumbar *et al*[50], 2018	Retro	India	2018	MWA	25	(40-85)	92	33	NR	13/8/4	15
				RFA	25		88	35		17/8/0	
Lee *et al*[51], 2017	Retro	Hong Kong	2003-2011	MWA	26	62.5 (49-79)	73.1	28	37.5 (20-60)	23/3/0	47.5 (11.3-62.5)
				RFA	47	58 (43-77)	85.1	52	31 (20-60)	42/5/0	52.9 (3.6-121.8)
Liu *et al*[52], 2018	Retro	China	2002-2017	MWA	126	54 (45, 60)	90.5	162	22.5 (17, 29)	NR	36.8 (1-115)
				RFA	436	56 (46, 65)	89.7	482	23.0 (18, 30)		34.1 (1-171)
Loriaud *et al*[53], 2018	Retro	France & Switzerland	2007-2015	MWA	NR	69 (61–75)	92.5	40	22.5 (10–47)	40/0/0	28 (10-46)
				RFA		67 (58-74)	85.8	120	21.3 (10-46)	111/9/0	
Lu *et al*[54], 2005	Retro	China	1997-2002	MWA	49	50.1 (24–74)	89.8	98	25 (9–72)	22/27/0	25.1 (2.0–50.6)
				RFA	53	54.5 (20–74)	81.1	72	26 (10–61)	47/6/0	24.8 (2.0–51.0)
Mocan *et al*[55], 2017	Retro	Romania	2010-2016	MWA	NR	NR	NR	22	NR	NR	12 (5.6-18.4)
				RFA				79			22.8 (7.8-37.4)
Nocerino *et al* [56], 2016	Retro	Italy	2016	MWA	106	NR	NR	134	20.4 (11-37)	NR	12 (5.6-18.4)
				RFA	27			35	20.1 (7-34)		22.8 (7.8-37.4)
Ohmoto *et al*[57], 2008	Retro	Japan	2002-2006	MWA	49	64 (38–75)	83.7	56	17 (8–20)	31/14/4	33.5 (9.8-57.2)

				RFA	34	67 (44–78)	73.5	37	16 (7–20)	20/11/3	25.9 (14.6-37.2)
Potretzke *et al* [58], 2016	Retro	US	2001-2013	MWA	99	61 (44–82)	81.8	136	22 (20–23)	NR	24
				RFA	55	62 (23–88)	72.7	69	24 (22–26)		31
Sakaguchi *et al* [59], 2009	Pros	Japan	2009	MWA	142	NR	NR	NR	NR	NR	NR
				RFA	249						
Santambrogio *et al*[60], 2017	Retro	Italy	2009-2015	MWA	60	70 (61.7-78.3)	72	NR	21.5 (16.2-26.8)	60/0/0	31 (15–46)
				RFA	94	69 (60-78)	73		19.2 (14.2-24.2)	94/0/0	
Sever *et al*[61], 2018	Retro	Turkey	2012-2015	MWA	20	63.6 (57.3-69.9)	65	37	28 (18-38)	14/4/2	12 (1-40)
				RFA	20	64.3 (55.3-73.3)	70	34	24 (13-35)	11/4/5	
Shum *et al*[62], 2016	Retro	Hong Kong	2014-2015	MWA	22	NR	NR	NR	NR	NR	19
				RFA	44						18
Simo *et al*[63], 2011	Retro	US	2006-2008	MWA	13	59.6 (49–72)	54	15	23.1 (14–39)	12/7/3	7 (2.5–10.5)
				RFA	22	58 (45–79)	86	27	25.3 (12–44)	7/6/0	19 (1.5–31)
Suwa *et al*[64], 2021	Retro	Japan	2014-2020	MWA	72	74.9 (66.5-83.3)	65.3	NR	17.7 (10.9-24.5)	58/14/0	12
				RFA	72	74.4 (65.2-83.6)	68.1	NR	17.6 (11.3-23.9)	61/11/0	37.8
Suwa *et al*[65], 2020	Retro	Japan	2016-2019	MWA	44	73.4 (65.7-81.1)	68	52	17.2 (12.3-22.1)	12/3/29	NR
				RFA	55	73.4 (65.7-81.1)	80	70	17.7 (11.3-24.1)	16/8/31	
Vogl *et al*[66], 2015	Retro	Egypt	2008-2010	MWA	28	60 (45-68)	82.1	32	36 (9-50)	NR	NR
				RFA	25	57 (40-64)	76	36	32 (8-45)		
Xu *et al*[67], 2004	Retro	China	1997-2001	MWA	54	53.4 (24–74)	86.6	112	25 (15-36)	53/33/11	27.4 (2–53)
				RFA	43			78	26 (12-40)		
Xu *et al*[68], 2017	Retro	China	2007-2012	MWA	301	54.2 (43.2-65.2)	78.1	NR	17 (14-20)	278/23/0	53 (8–98)
				RFA	159	54.0 (43-65)	83		17 (14-20)	140/19/0	62 (6–102)
Yin *et al*[69], 2009	Retro	China	1997-2007	MWA	49	53 (41-65)	87.2	NR	39 (31-47)	NR	22 (2.2-93.5)
				RFA	59						
Zhang *et al*[70], 2013	Retro	China	2006	MWA	77	54 (26–76)	70.2	105	NR	77/0/0	24.5 (6–64)
				RFA	78	54 (30–80)	82.1	93		78/0/0	26.3 (7–65.6)
Zhang *et al*[71], 2014	Pros	China	2014	MWA	45	NR	NR	60	NR	NR	NR

RFA	56		68

CPC: Child Pugh Score; MWA: Microwave ablation; NP: Number of patients; NL: Number of lesions, NR: Not reported; RFA: Radiofrequency ablation.

RFA in both RCTs (OR 1.13, 95%CI 0.88–1.46) and cohort studies (OR 0.96, 95%CI 0.77–1.20) (Supplementary Figure 1). Furthermore, there was no significant difference in mean tumour size amongst RCTs (OR 0.05, 95%CI -0.07 to 0.18; P = 0.395) and cohort studies (OR -0.01, 95%CI -0.09 to 0.07; P = 0.777) (Supplementary Figure 2). The total number of lesions treated per study with MWA and RFA ranged from 15 to 1090 and 20 to 562, respectively.

Quality assessment

Seven of the eight RCTs assessed were deemed to be high quality with one study[22] deemed to be of low quality (Supplementary Table 6). All RCTs were determined to be at high risk of performance bias as it was not practical to blind the administrator to the procedure. However, four RCTs[23,34,37,38] were able to blind the outcome of assessment. Potential for selection and detection bias was identified in four RCTs[22,35,36,72]. Of the 34 cohort studies identified, 30 scored a value of 7 or higher, meeting the definition of a high-quality study (Supplementary Table 7).

CA

Seven RCTs[22,23,34-37,72] and 24 cohort studies[39,42-46,48-51,54,55,60-71] reported data on CA post-treatment. No significant difference in the CA rate was found between the MWA and RFA groups in the prospective cohort studies (OR 0.95, 95%CI 0.28–3.23; P = 0.82)[41,46,49,59,71] and RCTs (OR 1.18, 95%CI 0.64–2.18; P = 0.60)[22,23,34-37,72]. However, retrospective cohort studies reported higher CA rates with MWA compared to RFA (OR 1.29, 95%CI 1.06–1.57; P = 0.01) (Figure 2A)[39,42-45,48,50,51,54,55,60-70]. No evidence of heterogeneity was found in these studies (P = 0.99). Funnel plot analysis concluded that publication bias was unlikely (Figure 2B).

OS

Five RCTs[22,34,35,38,72] and 17 cohort studies[33,41,43,47,51,52,54,57,59-63,66,68,70,71] reported data on OS post-ablation (Table 2). Heterogeneity was identified in the results reported at 3 and 4 years by retrospective cohort studies (Table 2)[33,43,51,52,54,57,66,68,70]. In studies that categorised data into OS into specific years, no significant difference in OS was noted between MWA and RFA groups. Meta-analysis of four retrospective studies that did not specify the follow-up period[52,54,59,63] reported significantly higher OS in patients treated with MWA. No potential bias was identified during visual assessment and Egger's test of funnel plot.

Individual study OS rates were plotted on a dot graph for both MWA and RFA treated subjects (Figure 3) with median OS rates according to year of follow-up post-treatment shown in Table 3. Of note, MWA was associated with improved median OS at 3 and 4 years of follow-up but this difference was lost at 5 years.

LRR

Six RCTs[22,23,35,36,38,72] and 26 cohort studies[39-41,43,44,46,47,49,51-58,60,61,63-70] reported data regarding LRR following ablation (Table 2). One RCT[22] reported lower 5-year LRR when patients were treated with MWA (OR 0.52, 95%CI 0.30–0.91; P = 0.023). Heterogeneity was identified in the results reported at 1, 2 and 3 years by retrospective cohort studies while meta-analysis of two retrospective cohort studies[53,57] reported a higher 4-year LRR in patients treated with MWA (OR 2.14, 95%CI 1.12–4.07, P = 0.021) (Table 2). However, meta-analysis of 20 retrospective cohort studies that reported LRR over an unspecified period[39-41,43,44,46,52-54,56-58,60,63,65-70] concluded that LRR was significantly lower in patients treated with MWA (OR 0.67, 95%CI 0.51–0.87, P = 0.002). Three cohort studies reported LRR according to tumour size ≤ 3 cm[43,52,54] with no statistcally significant differences identified between the MWA and RFA groups (OR 0.86, 95%CI 0.45–1.64, P = 0.64). No potential bias was identified during visual assessment and Egger's test of funnel plot.

HR for OS and LRR

Four RCTs[22,34,38,72] and 18 cohort studies[39,41,43-45,51-53,57-61,64,66,68,70] reported HR data regarding OS (Table 4). No significant differences were noted in OS between both arms. However, there was a trend towards better OS rates in patients treated with MWA in both RCTs (P = 0.08) and prospective cohort studies (P = 0.08) over an unspecified period (Table 4). Five retrospective cohort studies reported HR data regarding LRR[39,53,58,61,64]. No significant differences were noted in LRR between both arms. No potential bias was identified during visual assessment and Egger's test of funnel plot.

Table 2 Summary of the comparison of OS and local recurrence rates between microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular lesions in both cohort studies and RCTs according to year of follow-up

Endpoint	Study design	No. of studies	OR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Overall survival – OR							
1Y	Prospective	1	3.00	0.33-27.48	0.331	-	-
	Retrospective	11	1.19	0.71-1.99	0.513	0	0.72
	RCT	4	1.95	0.71-5.34	0.194	35.5	0.20
2Y	Retrospective	7	1.27	0.75-2.18	0.377	36.6	0.15
	RCT	1	1.84	0.54-6.28	0.333	-	-
3Y	Prospective	1	1.69	0.59-4.81	0.328	-	-
	Retrospective	9	1.14	0.75-1.73	0.554	58.1	0.01
	RCT	2	0.98	0.62-1.54	0.929	0	0.62
4Y	Retrospective	5	0.77	0.46-1.29	0.323	60.8	0.04
5Y	Prospective	2	1.49	0.31-7.22	0.620	71.2	0.06
	Retrospective	5	0.86	0.62-1.19	0.357	34.8	0.19
	RCT	2	0.79	0.50-1.15	0.197	0	0.76
Unspecified	Retrospective	4	1.54	1.15-2.05	0.004	0	0.50
	RCT	2	1.47	0.73-2.96	0.282	0	0.50
Local recurrence rate – OR							
1Y	Retrospective	4	0.78	0.29-2.11	0.619	62.8	0.04
	RCT	3	1.09	0.39-3.05	0.872	0	0.40
2Y	Retrospective	4	1.00	0.40-2.45	0.992	76.2	0.06
	RCT	2	1.02	0.23-4.58	0.975	70.4	0.07
3Y	Retrospective	2	0.80	0.11-5.97	0.826	84.8	0.01
	RCT	1	0.73	0.30-1.8	0.493	-	-
4Y	Retrospective	2	2.14	1.12-4.07	0.021	0	0.86
5Y	Prospective	1	2.22	0.49-10.02	0.301	-	-
	RCT	1	0.52	0.30-0.91	0.023	-	-
Unspecified	Prospective	3	0.60	0.25-1.39	0.233	0	0.44
	Retrospective	20	0.67	0.51-0.87	0.002	37.2	0.05
		1	0.26	0.06-1.07	0.063	-	-

OS: Overall survival; OR: Odds ratio; CI: Confidence interval; RCT: Randomised controlled trial.

LRFS

One RCT[35] reported that there was no significant difference between MWA and RFA with regards to 1-year LRFS (OR 1.175, 95%CI 0.178–7.737, $P = 0.93$). One cohort study[63] reported that there was no significant difference between MWA and RFA with regards to LRFS (OR 0.53, 95%CI 0.148–1.86).

Safety

Three RCTs[34,35,38] and 14 cohort studies[33,39,47,48,51,58,60,62-64,67-70] reported data regarding 30-d mortality (Figure 4). No significant differences were identified between the MWA and RFA groups in both RCTs (OR 1.00, 95%CI 0.19–5.14, $P = 1.0$) and cohort studies (OR 0.67, 95%CI 0.27–1.68, $P = 0.39$). There was no heterogeneity identified between studies. A sensitivity analysis excluding studies that reported no deaths in both arms was performed (Figure 4), but results remained consistent with the main analysis (OR 0.61, 95%CI 0.25–1.51, $P = 0.29$). No potential bias was identified during visual assessment and Egger's test of funnel plot.

Table 3 Summary of the comparison of median and mean overall survival rates between microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions in both cohort studies and randomised controlled trials

Year	MWA sample size	RFA sample size	Median OS		*P* value
			MWA	RFA	
1	1135	1623	96.2%	95.4%	0.31
2	651	789	90.7%	88.0%	0.10
3	1004	1480	80.5%	75.3%	0.002
4	421	464	76.8%	70.0%	0.02
5	764	1221	67.3%	69.5%	0.30

OS: Overall survival; MWA: Microwave ablation; RFA: Radiofrequency ablation.

Table 4 Summary of overall survival and local recurrence rate HRs

Endpoint	Study design	No. of studies	HR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Overall survival – HR							
Univariate	Retrospective	2	1.17	0.75-1.83	0.497	17.5	0.27
Multivariate	Retrospective	3	1.32	0.92-1.89	0.130	0.8	0.36
Unspecified	Prospective	1	1.45	0.96-2.19	0.078	-	-
	Retrospective	13	1.06	0.86-1.32	0.580	58.6	0.004
	RCT	4	1.34	0.97-1.86	0.079	0	0.58
Local recurrence rate – HR							
Univariate	Retrospective	3	1.77	0.81-3.88	0.151	63.9	0.06
Multivariate	Retrospective	2	1.88	0.79-4.47	0.151	56.1	0.13
Cox proportional	Retrospective	1	2.17	1.04-4.50	0.040	-	-
Fine and gray	Retrospective	1	2.07	0.95-4.26	0.070	-	-
Unspecified	Retrospective	1	2.00	0.50-8.00	0.326	-	-

HR: Hazard ratio; CI: Confidence interval; RCT: Randomised controlled trial.

Table 5 Microwave ablation *versus* radiofrequency ablation for hepatocellular lesions: Meta-analysis of adverse events

Adverse event	No. of studies	OR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Liver-related morbidity	11	1.51	0.64-3.55	0.342	0	0.91
Postprocedural infections	19	1.3	0.85-1.97	0.222	0	0.83
Postprocedural bleeding	10	2.36	0.92-6.07	0.075	0	0.97
Bile duct injury	5	1.88	0.57-6.23	0.299	0	0.99
Respiratory events	14	1.99	1.07-3.71	0.03	0	0.87
Local events	4	1.62	0.49-5.36	0.426	0	0.57

Liver related morbidity: Decompensation, jaundice, infarction, and portal vein thrombosis; Post-procedural infections: General, peritonitis, and liver abscess. Local events: Burns, pain, and wound complication; Respiratory events: Pleural effusion and pneumothorax. OR: Odds ratio; CI: Confidence interval.

With regard to morbidity, five RCTs[23,35,36,38,72] and 20 cohort studies[33,39,43,44,47-49,51,52,54,57,58,60,61,63-66,68,70] reported data on adverse events (Table 5). There were no significant differences in rates of liver-related morbidity, postprocedural bleeding and infections, local events, and bile duct injury when comparing the two interventions. MWA had a significantly increased rate of adverse

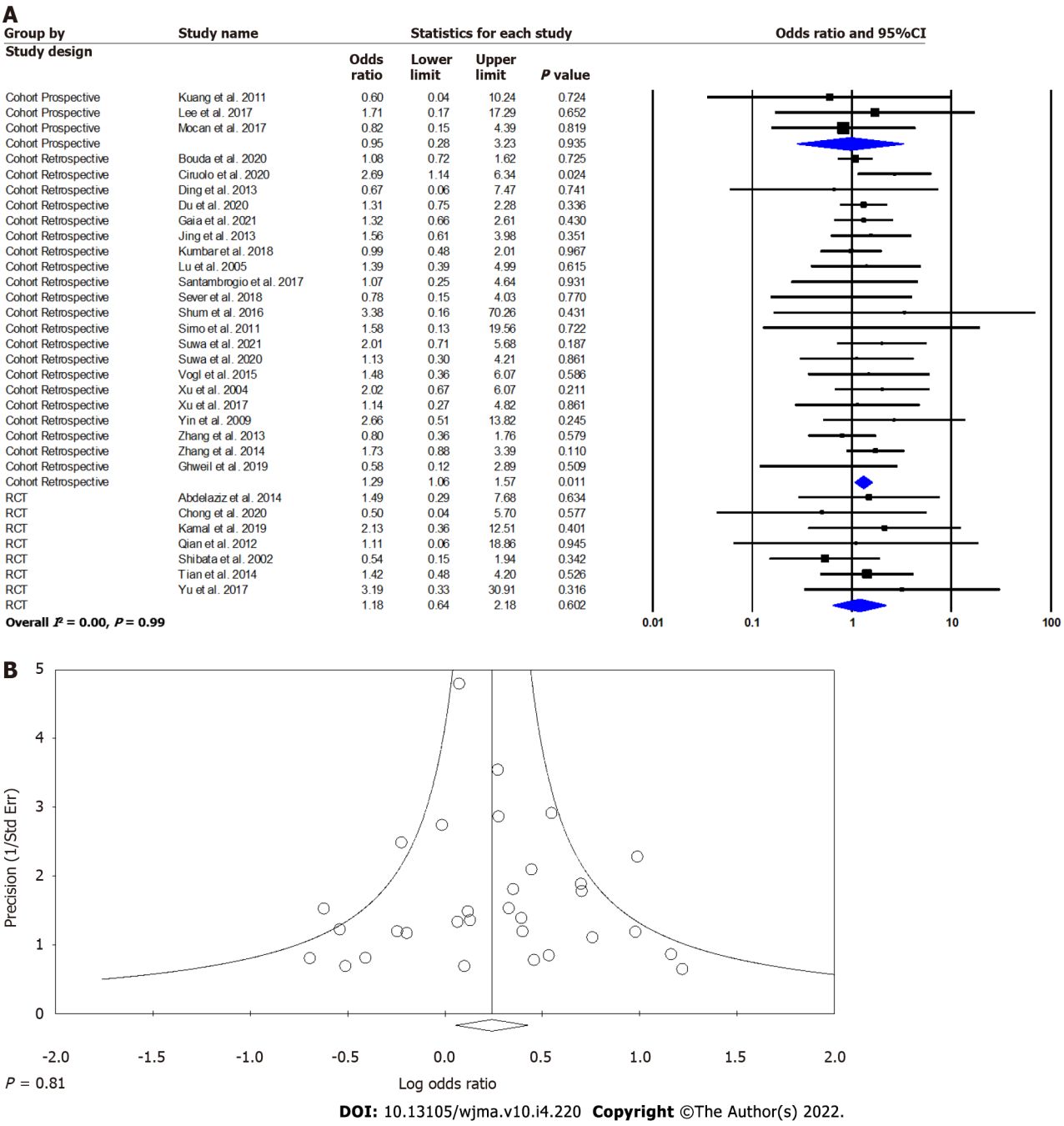

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Figure 2 Forest plot and funnel plot. A: Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions. Forest plot for complete ablation; B: Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions: Funnel plot for publication bias.

respiratory events when compared to RFA (OR 1.99, 95%CI 1.07–3.71, P = 0.03). No potential bias was identified during visual assessment and Egger's test of funnel plot.

DISCUSSION

Local thermal ablation is the standard of care for patients with unresectable early-stage HCC. MWA is increasingly preferred to RFA because of its ability to produce wider and more predictable ablation volumes over a shorter procedural time[17,19,22]. Moreover, MWA has theoretical advantages including minimising heat-sink effect that limits the use of RFA to lesions with proximity to adjacent structures. To our knowledge, our study is the most detailed systematic review and meta-analysis to date having identified 42 studies including eight RCT's and 34 cohort studies involving a total of 6719 subjects, that compared the outcomes of the two treatment modalities. Our main findings were that MWA achieves similar complete ablation rates compared with RFA, as well as lower LRR and similar OS. However, adverse events associated with MWA appear higher, particularly in relation to proc-

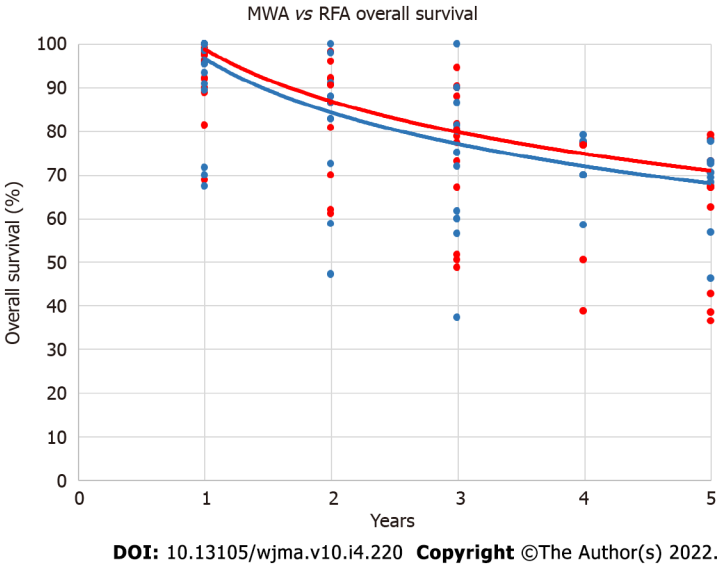

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Figure 3 Dot plot of microwave ablation *versus* radiofrequency ablation overall survival rates over time. Trendlines are based on median survival. Microwave ablation is represented by red dots and red trendline while radiofrequency ablation is represented by blue dots and blue trendline. MWA: Microwave ablation; RFA: Radiofrequency ablation.

edure-related respiratory events.

In our study, we found MWA achieved similar or better CA rates than RFA depending on the study design. Notably CA rates were similar between the two modalities among RCTs, as previously reported [73,74], as well as among prospective cohort studies. However, higher CA rates were associated with MWA among retrospective cohort studies, which was likely due to multiple factors including patient selection, tumour size and the technique used; notwithstanding the fact that nearly threefold more cohort studies were captured in our study compared to other smaller meta-analyses of this type[24,40,73]. These findings align with preclinical data that MWA results in higher intratumoral temperature and greater ablation range[75], that should in theory lead to faster ablation times and high rates of CA[76].

In addition, we identified MWA utilisation was overall associated with similar rates of local recurrence to RFA among RCTs and prospective cohort studies. However lower recurrence rates with MWA were reported among retrospective cohort studies, although results were inconsistent with two retrospective cohort studies reporting lower rates of local recurrence with RFA at the 4-year mark, while one RCT reported lower rates of LRR with MWA at the 5-year mark[22,53,54]. Moreover, because this was an analysis of LRR data without a specific timeframe, caution should be exercised as the follow-up for individual studies varied. Potential reasons for discordance in results include the fact that different generators were among studies as well as variation in the reporting outcomes with some studies reporting cumulative LRR. Notably, previous meta-analyses evaluating MWA and LRR have also drawn different conclusions, with two reports concluding that MWA resulted in significantly lower LRR [73,77], while a more recent study found no difference between both interventions[74]. These data combined with ours point to the fact that LRRs following MWA of HCC are at least as good as that following RFA.

An important finding from our study was the identification that MWA appears to lead to better OS, particularly among retrospective cohort studies. However, because this was mainly among studies with no specified follow-up period, we were unable to determine the timeframe to which the improvement in OS applies. Still, median OS rates tend to favour MWA particularly within the first few years postablation. Previous meta-analyses found that up until the 5-year mark, there was no difference between OS rates[24,40,73,74,77]. Except for Huo and colleagues[24]], these meta-analysis did not look at yearly OS. Long-term OS could be affected by interventional factors such as frequency, duration, and power of the ablative machines used. Furthermore, patient factors such as age, pre-existing liver disease and severity, and socioeconomic status could all contribute to OS. As we were unable to account for all these potentially confounding factors, it raises the question whether our results can be applied to the clinical setting with certainty.

In relation to adverse events, previous meta-analyses have concluded that there was no difference in complication rates between both interventions[24,73,74]. In our study, we identified a significantly increased rate of adverse respiratory events (*i.e.*, pleural effusion and pneumothorax) associated with MWA in 14 studies but no significant differences in local and/or liver related complications. This novel finding could influence the current perception that MWA has a similar safety profile to that of RFA despite the larger ablation zone. One possible explanation of the presence of pleural effusions could be due to thermal injury to the diaphragm resulting in an inflammatory response and/or diaphragmatic

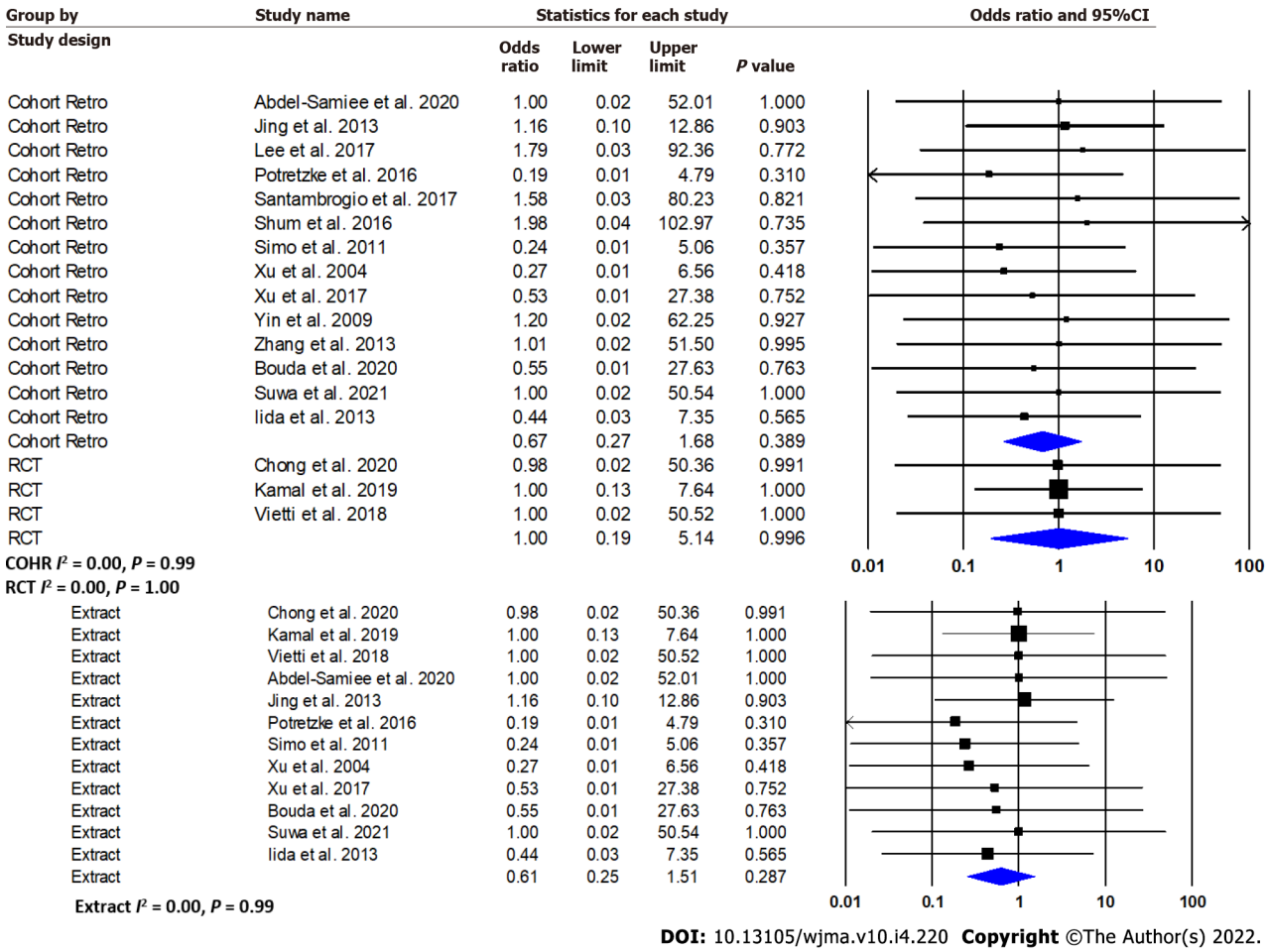

Figure 4 Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions: Forest plot for 30-d mortality.

microperforations resulting in leakage of fluid from the peritoneal cavity to the pleural space. Similarly, the increased rates of pneumothorax could reflect inadvertent pleural puncture with subsequent air leakage into the pleural space. Ultimately, this novel safety finding adds a layer of complexity when making the decision to choose between MWA or RFA for ablating HCC.

The strengths of our study included it being, to our knowledge, the most comprehensive study on this topic to date. We examined a large cohort of 6719 patients that enabled us to identify outliers and provide results with a smaller margin of error. In addition, data were categorised based on follow-up period, allowing us to identify if the difference between our primary outcomes for each individual year was significant. Finally, an analysis of tumour size was performed ruling out a potential confounding factor. Nevertheless, our findings should be interpreted with caution in view of certain limitations. Firstly, only studies published in English were included, which could lead to selection bias. Secondly, we did not explore the influence of generators and antennas used to perform the procedures which could present as a confounding factor. Furthermore, although we had a significant number of RCTs, the majority of studies were retrospective cohort studies that are susceptible to both selection bias and information bias due to the difficulty in achieving accurate record keeping and recounts of events, as well as complete data retrieval. Conference abstracts were included in our study which allowed for a more comprehensive look at the subject matter but potentially at the cost of preliminary results. Also, a significant number of studies included were conducted by a single centre, and hence subject to patient selection bias. Moreover, eligibility criteria for inclusion of patients were not standardized among studies.

CONCLUSION

Our results suggest that compared to RFA, MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS. Our analysis of tumour size suggests that it is unlikely to affect our conclusion. Apart from an increased likelihood of postprocedural respiratory events, MWA is as safe as RFA. Current guidelines recommend RFA to bridge transplantation or in early HCC[10,78].

Our novel results suggest that all guidelines should consider these ablative techniques as being interchangeable as standard of care.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the seventh most common cancer and second leading cause of cancer mortality. Of the common modalities used to ablate HCC, radiofrequency ablation (RFA) is the most strongly recommended. Recently, microwave ablation (MWA) has become a popular ablative technique because of its reduction in heat-sink effect, ability to produce wider and more predictable ablation volumes.

Research motivation

Studies to date comparing outcomes of MWA with RFA have yielded conflicting results, with no clear superiority of one technique over the other. In this context, additional evidence particularly from a comprehensive meta-analysis that incorporate all RCTs and data from large real-world observational cohort studies would provide clinicians with a better understanding.

Research objectives

This study was a contemporary systematic review and meta-analysis of RCTs and cohort studies to determine whether MWA is equivalent to or more effective than RFA in relation to the primary treatment endpoints of complete ablation (CA), local recurrence rate (LRR), local recurrence-free survival, overall survival (OS), and safety including adverse events.

Research methods

A systematic electronic search was conducted independently by two authors. Quality of included studies were assessed using the Jadad scale for RCTs and Newcastle–Ottawa Scale for cohort studies. A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies.

Research results

A total of 42 studies, eight RCTs and 34 cohort studies were included in the meta-analysis, allowing us to examine a total cohort of 6719 patients. CA rates between MWA and RFA groups were similar in prospective cohort and RCTs; however, retrospective studies reported higher rates with MWA. Retrospective cohort studies reported higher OS and lower LRR. MWA had an increased rate of adverse respiratory events when compared to RFA.

Research conclusions

MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS compared to RFA. Apart from an increased rate of respiratory events post procedure, MWA is as safe as RFA.

Research perspectives

Current literature on local recurrence free survival is lacking and has potential to be explored in future studies.

FOOTNOTES

Author contributions: Tang MJ performed the systematic review, acquisition and interpretation of the data, drafting the article, and final approval; Eslick GD performed the statistical analysis and interpretation of the data, drafting the article, and final approval; Lubel JS performed the systematic review, acquisition and interpretation of the data, drafting the article, and final approval; Majeed A performed interpretation of the data, review of the article, and final approval; Majumdar A contributed to the study design, interpretation of the data, review of the article, and final approval; Kemp W contributed to study concept and design, interpretation of the data, drafting and review of the article, and final approval; Roberts SK contributed to study concept and design, interpretation of the data, drafting and review of the article, and final approval.

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EDITORIAL

Maintaining the metabolic homeostasis of *Helicobacter pylori* through chronic hyperglycemia in diabetes mellitus: A hypothesis

Vasiliy Ivanovich Reshetnyak, Igor Veniaminovich Maev

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Abstract

Helicobacter pylori (H. pylori) infection occurs in almost half of the world's population, most of whom are merely carriers of this microorganism. *H. pylori* is shown to be detected more frequently in patients with diabetes mellitus (DM) than in the general population, which is accompanied by a significantly increased risk of developing *H. pylori*-associated diseases. In addition, eradication therapy shows a low efficiency for *H. pylori* infection in patients with DM. There is a relationship between the level of chronic hyperglycemia and a higher detection rate of *H. pylori* as well as a lower efficiency of eradication therapy in patients with DM. The exact mechanisms of these phenomena are unknown. The authors make a hypothesis that explains the relationship between chronic hyperglycemia and the increased detection rate of *H. pylori*, as well as the mechanisms contributing to the improved survival of this bacterium in patients with DM during eradication therapy.

Key Words: *Helicobacter pylori*; Diabetes mellitus; Glycated hemoglobin A; *H. pylori* eradication; Amino acids and glucose as nutrients for *H. pylori*

Core Tip: The authors hypothesize that in patients with diabetes mellitus (DM), *Helicobacter pylori* (*H. pylori*) are most likely to rely on both amino acids and glucose for its vital activity. The hypothesis makes it possible to explain the high detection rate of *H. pylori* in patients with DM, as well as the lower efficiency of eradication therapy in them.

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INTRODUCTION

Forty years have passed since the description of *Helicobacter pylori* (*H. pylori*) as a pathogen in the development of atrophic gastritis and peptic ulcer disease[1-3]. It has been shown that *H. pylori* infection occurs in almost half of the population in the world, most of whom are merely carriers of this microorganism[4,5]. In addition, many researchers have indicated that *H. pylori* are detected more frequently in patients with diabetes mellitus (DM) than in the general population[6-11]. This is accompanied by a substantial increase in the risk of developing *H. pylori*-associated diseases[6,11,12]. At the same time, there are studies which report reverse results about the incidence of type 2 DM (T2DM) in *H. pylori*-positive patients[13-15]. However, the relationship between *H. pylori* infection and the risk of developing T2DM remains controversial and ambiguous. Hence, a prospective cohort study by Jeon *et al*[16] has shown that *H. pylori* infection correlates with a high risk of T2DM. Similarly, a meta-analysis carried out by Mansori *et al*[11] suggests that *H. pylori* may be one of the risk factors for T2DM. On the contrary, other studies report that *H. pylori* is not associated with either insulin resistance or the prevalence of T2DM[17-20]. Data from Tamura *et al*[21] suggest that East Asian CagA-positive *H. pylori* infection is not a risk factor for T2DM. The successful *H. pylori* eradication rates in patients with type 1 and type 2 DM are 62% and 50%, respectively, which are much lower than those in people without these two forms of the disease[22-25]. The low efficiency of eradication therapy for *H. pylori* infection in diabetic patients is uniquely presented in many studies[26-29].

There is a clear correlation between the higher detection rate of *H. pylori* in diabetic patients and lower efficacy of eradication therapy, depending on the level of hyperglycemia[10,13,29]. Uncontrolled diabetes with the development of chronic hyperglycemia causes a number of metabolic changes[30]. Chronic hyperglycemia in turn leads to increased susceptibility to infective agents in diabetic patients[9,10,30,31]. The exact mechanisms underlying the link of chronic hyperglycemia and the higher detection rate of *H. pylori*, as well as the mechanisms that improve the survival of this bacterium in diabetic patients during eradication therapy remain unknown. An understanding of how chronic hyperglycemia is related to the maintenance of the metabolic homeostasis of *H. pylori* for its vital activity and reproduction in diabetic patients is of great scientific and practical importance.

It is hypothesized that chronic hyperglycemia is associated with: (1) The increased detection rate of *H. pylori*; (2) possible metabolic changes in the bacterial cells ; and (3) the results of eradication therapy.

It is well known that *H. pylori* colonizes the gastric mucosa. To establish long-term colonization, the bacterium must sense and adapt to the nutritional conditions that exist in its habitat. Surprisingly, little attention has been paid to the preferred sources of nutrients and energy for the life, growth, and reproduction of *H. pylori*, as well as changes in the source of food ingredients and energy for *H. pylori* in diabetic patients. The available data suggest that for its life, growth, and reproduction, *H. pylori* utilizes amino acids and carboxylic acids, which are produced in sufficient quantities in the stomach as a result of hydrolysis of food proteins[32-34]. *H. pylori* catabolize a large amount of amino acids with the most substantial being alanine, arginine, asparagine, aspartate, glutamate, glutamine, proline, and serine[32,35-37]. *H. pylori* can also catabolize fumaric acid[38], malic acid[35], and lactic acid[39]. Thus, amino acids and carboxylic acids are sources of carbon, nitrogen, and energy.

In a healthy individual, *H. pylori* are almost independent of sugars, such as glucose[32-34]. However, glucose is known to be one of the most important carbohydrates, which is used for life by many microorganisms, including inhabitants in the digestive system. Moreover, Wang *et al*[40] believe that glucose plays a key role in the outcome of bacterial infection in humans. A question is raised as to whether *H. pylori* can utilize glucose as a plastic and energy material. Studies conducted in the 1990s and later indicate that *H. pylori* has enzyme systems capable of utilizing carbohydrates, D-glucose in particular[41-43]. These data suggest that in its evolutionary phylogenetic development and adaptation to life and reproduction in the stomach, *H. pylori* not only acquire the ability to restructure its metabolism for the use of amino acids as a plastic and energy material, but most probably retain the ability to utilize carbohydrates for their life activity. There are experimental data showing that adding glucose to the nutrient medium when growing *H. pylori*, enhances its growth[29,44].

Chronic hyperglycemia in diabetic patients involves compensatory mechanisms aimed at normalizing the blood level of glucose[5]. To remove excess glucose in patients with DM and chronic hyperglycemia, it is most likely that the extradigestive (excretory) function of the gastric mucosa is switched on. This leads to the fact that in patients with DM and chronic hyperglycemia, *H. pylori* gain advantages for its growth, reproduction, and survival as it can use not only amino acids for its life, but also glucose available in excess in patients with DM. This hypothesis may explain the more frequent detection of *H. pylori* in patients with DM than in the general population.

Based on this hypothesis, it is possible to explain also the lower efficiency of eradication therapy in patients with DM.

H. pylori eradication regimens contain antibacterial drugs (clarithromycin, metronidazole, bismuths, *etc.*) and agents that reduce hydrochloric acid production. The use of antacids aimed at creating optimal conditions for acid-dependent antibacterial agents[45-48]. The data presented in recent studies suggest that it is extremely important to determine gastric pH for *H. pylori* eradication[45,46]. In addition, the antacids have a double effect on *H. pylori* with an opposite effect. Increased gastric pH is a favorable factor for the vital activity of *H. pylori*. But at the same time, the antacids deprive *H. pylori* of nutrients. Exposure to hydrochloric acid in the stomach causes denaturation of food proteins and initiates their hydrolysis by the gastric juice enzymes pepsin and gastrixin. This gives rise to oligopeptides with different lengths and to a certain amount of amino acids, which are utilized by *H. pylori* for its life activity. Taking antacids practically does not lead to denaturation of food proteins. Consequently, the rate of protein hydrolysis is considerably reduced. As a result, the stomach practically does not produce amino acids that are essential for maintaining the vital activity of *H. pylori*. The lack of nutrients and the intake of antibacterial drugs result in the death of the microorganism or in its transition to a dormant form[49]. The latter is rare during powerful antibiotic therapy.

There is an opportunity for *H. pylori* to utilize glucose as an energy and plastic material in diabetic patients receiving eradication therapy against the underlying chronic hyperglycemia and amino acid deficiency. It is likely that this mechanism enables this microorganism to successfully survive the extreme conditions of eradication. But this can happen only in the presence of chronic hyperglycemia. That is to say, the survival of *H. pylori* under extreme conditions of eradication should depend on the level of hyperglycemia. And the longer period of hyperglycemia is, the more likely *H. pylori* survive the extreme conditions of eradication.

Chronic hyperglycemia can be assessed by the blood level of glycated hemoglobin A (HbA1c) (Figure 1). The HbA1c level is the result of nonenzymatic glycosylation of hemoglobin, with the formation of a bond between glucose and the free N-terminal proline amino group in the hemoglobin β-chain[50]. The indicator plays an important role in monitoring the time course of changes in blood glucose levels in diabetic patients and for evaluation of the efficacy of hypoglycemic drugs[51]. In 2011, the World Health Organization officially recommended an HbA1c level of ≥ 6.5% as a diagnostic cut-off value for DM[52]. This indicator reflects the integrated blood glucose level for the last 3-4 mo[53-55]. The association between *H. pylori* infection and HbA1c in diabetic patients has been confirmed in many studies[51,56,57]. Glycated hemoglobin A levels were significantly higher in patients with DM and *H. pylori* infection than in those with DM and without *H. pylori* infection (WMD = 0.50, 95%CI: 0.28-0.72, $P < 0.001$)[51]. Subgroup analysis by the subtype of DM has revealed a correlation between *H. pylori* infection and an elevated glycated hemoglobin A level in type 1 DM ($I^2 = 74\%$, $P < 0.001$, WMD = 0.46, 95%CI: 0.12-0.80) and in T2DM ($I^2 = 90\%$, $P < 0.001$, WMD = 0.59, 95%CI: 0.28-0.90, $P < 0.001$)[51].

Bektemirova *et al*[58] used the HbA1c level to evaluate the efficacy of hypoglycemic drugs taken by 83 patients with T2DM and *H. pylori*-associated diseases during eradication therapy. Glycated hemoglobin A was shown to reach a target level of < 6.5% in 62 of the 83 examinees, while it remained elevated (> 7.0%) in 21 patients. This means that despite the use of hypoglycemic drugs, the level of hyperglycemia persisted in these patients for at least 2-3 mo. And it was in these patients who did not reach the target HbA1c level had a significantly ($P < 0.017$) lower efficiency of eradication therapy than those who achieved the target level of HbA1c < 6.5%. The data obtained by Bektemirova *et al*[58] indirectly suggest that *H. pylori* most likely take advantage of chronic hyperglycemia to survive under the extreme conditions of eradication.

According to Tseng, the use of insulin to normalize blood glucose levels in patients with T2DM substantially increases the rate of *H. pylori* eradication compared to those with DM without insulin administration[25]. The higher efficiency of *H. pylori* eradication in T2DM patients taking insulin suggests that these patients are more likely to normalize their blood glucose levels during insulin therapy. And this is most likely to cause an increase in the efficiency of *H. pylori* eradication.

CONCLUSION

The data available in the literature advance the following hypothesis that in diabetic patients, *H. pylori* are most likely to utilize both amino acids and glucose for its vital activity. The hypothesis makes it possible to explain the high detection rate of *H. pylori* in diabetic patients, as well as their lower eradication therapy efficiency. Undoubtedly, this hypothesis requires further conformations by biochemical, microbiological, molecular genetics, and other studies. Further multicenter studies are needed to confirm this hypothesis. But if this hypothesis is correct, then before *H. pylori* are eradicated in DM patients, there is a need for mandatory monitoring and targeted correction of blood glucose and HbA1c levels according to the algorithm given in Figure 1. The algorithm can be used for the management of patients with DM and concomitant *H. pylori*-associated diseases, which is of great practical importance for their successful eradication therapy.

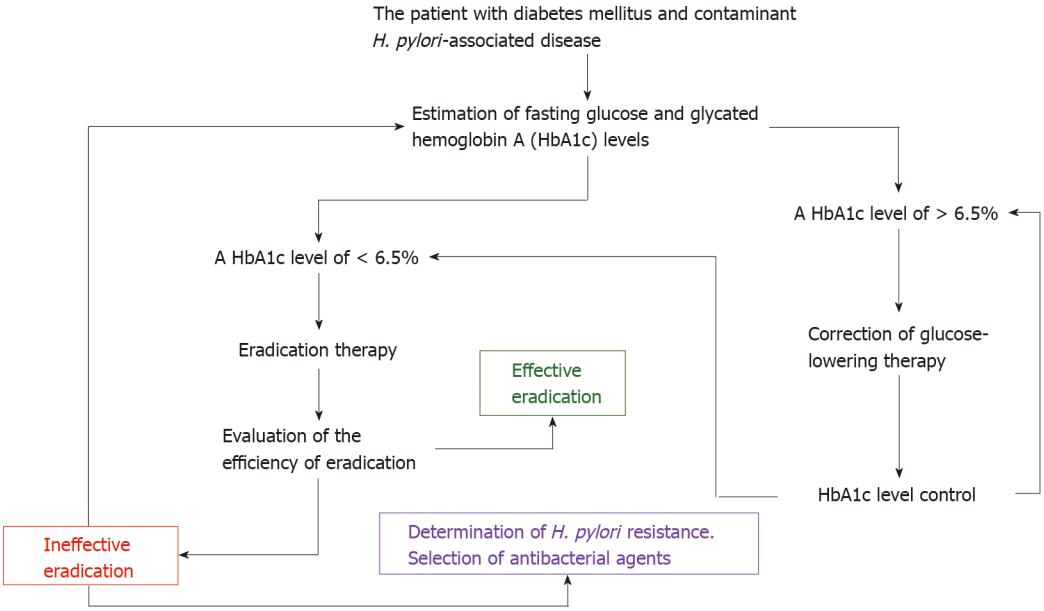

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Figure 1 Algorithm for monitoring and targeted correction of glycated hemoglobin A levels in patients with diabetes mellitus and *Helicobacter pylori*-associated diseases. *H. pylori: Helicobacter pylori.*

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FOOTNOTES

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SYSTEMATIC REVIEWS

Disordered eating behaviour and eating disorder among adolescents with type 1 diabetes: An integrative review

Maria Conceição Santos Oliveira Cunha, Francisco Clécio Silva Dutra, Laura Martins Mendes Cavaleiro Brito, Rejane Ferreira Costa, Maria Wendiane Gueiros Gaspar, Danilo Ferreira Sousa, Márcio Flávio Moura de Araújo, Maria Veraci Oliveira Queiroz

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Abstract

BACKGROUND

Type 1 diabetes (DT1) in adolescents brings behavioural changes, altered nutritional habits, and eating disorders.

AIM

To identify and analyze the validated instruments that examine the disordered eating behaviour and eating disorders among adolescents with DT1.

METHODS

An integrative review was accomplished based on the following databases: PubMed, LILACS, CINAHL, Scopus, Web of Science, and Reference Citation Analysis (RCA), including publications in Portuguese, English, or Spanish, without time limit and time published.

RESULTS

The main instruments to evaluate disordered eating behaviour were The Diabetes Eating Problem Survey-Revised, The Diabetes Eating Problem Survey, and the

eating attitudes test-26, and for eating disorders the main instruments used were The Bulimic Investigation Test of Edinburgh, The Binge Eating Scale, The Child Eating Disorder Examination, The five questions of the (Sick, Control, One, Fat and Food), and The Mind Youth Questionnaire. These instruments showed an effect in evaluating risks regarding nutritional habits or feeding grievances, with outcomes related to weight control, inadequate use of insulin, and glycaemia unmanageability. We did not identify publication bias.

CONCLUSION

Around the world, the most used scale to study the risk of disordered eating behaviour or eating disorder is The Diabetes Eating Problem Survey-Revised. International researchers use this scale to identify high scores in adolescents with DT1 and a relationship with poorer glycemic control and psychological problems related to body image.

Key Words: Adolescent; Type 1 diabetes mellitus; Validation studies; Nutritional behaviour; Eating disorder; Review

Core Tip: Adolescents with type 1 diabetes are more vulnerable to disordered eating behaviour.

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INTRODUCTION

Type 1 diabetes (DT1) in adolescents brings behavioural changes, highlighting altered nutritional habits and eating disorders (ED). It is worth emphasizing that the greatest challenge of diabetes treatment is glycaemic control through insulin therapy, good nutritional habits, and regular physical activity[1], in addition to other health behaviours. However, studies about behaviours with DT1 showed a higher risk of developing ED and dissatisfaction with their body image than their pairs without diabetes[2,3].

The disordered eating behaviour (DEB) is related to active behaviouring on a diet or to feast, compulsive eating, or purging (inefficient use of laxatives, diuretics, and self-induced vomit) and its frequency has become considerably higher in the last years at different parts of the world[4,5].

The prevalence of DEBs among adolescents is estimated at 10% in Western cultures[6]. In Israel, the estimates are 8.2% among female adolescents and 2.8% for male adolescents[7]. DEB and ED were already associated with diabetes mellitus (DM)[8,9].

ED encompass a group of psychiatric conditions that may lead to a persistent failure in attending to nutritional and metabolic needs, thus resulting in severe psychosocial impairment[10]. EDs are most prevalent among individuals with DM1 than in the average population[11].

EDs are eating disorder habits with central psychopathology related to eating, food concerns, and body image. There are four main types of ED: Anorexia nervosa, bulimia nervosa, periodic compulsive eating disorder, and specified eating or ED[12].

The knowledge of validated instruments that examined DEB and ED of adolescents with DT1 may subsidize prevention actions for potential risks to altered eating habits and the handling of grievances related to these disorders, thus supporting the decision in nursing clinical practice and other professionals that give care to adolescents with DT1. Therefore, the purpose of this study was to identify and analyze validated instruments that examined disordered eating behaviour and ED among adolescents with DT1.

MATERIALS AND METHODS

This is an integrative review of the literature conducted from February to April 2021 on a single desktop machine. The PICO strategy, which represents the acronym Patient, Intervention, Comparison, and Outcomes, was used to construct the guiding question of the research. The categories of this strategy are respectively fulfilled by: "Adolescents with type 1 diabetes mellitus"; "validation studies"; and "eating

disorders" and "disordered eating behaviour". Therefore, the following question was made: What validated instruments examined the DEB or ED of adolescents with DT1?

The article selection was based on titles and abstracts of the quoted articles, with the selection of the studies' inclusion and exclusion conditions, without establishing a temporal cut for the inclusion of studies. The inclusion conditions were as follows: Fully available articles in the electronic networks; national and international periodicals; studies regarding validated tools about disordered behaviour or eating disorder of adolescents with DT1; written in Portuguese, Spanish, or English. In contrast, the exclusion conditions were: Incomplete or incompatible texts about the subject, case reports, book chapters, monographs, review studies, editorials, stories in newspapers, or any non-scientific text.

The search for articles was done in the following databases: PubMed/Medline, LILACS, Cinahl, Scopus, Reference Citation Analysis (RCA), and Web of Science. The Periodical Portal, CAFe, from the Coordination for Improving Higher Education Personnel (CAPES), was used to access these five databases. The following Health Science Descriptors (DeCS) and (MeSH) were used: "*Adolescente*", "*diabetes mellitus tipo 1*", and "*Transtornos da Alimentação e da Ingestão de Alimentos*", and their respective English versions are "Adolescent", "type 1 diabetes mellitus", and "disorders from eating and food intake". The crossings were made using the Boolean operator "AND" to combine the descriptors: A *dolescent*" AND "*diabetes mellitus type 1*" AND "*feeding and eating disorders*".

The descriptors were delimited for each selected database (Medical Subject Headings – MeSH, Health Science Descriptors – DeCS, and CINAHL Headings – MH). There was no publication year threshold. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[13].

The evidence level classification regarding the guiding question concerning studies of Intervention/Treatment or Diagnosis/Diagnostic test[14] was added and presented the following seven levels: (1) Evidence of a systematic review or a meta-analysis of all relevant randomized controlled studies; (2) evidence obtained from well-made randomized controlled studies; (3) evidence obtained from adequately designed controlled studies without randomization; (4) evidence of well-designed case-control and cohort studies; (5) evidence of systematic reviews from descriptive and qualitative studies; (6) evidence of unique descriptive or qualitative studies; and (7) evidence from authorities opinions or reports from a committee of experts.

Random effects meta-analysis of proportions was perform using the 'meta' package in R 4.0.

RESULTS

An initial search for the literature that composed the integrative review obtained a result of 728 studies, distributed in 258 articles published in PubMed/MedLine, 6 in Lilacs, 100 in Cinahl, 207 in Scopus, and 157 in Web of Science. After the application of the inclusion and exclusion conditions, the final sample was composed of 13 studies in the following databases: LILACS (1); PubMed/MedLine (4); Cinahl (2); Scopus (3); and Web of Science (3).

The stages of search and selection of studies for the review are summarized in Figure 1, which was made according to the PRISMA[13].

Thirteen studies from nine different English and non-English countries were found; two each were conducted in Norway, Italy, Canada, and Turkey. The others were published in the following countries: Brazil, United States, Germany, Netherlands, and China, each with one study. There was an intense time variation regarding the publication year, where only one study was published annually and, exceptionally, two studies in a few years. The first study was published in 2010, and the most recent in 2021. Two studies each were conducted in 2013 and 2018 and three in 2017. The other years had one study as per Table 1.

Concerning the evidence level, based on the methodological analysis of the studies, nine are descriptive studies with a quantitative approach, and four are experimental studies of the clinical trial type. Among the observational studies, nine are descriptive with a quantitative approach.

All studies varied in the evidence level among II, III, IV, and VI. Two clinical trials[15,16] were classified as level II. A clinical trial without randomization and a quasi-experimental study[17,18] were classified as level III. A cohort study[19] was classified as level IV. The other studies[8,20-26] that identified the clinical question associated with the diagnosis/diagnostic test, were classified as level VI.

Due to the asymmetry of the points, we did not identify publication bias (Figure 2). We observed a proportion of 0.29 with a confidence interval of 0.18 to 0.44 and a significant *P* value representing almost 30% of the analyzed cases (Figure 3).

DISCUSSION

We have concluded that the most used psychometric scale for analyzing eating behaviour and risk for ED is The Diabetes Eating Problem Survey-Revised (DEPS-R).

Table 1 Characterisation of primary studies, according to author(s), year, title, objective, instruments, conclusion, and evidence level (Fortaleza, Ceará, Brazil, 2021)

Ref.	Title	Objective	Instrument	Conclusion	Evidence level
Philippi *et al*[20], 2013	Risk behaviours for eating disorders in adolescents and adults with type 1 diabetes	To evaluate the frequency of risk behaviour concerning the risk of eating disorder in patients with diabetes (DT1) and its association with sex, nutritional status, variables related to DT1, and satisfaction with their body	The Eating Attitude Test (EAT-26); The Bulimic Investigation Test of Edinburgh (BITE); The Binge Eating Scale (BES)	Patients with DT1 demonstrated a high frequency of dissatisfaction with their body image and risk of an eating disorder; the omission or reduction of insulin was a significant risk factor for eating disorders	Level VI
Frampton *et al*[15], 2011	Reliability and validity of the Norwegian translation of the Child Eating Disorder Examination (ChEDE)	To evaluate the psychometric properties of the Norwegian version of the ChEDE 12.0	The Child Eating Disorder Examination (ChEDE)	The Norwegian version of the ChEDE has good psychometric properties and can be recommended for clinical use and in research with young people with eating disorders in Norway	Level II
Cherubini *et al*[8], 2018	Disordered eating behaviours in adolescents with type 1 diabetes: A cross-sectional population-based study in Italy	To evaluate the association of the following factors: Clinical, metabolic, and socio-economical with disordered eating behaviour (DEB) among adolescents with DT1, tracked through the Diabetes Eating Problem Survey-Revised (DEPS-R)	TheDiabetes Eating Problem Survey-Revised (DEPS-R)	The study suggests that skipping insulin injections, little time in physical activities, having an elevated BMI, and having a family profile of low education and occupation must be considered a sign of attention for DEB among pre-adolescents and adolescents with DT1	Level VI
Akgül *et al* [16], 2018	Can having a sibling with type 1 diabetes cause disordered eating behaviours?	To evaluate if the risk of disordered eating behaviour (DEB) is also applied to the brother who shares the same environment	The eating attitudes test-26 (EAT-26)	Although a direct relation was not observed, the probability of having a pathological EAT-26 was higher among groups whose brothers had DT1	Level III
Zuijdwijk *et al*[21], 2014	The mSCOFF for Screening Disordered Eating in Pediatric Type 1 Diabetes	To validate the screening for eating disorders in female adolescents with type 1 diabetes	The five questions of (Sick, Control, One, Fat, and Food) (mSCOFF)	It is a tool that shows a great potential to track the risk of eating disorders in female adolescents with DT1 and requires validation against a gold standard	Level VI
Gagnon *et al*[17], 2017	Psychometric Properties of the French Diabetes Eating Problem Survey Revised (DEPS-R)	To develop and examine the psychometric properties and factorial structure of a French version of the Diabetes Eating Problem Survey Revised (DEPS-R) among participants with type 1 and 2 diabetes	A French version of the Diabetes Eating Problem Survey–Revised (DEPS-R)	Although it cannot be used alone to establish a formal diagnosis of an eating disorder, the French version is a valid and reliable scale to evaluate the risk of eating disorders among patients with any type of diabetes	Level III
Atik Altınok *et al* [22], 2017	Reliability and Validity of the Diabetes Eating Problem Survey in Turkish Children and Adolescents with Type 1 Diabetes Mellitus	To show the reliability and validity of a Turkish version of the Eating Problem Survey-Revised (DEPS-R) among children and adolescents with type 1 diabetes mellitus	The Diabetes Eating Problem Survey-Revised (DEPS-R)	Disordered eating behaviours and insulin restriction were associated with poor metabolic control. The screening tool for diabetes to DEB can be used daily during the clinical care of adolescents with DT1	Level VI
Saßmann *et al*[23], 2015	Psychometric properties of the German version of the Diabetes Eating Problem Survey Revised: additional benefit of disease-specific screening in adolescents with Type 1 diabetes	To examine psychometric properties of the German version of the *Diabetes Eating* concerning 16 items, research was performed in a sample of adolescents with type 1 diabetes	The Diabetes Eating Problem Survey Revised (DEPS-R)	The DEPS-R delivered more specific information than the tracking of generic instruments and identified more Young ones with an eating disorder than reported by the doctor, especially concerning the detection of boys at risk. The DEPS-R identifies the eating disorder in the initial stage of adolescents	Level VI
Wit *et al* [24], 2012	Assessing the diabetes-related quality of life of youth with type 1 diabetes in routine clinical care: the MIND Youth Questionnaire (MY-Q)	To report the development and validation of the MIND Youth Questionnaire (MY-Q) among Dutch adolescents with type 1 diabetes	The MIND Youth Questionnaire (MY-Q)	The MY-Q is a survey of QVRS projected for use in clinical care. It has good measurement properties and seems adequate to implement in the daily care of adolescents with diabetes	Level VI
Wisting *et*	Psychometric Properties,	To examine psychometric	The Diabetes Eating Problem-	The DEPS-R is a useful screening	Level IV

al[19], 2013	Norms, and Factor Structure of the Diabetes Eating Problem Survey Revised in a Large Sample of Children and Adolescents with Type 1 Diabetes	properties of the Diabetes Eating Problem Survey – Revised (DEPS-R) in a large sample of young patients with DT1 to establish rules and validate it against the Eating Attitudes Test 12 (EAT-12)	Survey–Revised (DEPS-R)	tool for DEB in people with DT1, which is relevant in practical clinics. The discoveries support this important screening tool's utility in identifying eating disorders among young patients with type 1 diabetes	
Markowitz *et al*[25], 2010	Brief Screening Tool for Disordered Eating in Diabetes	To update and validate a specific diabetes tracking tool for eating disorders (Diabetes Eating Problem Survey DEPS) in young ones with type 1 diabetes.	The Diabetes Eating Problem-Survey-Revised (DEPS-R)	Future studies must focus on using DEPS-R to identify high-risk populations for the prevention and early intervention of disordered eating behaviours	Level VI
Pinna *et al* [26], 2017	Assessment of eating disorders with the diabetes eating problems survey revised (DEPS-R) in a representative sample of insulin-treated diabetic patients: a validation study in Italy	To evaluate patients with type 1 and type 2 diabetes treated with insulin and the psychometric characteristics of the Italian version of the DEPS-R scale	The Diabetes Eating Problem Survey-Revised (DEPS-R)	Adults and adolescents with type 1 and type 2 diabetes treated with insulin participated in the study. The Italian version of the DEPS-R scale showed a good construct validity, internal consistency, and an excellent reasonable degree of reproducibility in this public	Level VI
Lv *et al*[18], 2021	Instrument Context Relevance Evaluation, Translation, and Psychometric Testing of the Diabetes Eating Problem Survey-Revised (DEPS-R) among People with Type 1 Diabetes in China	To adapt the DEPS-R for Mandarin and test its psychometric properties among adolescents and adults with type 1 diabetes in China	The Diabetes Eating Problem Survey-Revised (DEPS-R)	The Chinese version of the DEPS-R described a high proportion of disordered eating behaviour among adolescents and adults with DT1, thus indicating a need for special attention by health professionals and researchers in China	Level III

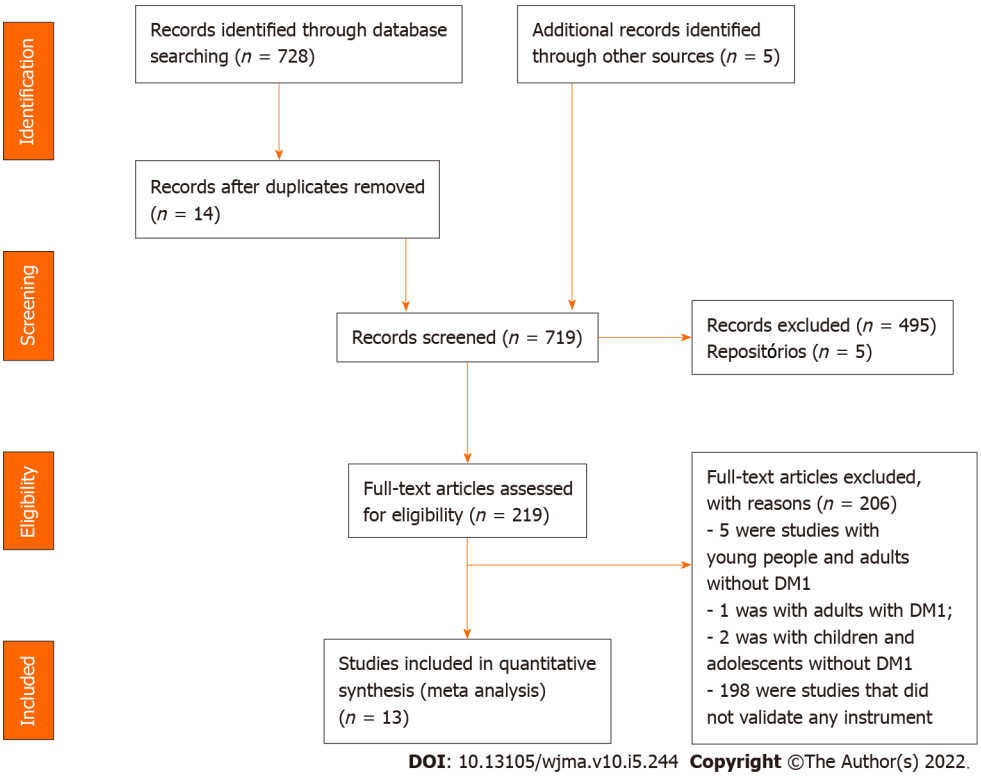

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Figure 1 Flowchart of study selection process adapted from the Preferred Reporting Items for Systematic Review and Meta-Analyses.

Previous research showed that patients with DT1 have a higher frequency of ED and nutritional risk behaviours than the standard population[20]. For sure, these disorders contribute to an increased risk of complications from diabetes, such as abnormal lipid profiles, diabetic ketoacidosis, retinopathy, neuropathy, nephropathy, and mortality increase[11,27,28]. Therefore, evaluating these clinical conditions for follow-up and damage reduction with the subjects' effective participation is relevant[29].

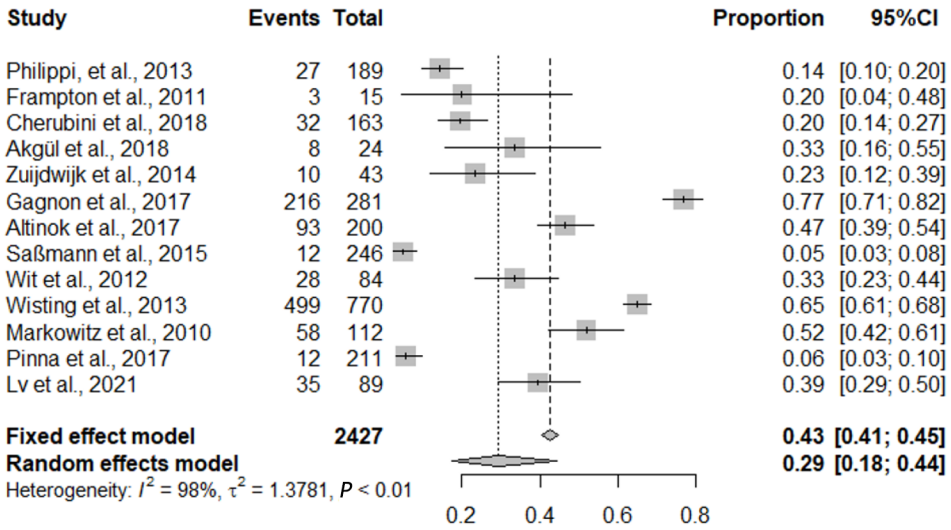

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Figure 2 Study proportion meta-analysis.

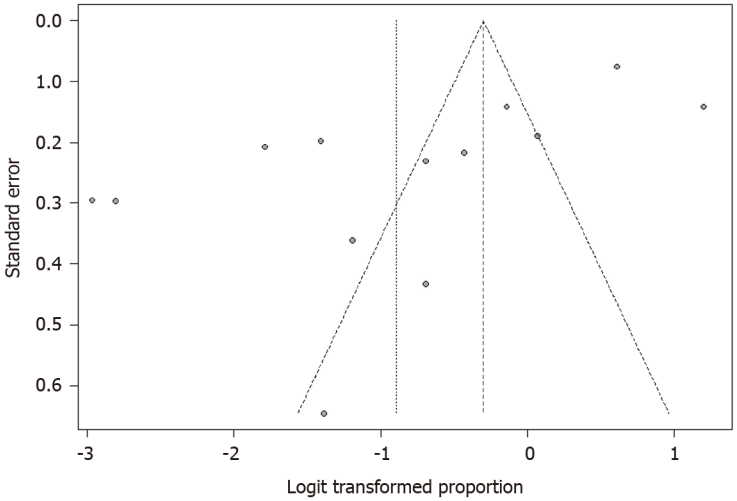

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Figure 3 Publication bias analysis.

A study evaluated risks of eating disorders using the following tools: The Eating Attitude Test (EAT-26), The Bulimic Investigation Test of Edinburgh (BITE), and the Binge Eating Scale (BES). It showed that the percentages of patients at risk of eating disorders were 45% per EAT, 40% per BITE, and 16% per BES[20]. These tools evaluated a specific type of disorder. Although of great value, they are not directed to patients with DT1, but to the standard population.

Researchers affirmed that ED are characterized by significant hassles in the cognition of the body's image and morbid concern with food, weight, and shape. Adolescents, when trying to control their weight, appeal to behaviours that include self-starvation, self-induced vomit, abusive use of laxatives and diuretics, and a tremendous and significant volume of physical exercise[15].

One considers habits such as the restriction or omission of insulin as an exclusive disorder eating behaviour of people with DT1. They are usually considered boundary conditions to an eating disorder because their symptoms have yet to reach a threshold of high degree. Such conditions would be classified as an eating disorder as such[8,30].

A study involving adolescents with DT1 demonstrated that a higher body mass index (BMI) was significantly associated with a less positive body image among girls with diabetes. This data emphasizes that higher BMI is associated with low self-esteem and lower levels of social support among adolescents with diabetes, especially girls. Another addition is that worries about body image and several psychosocial factors can be forerunners to developing eating disorder symptoms[31].

Instruments capable of validating the eating disorder must be projected to combine the participants' cognitive capacity and the adolescents' development stage. Researchers from Norway observed that no

evaluation measures for ED were available to the younger population. Therefore, they used an adaption of the EDE 12.0 tool, which is recognized as a gold standard measure of psychopathology about ED among adults[32]. For this, they adapted and evaluated the psychometric properties of the Norwegian version of the "ChEDE" for children and adolescents[15].

It is worth highlighting that adolescents with DT1 usually have a complicated state of worries around eating and diet but generally are not associated with weight and body shape issues. This finding confirms that the ChEDE tool could distinguish eating problems in this group and cognitive and behavioural psychopathology in anorexia[15].

Another study in Norway to evaluate DEB adapted and validated the DEPS-R with children and adolescents with DT1. When comparing the DEPS-R with the EAT-12, the DEPS-R seemed to be a better screening tool for DEB among young patients with DT1. In addition to the internal consistency, the DEPS-R was strongly correlated with glycated hemoglobin (HbA1c), rather than EAT-12, although both correlations were presented as relatively weak. Overall, male adolescents reported fewer DEBs than female ones[19].

Concerning the risk of ED, a study analyzed it using the mSCOFF tool, an adaptation of the SCOFF, for people with DT1. The tool mCOFF was adapted and evaluated for the risk of ED among female adolescents with DT1[21]. The researchers affirmed that when the mSCOFF tool was applied to 43 female adolescents with DT1, compared with the mEDI instrument, 10 (23.2%) participants were identified as being at high risk of developing an eating disorder[21].

In other studies that investigated ED in a similar population, the female participants presented more elevated results compared to male participants. The studies[15,21] showed these results as intrinsically connected to personal dissatisfaction with body image. Such an issue is the one the girls report the most. It is stated that the genesis and occurrence of ED can diverge between boys and girls, and the prevalence in male adolescents with DT1 is low[33].

One study highlights another tool to analyze the DEB in children and adolescents with DT1 – DEPS-R. Researchers from the USA used a DEPS adapted tool developed for adults with DT1[25]. Such specific tools for diabetes are needed due to the inefficient use of insulin and a potential purgative behaviour. These issues are seen as exclusive to individuals with diabetes[34]. The DEPS-R can avoid developing ED, such as bulimia and anorexia.

Therefore, the DEPS-R tool was adapted and validated in several countries, and a study[8] evaluated the prevalence of DEB in the region of Marche, Italy, through the use of the Italian version of the DEPS-R for the screening adolescents with DT1. The finding indicates a significantly higher prevalence (a score of ≥ 20 DEPS-R of 34.4%), among patients with overweight (65.7%). It was also identified that the participants with a score ≥ 20 in the DEPS-R had significantly higher levels of HbA1c, used higher doses of insulin, and spent less time doing physical exercise.

Researchers observed that there was no instrument planned to support health professionals in identifying DEBs in the French adult population with diabetes. Due to this, there was a need to adapt and validate the DEPS-R. Therefore, a study was performed to validate the DEPS-R tool in adolescents and adults with DT1 and DT2[17].

The study aforementioned adapted and validated the tool to compare it with the following instruments: The Eating Disorders Examination Questionnaire (EDE-Q6)[35] and Eating Disorder Inventory 2-Body (EDI-2)[36]. However, the study found significant barriers and limitations, one of which was the reduced participation of adolescents. Thus, the adults prevailed. In addition to this, different constructs of body dissatisfaction could be used to provide more empirical support for the tool The Questionnaire des Attitudes et des Comportements liés à la gestion du Diabète (QACD). This study's innovation was the use of a tool for a heterogeneous public, where there were adolescents and adults diagnosed with DT1 and DT2[17].

The Turkish version of the DEPS-R adapted and validated this tool for children and adolescents with DT1[22]. The results have shown that 25% of the participants had a score of DEPS-R ≥ 20. Of these, most were women, and the patients with a score ≥ 20 were not adequately using their insulin to fulfill the demand from the meals at times where they ate beyond what is recommended; a few skipped the follow-up dose of insulin after overeating.

In Germany, researchers adapted and validated the DEPS-R for adolescents with DT1. They reported that the insulin restriction or its omission reported to the doctor seems not to be insufficient to the identification of ED. The disordered behaviour may come accompanied by feelings of shame and guilt, which can be a barrier for adolescents to talk about their eating behaviours[23].

For the Italian population, a study used the DEPS-R adapted and validated with patients with DT1 and DT2, aged between 13 to 55 years old, being treated with insulin. In general, 21.8% of the sample met the conditions for at least one diagnosis of DSM-5 eating disorder, and 12.8% met the conditions for at least one diagnosis of DSM-IV eating disorder[26]. Moreover, in China, a study adapted and validated the DEPS-R in adolescents aged 8 to 17 years old with DT1 and 61 adults with DT1. It was registered that the average score of C-DEPS-R was 21.0. The high risk of DEBs among adolescents in this study was 39.3%[18].

Another tool that evaluated the risk of DEB is the Eating Attitudes Test-26 (EAT-26), which had a valid, sensitive, and specific measure to detect individuals at high risk for a diagnosable eating disorder. The researchers used the tool EAT-26 in eight cases in a group of healthy brothers. Three were

diagnosed with DEB, and one case with anorexia nervosa. In the control group, five cases had a pathological score, where three of these cases were diagnosed with DEB. From this control group, no case was diagnosed with an eating disorder[16].

Norwegian researchers[24] developed and validated the tool "MIND Youth Questionnaire (MY-Q)" for adolescents with DT1. The tool adopted the following domains: Family functioning, depression symptoms, and disordered eating. The multidimensional survey consists of seven subscales (social impact, country, control perceptions of diabetes, responsibility, worries, satisfaction with the treatment and body image, and eating behaviour). The results showed that the body image had a higher association with what was disclosed by the female group, in contrast to what the male group verbalized.

It was observed that the common ground of all research is the fact of applying the tools and evaluating some critical variables related to DT1, such as BMI evaluation, HbA1c, and insulin use, to ascertain the possible metabolic changes and DEB. A study[37] quoted the importance of analyzing the sociodemographic data with emphasis on the age group and sex as relevant variables to correlate with BMI and HbA1c.

Another observation is related to the age group and the type of diabetes. A study[15] explored a younger public beginning at nine years old with DT1. In contrast, another study[17] explored a younger public and adults with an age limit of 84 years old with DT2. Therefore, the tools have shown themselves as essential for identifying DEB or ED of adolescents and adults afflicted by DT1, thus possibly contributing to the prevention of possible complications related to this type of grievance.

It is essential to highlight some limitations of this review before any external generalization. The analyzed studies did not employ the same psychometric instrument in all their investigations. Overall, the authors employed four different scales, however, in the same population: Adolescents with DT1. Even though we have conducted a broad sweep of the central databases, publication bias is possible because some industry pharmaceuticals privately own some scales. In this point of view, the scales can be marketed to the public and are not necessarily published in scientific journals.

CONCLUSION

Based on the scales analyzed, we concluded that adolescents with DT1 achieve high scores that indicate risk for eating behaviour and ED. Both eating phenomena are related to variables such as female gender, BMI, and HbA1c in adolescents with DT1.

ARTICLE HIGHLIGHTS

Research background

The disordered eating behaviour (DEB) is related to active behaviouring on a diet or to feast, compulsive eating, or purging (inefficient use of laxatives, diuretics, and self-induced vomit) and its frequency has become considerably higher in the last years at different parts of the world

Research motivation

The knowledge of validated instruments that examined DEB and eating disorders of adolescents with type 1 diabetes (DT1) may subsidize prevention actions for potential risks to altered eating habits

Research objectives

To identify and analyze the validated instruments that examine the DEB and eating disorders among adolescents with DT1.

Research methods

This is an integrative review of the literature conducted from February to April 2021 on a single desktop machine.

Research results

We concluded that the most used psychometric scale for analyzing eating behaviour and risk for eating disorders is The Diabetes Eating Problem Survey-Revised.

Research conclusions

Therefore, the tools have shown themselves as essential for identifying DEB or eating disorders of adolescents and adults afflicted by DT1.

Research perspectives

Further studies should be conducted to explore the best scale to study the eating behaviour of

adolescents with diabetes.

FOOTNOTES

Author contributions: Oliveira Cunha MCS, Queiroz MVO, and Moura de Araújo MF designed the study; Dutra FCS, Cavaleiro Brito LMM, Sousa DF, Gaspar MWG, and Costa RF performed the study equally, contributed to the extraction of the data, analyzed the data, wrote the paper, and approved the manuscript; Oliveira Cunha MCS, Queiroz MVO, and Moura de Araújo MF critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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