ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2023 January 12; 11(1): 1-46

Published by Baishideng Publishing Group Inc

WJMA

World Journal of Meta-Analysis

Contents

Continuous Publication Volume 11 Number 1 January 12, 2023

World Journal of Meta-Analysis

Continuous Publication Volume 11 Number 1 January 12, 2023

Contents

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Saurabh Chandan, Jing Sun

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

PUBLICATION DATE
January 12, 2023

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World J Meta-Anal 2023 January 12; 11(1): 1-4

DOI: 10.13105/wjma.v11.i1.1

ISSN 2308-3840 (online)

OPINION REVIEW

Opinion on double strategy to fight against COVID-19: Vaccination and home treatment with non-steroidal anti-inflammatory drugs

Serafino Fazio, Flora Affuso

Specialty type: Medicine, general and internal

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Barve P, United States; Laranjeira C, Portugal; Wijaya JH, Indonesia

Received: October 24, 2022
Peer-review started: October 24, 2022
First decision: November 2, 2022
Revised: November 7, 2022
Accepted: December 23, 2022
Article in press: December 23, 2022
Published online: January 12, 2023

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Abstract

The goals of global vaccination are to control, eliminate, or eradicate infectious diseases in a sustainable way that strengthens public health systems. Although the use of vaccines is essential for the control of epidemics, the vaccines against coronavirus disease 2019 (COVID-19) proved to be inadequate to end the pandemic and thus are considered incomplete. These vaccines failed to prevent infection, so their primary purpose has been shifted to prevent severe disease and reduce hospitalizations and deaths. Therefore, we believe that all the strategies available to reduce transmission, hospitalizations and deaths due to COVID-19 will be put in place. It is reported that uncontrolled inflammation and thrombosis are the principal mechanisms for aggravation and death in patients with COVID-19. Unlike corticosteroids that should not be administered at the beginning of the symptoms for their immunosuppressive action, which could worsen the evolution of the disease, the usefulness of non-steroidal anti-inflammatory drugs in the early at-home treatment of the disease is becoming evident.

Key Words: Vaccination; Non-steroidal anti-inflammatory drugs; COVID-19; Early Treatment; Indomethacin; Hospitalizations

Core Tip: The goals of global vaccination are to control, eliminate, or eradicate infectious diseases in a sustainable way that strengthens public health systems. Although the use of vaccines is essential for the control of epidemics, the vaccines against coronavirus disease 2019 (COVID-19) proved to be inadequate to end the pandemic and thus are considered incomplete. These vaccines failed to prevent infection, so their primary purpose now has been shifted to prevent severe disease and reduce hospitalizations and deaths. Therefore, we believe that all the strategies available to reduce transmission, hospitalizations and deaths due to COVID-19 will be put in place. In this regard, many observational studies have constantly shown beneficial effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with low to moderate degree of COVID-19, in particular when administered within the first 72 h of symptom onset. Randomized controlled studies with NSAIDs should be carried out as soon as possible to confirm these results.

Citation: Fazio S, Affuso F. Opinion on double strategy to fight against COVID-19: Vaccination and home treatment with non-steroidal anti-inflammatory drugs. *World J Meta-Anal* 2023; 11(1): 1-4
URL: https://www.wjgnet.com/2308-3840/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i1.1

INTRODUCTION

In a recent article regarding coronavirus disease 2019 (COVID-19) vaccinations, the authors stated that "current vaccines provide only modest protection against infection and transmission with omicron variant, even at peak immunity after boosting", that "boosting every 4 to 6 mo to maintain high serum neutralizing antibody titers may not be a practical or desirable long-term strategy" and that "boosting with mRNA vaccines is not risk free"[1].

The goals of global vaccination are to control, eliminate, or eradicate infectious diseases in a sustainable way that strengthens public health systems. Although the use of vaccines is essential for the control of epidemics, the vaccines against COVID-19 proved to be inadequate to end the pandemic and thus are considered incomplete. These vaccines failed to prevent infection, so their primary purpose has been shifted to prevent severe disease and reduce hospitalizations and deaths. Therefore, we suggest that all the strategies available to reduce transmission, hospitalizations and deaths due to COVID-19 should be put in place.

AT-HOME EARLY TREATMENT WITH NSAIDS

At the beginning of pandemic, we proposed that it is not ethical to leave the patients with COVID-19 without any treatment, waiting certainties to be established by evidence-based medicine, and, among the various drugs that we could have used, we have proposed the use of indomethacin for its peculiar mechanisms[2]. At present we suggest that vaccination and early at-home pharmacologic treatment should be used together to fight against severe acute respiratory syndrome coronavirus 2 infection. Pharmacologic treatment is simple and cheap, and should be carried out promptly at home worldwide, especially for the population with no access to vaccines and the expensive approved antivirals. It has been reported that uncontrolled inflammation and thrombosis are the principal mechanisms for aggravation and death in patients with COVID-19[3]. Unlike corticosteroids that should not be administered at the beginning of the symptoms for their immunosuppressive action, which could worsen the evolution of the disease, non-steroidal anti-inflammatory drugs (NSAIDs) are now indicated for the early at-home treatment of the disease. Unfortunately, at the beginning of pandemic, NSAIDs were discouraged because of fears that they would result in a worsened disease [4], but recently Perico *et al*[5], in their review published in Lancet Infectious Diseases have reported that NSAIDs, in particular selective anti-Cox2 drugs and indomethacin may be useful in the treatment of COVID-19. Indomethacin has anti-inflammatory, antiviral and anti-platelet properties[6]. It has shown a better efficacy in a randomized controlled study in comparison with paracetamol, by greatly reducing the percentage of patients with desaturation (Spo2 ≤ 93) in the course of the disease from 20% in the paracetamol group to 0% in the indomethacin group[7]. In addition, our group showed that treatment of COVID-19 patients with indomethacin plus cardioaspirin, started within the first 3 days of onset of symptoms led to a zero hospitalization, and reduced significantly the symptom duration and the number of patients who had increased D-dimer after polymerase chain reaction negativization and complete recovery in comparison with a group of patients who started the same treatment after 3 d[8].

In a further retrospective observational study, we confirmed the significant reduction of hospitalizations not only with indomethacin, but also with other NSAIDs, in a group of over 50 years old patients

Table 1 Characteristics of published manuscripts on early at home treatment of coronavirus disease 2019 with non-steroidal anti-inflammatory drugs

Ref.	NSAID	Study design
Fazio *et al*[8], 2021	Indomethacin	Retrospective-observational
Perico *et al*[5], 2022	Various	Review
Fazio *et al*[9], 2022	Various	Retrospective-observational
Consolaro *et al*[10], 2022	Various	Matched cohort
Ravichandran *et al*[7], 2022	Indomethacin	Open label-randomized
Cosentino *et al*[11],2022	Various	Retrospective-observational

NSAID: Non-steroidal anti-inflammatory drug.

(mean age 60 ± 9 years) treated early at home for COVID-19[9].

Consolaro *et al*[10] have shown that a home-treatment algorithm based on anti-inflammatory drugs prevented hospitalization of patients with early COVID-19[10].

Another recent study by Cosentino *et al*[11], reporting the results of a retrospective analysis of 392 cases of COVID-19 in Italy, treated early at home mainly with NSAIDs, shows a very low number of hospitalizations (5.8%) and lethality (0.2%).

Taken together, these studies (Table 1), although most of them with an observational design, consistently indicate that prompt therapy at home with NSAIDs may be very beneficial in patients with mild to moderate COVID-19[5,7-11]. While several observational studies consistently showed the same beneficial result, prompt randomized controlled trials should be performed to validate the result. However, inexplicably, this was not done.

CONCLUSION

We hope that prospective randomized controlled trials on the efficacy of early at-home treatment with NSAIDs in patients with mild to moderate COVID-19, with a design of non-inferiority compared to the antiviral drugs currently authorized for treatment, will start as soon as possible. The demonstration of NSAIDs' efficacy in the therapy of COVID-19 would make an extended use of these drugs which are easily accessible and cheap, thus greatly saving health care costs.

FOOTNOTES

Author contributions: Affuso F, and Fazio S contributed equally to this work; both authors have read and approved the final manuscript.

Conflict-of-interest statement: Flora Affuso and Serafino Fazio have no competing conflict of interest.

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S-Editor: Liu JH
L-Editor: Ma JY
P-Editor: Liu JH

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World Journal of Meta-Analysis

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World J Meta-Anal 2023 January 12; 11(1): 5-17

DOI: 10.13105/wjma.v11.i1.5

ISSN 2308-3840 (online)

REVIEW

Liver dysfunction-related COVID-19: A narrative review

Taghreed S Saeed Al-Rawi, Raid M Al-Ani

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Duan Z, China; Ren S, China

Received: September 9, 2022
Peer-review started: September 9, 2022
First decision: November 17, 2022
Revised: November 25, 2022
Accepted: December 13, 2022
Article in press: December 13, 2022
Published online: January 12, 2023

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Abstract

The coronavirus 2019 disease (COVID-19) is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2. This disease was designated by the World Health Organization as a pandemic on March 11, 2020, which is not seen before. There are no classical features among the cases of the disease owing to the involvement of nearly all body tissues by the virus. Hepatic involvement is one of the characteristics of the COVID-19 course. There are six possible mechanisms of such involvement: Direct virus injury, drug-induced effect, inflammatory cytokine storm, hypoxia-ischemic destruction, abnormalities in liver function tests, and pre-existing chronic liver diseases. Liver abnormalities are seen commonly in the severe or critical stage of COVID-19. Therefore, these abnormalities determine the COVID-19 severity and carry a high rate of morbidity and mortality. The elderly and patients with comorbidities like diabetes mellitus and hypertension are more vulnerable to liver involvement. Another issue that needs to be disclosed is the liver manifestations following the COVID-19 vaccination, such as autoimmune hepatitis. Of note, complete vaccination with third and fourth booster doses is necessary for patients with previous chronic liver diseases or those who have been subjected to liver transplantation. This review aims to explore the various aspects of liver dysfunction during the COVID-19 course regarding the epidemiological features, predisposing factors, pathophysiological mechanisms, hepatic manifestations due to COVID-19 or following vaccination, role of liver function tests in the assessment of COVID-19 severity, adverse effects of the therapeutic agents for the disease, and prognosis.

Key Words: Liver dysfunction; Liver function test; SARS-CoV-2; Mortality; Critical illness; COVID-19

Core Tip: There is a diversity of clinical manifestations of the coronavirus 2019 disease (COVID-19), ranging from classical presentations like fever, cough, and dyspnea to non-classical presentations like liver involvement. Direct injury, drug-induced hypoxia, abnormal liver function tests, cytokine storm, and a history of chronic hepatic diseases are the proposed mechanisms of liver involvement during the COVID-19 course. Liver involvement can determine the severity of the disease. Old age and a history of chronic diseases like diabetes mellitus are recognized risk factors for this involvement. Autoimmune hepatitis is an example of liver involvement following COVID-19 vaccination. However, complete vaccination with 3rd and 4th booster doses is required in patients with chronic liver diseases. We aim to summarize the various aspects of hepatic involvement during the COVID-19 course or following its vaccination.

Citation: Al-Rawi TSS, Al-Ani RM. Liver dysfunction-related COVID-19: A narrative review. *World J Meta-Anal* 2023; 11(1): 5-17
URL: https://www.wjgnet.com/2308-3840/full/v11/i1/5.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i1.5

INTRODUCTION

The liver plays an essential role in the body. It deserves several physiological processes such as metabolism of the macronutrient, regulation of the blood volume, endocrine control of growth signaling pathways, support of body immunity, metabolism of cholesterol and lipid, and destruction of xenobiotic materials like certain drugs[1].

Among various causes of liver dysfunction, many viruses might attack the liver directly or indirectly. These include, but are not limited to, hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV). There is approximately 60% of patients in the previous pandemic in 2003, which was caused by the severe acute respiratory syndrome coronavirus (SARS-CoV), affected by different involvements of the liver[2]. Hence, from the beginning of the current coronavirus disease 2019 (COVID-19) pandemic, scientists have paid great attention to liver involvement due to the novel coronavirus (SARS-CoV-2). As such, a prior investigation from China reported that around 50% of the individuals with COVID-19 had dysfunction of the liver at a certain point in their disease course[3].

Liver abnormalities associated with COVID-19 might be due to direct liver damage by the SARS-CoV-2, drugs used for the disease, unrecognized previous liver abnormality, and cytokine storm, and as an indirect effect to the liver due to involvement of other body systems by the virus like the cardiopulmonary system[4].

Owing to the enormous research belonging to liver dysfunction-related COVID-19[4-8], we design this narrative review to update and summarize the epidemiological features, predisposing factors, pathophysiological mechanisms, hepatic manifestations due to COVID-19 or following vaccination, role of liver function tests in the assessment of COVID-19 severity, adverse effects of the therapeutic agents for the disease, and prognosis.

EPIDEMIOLOGY

The source of SARS-CoV-2 is unknown and spreads quickly throughout the world. The WHO declared that COVID-19 is a pandemic on March 11, 2020[9]. COVID-19 could be transmitted by two major routes: One is direct contact (close contact) from individual to individual through aerosol and respiratory droplets produced by talking, sneezing, and coughing, and the other is indirect noncontact through contaminated objects and surfaces. The incubation period ranges from 1 to 14 d, with a median of 5.5 d[10,11]. Based on the WHO dashboard on August 10, 2022, there were 584065952 confirmed cases of COVID-19 globally, with the vast majority from Europe at 243772549, the Americas at 172407904, and the Western Pacific at 76247604. The total number of cases of deaths across the globe was 6418958, with the vast majority of deaths happening in the Americas (2797327), followed by Europe (2058965) and South-East Asia (793446) [World Health Organization. WHO coronavirus disease (COVID-19) situation dashboard. 2022; cited August 10, 2022. Available from: https://www.who.int/]. The number of COVID-19 cases is still sharply increasing, with over three million cases weekly.

A prior study has illustrated that males are more likely to have abnormal liver biochemical tests related to higher concentrations of C-reactive protein (CRP) and procalcitonin and a longer period time of hospitalization, about 20 d during severe COVID-19 compared to the control group with the normal biochemical test (16 d)[12]. A meta-analysis by Xu *et al*[13] has documented that males were more potential to have severe pneumonia than females. In addition, obesity, older age, and comorbidities were dangerous factors for death among hospitalized SARS-CoV-2 patients[14].

COVID-19 is characterized by rapid transmission through the lack of herd immunity with increased mortality, and the infection is increased in elderly individuals and becomes a greater danger to those who have hypertension, diabetes mellitus, and cardiorespiratory diseases[15-17].

COVID-19 is not occurring in the elderly only but also occurs in the pediatric population with a range of ages between 0-18 years with only 3% involvement. The infection has a slight predominance of males (51%). In the same study, it has been found that the infected adolescents were mainly aged 15-18 years, and that the occurrence of COVID-19 gradually decreased with younger ages[18].

CHARACTERISTICS OF SARS-COV-2

SARS-CoV-2 is a positive sense single-stranded RNA virus. SARS-CoV and MERS-CoV are the original viruses that lead to the SARS-CoV-2 pandemic. Other subgenres of Sarbecovirus have caused the infection combined with acute respiratory symptoms in human beings, such as 229E, NL63, OC43, and HKU1. They lead to mild to severe diseases in the infected people[10,19]. The sequence of SARS-CoV-2 spike glycoproteins is significantly similar to that of SARS-CoV spike glycoproteins[20].

The receptor angiotensin-converting enzyme 2 (ACE-2) has been identified as the major viral receptor for SARS-CoV and SARS-CoV-2, and it facilitates these viruses to enter into target cells *via* the spike protein of the viruses. The mechanism includes the attachment of the virus to the surface of the host cell by linking to the ACE-2 receptor. SARS-CoV-2 gains access to the host *via* the ACE-2 receptor[21,22]. The expression of the ACE-2 receptor is widely shown on the surfaces of various types of human cells, systems, and organs. These include the muscular and nervous systems, alveolar epithelial cells in the lungs, nasal and oral mucosa, bronchial epithelial cells, nasopharynx, enterocytes of the small intestine, pancreas, liver, brain, heart, kidney, *etc.*[10,23-25].

The ACE-2 receptor is mainly expressed on cholangiocytes (bile duct) (60%) and has less expression (3%) on hepatocytes in the liver, while there is no expression of ACE-2 in Kupffer cells[26]. COVID-19-related hepatic injury could be defined as any impairment in infected individuals to the liver which occurs during the infection course and treatment phase of COVID-19 with or without the presence of liver disease.

PATHOPHYSIOLOGY

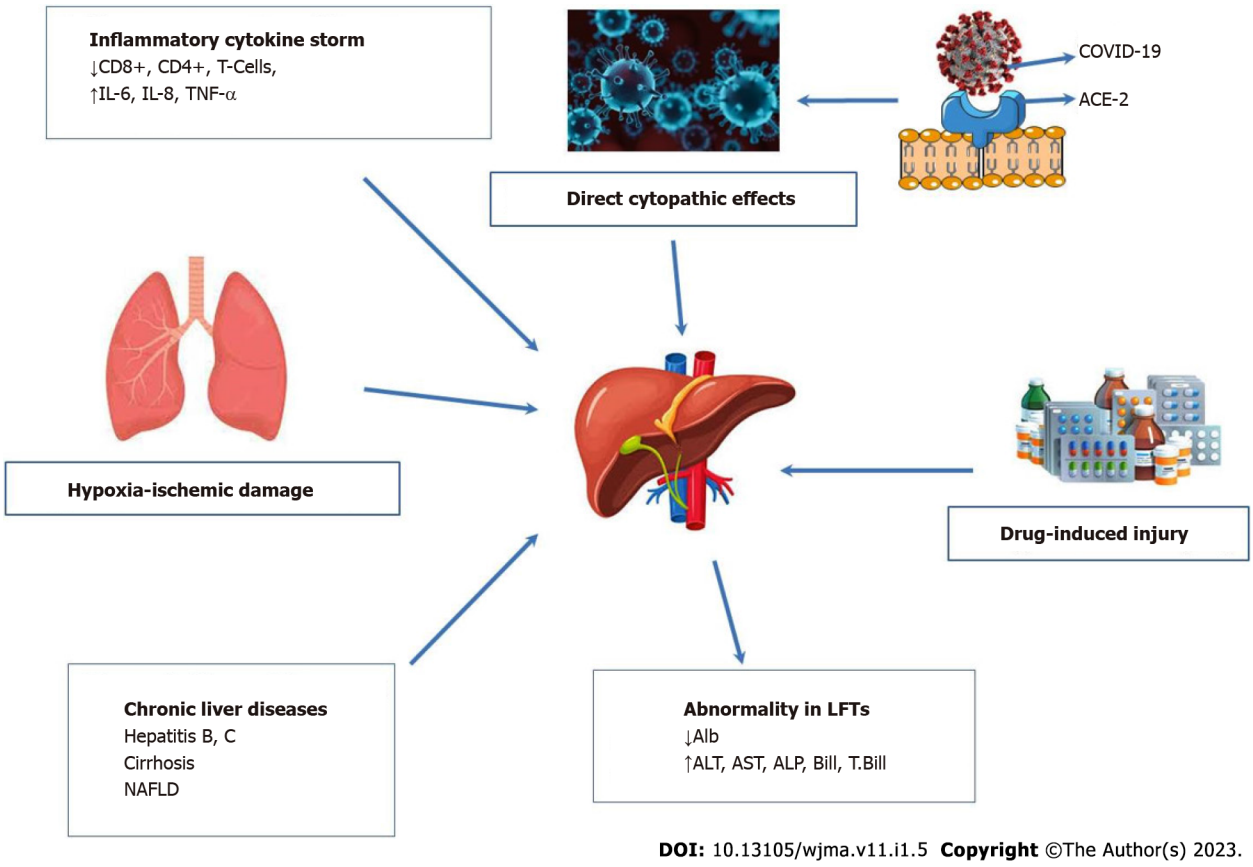
The pathophysiology of liver injury induced by COVID-19 is complex and multifactorial. Other liver diseases should be considered, such as chronic hepatic disease due to autoimmune or viral disease, metabolic dysfunction-related fatty liver disease, cirrhosis, or liver transplant. An autopsy study on tissue from the liver of a COVID-19 subject revealed a relatively low viral titer owing to the absence of a viral inclusion body in the hepatic tissue. However, the pathological evaluation reported two findings: Mild active inflammation and moderate microvascular steatosis of the lobular portal part of the liver [27].

The mechanisms of liver injury related to COVID-19 are varied. Six probable mechanisms are proposed to clarify COVID-19 with liver disease, as shown in Figure 1.

The first mechanism is hypoxic-ischemic liver injury. A high level of aspartate transaminase (AST) in hepatitis could characterize ischemic hepatitis. The common outcome of COVID-19 is cardiomyopathy which happened in 33% of infected individuals in a series of critically ill United States (US) patients[28]. The hepatic ischemia, hypoxia, as well as impaired tissue perfusion in the course of COVID-19 could develop as a result of circulatory failure, multiple organ failure, pneumonia-correlated hypoxemia, and respiratory distress syndrome[29]. In mechanically-ventilated patients, high positive end-respiratory pressure and hepatic congestion can also increase the degree of hypoxic damage in hepatocytes[30,31].

Direct viral injury is also a possible mechanism of liver injury. It has been assumed that COVID-19 might cause cytopathic effects. The expression of the ACE-2 receptor occurs during the pathogenesis of liver injury associated with COVID-19. The reason is that when SARS-CoV-2 enters the liver on cholangiocytes, the spike proteins of SARS-CoV-2 bind to the ACE-2 receptor, and the viral replication will occur *via* interaction between the virus and ACE-2[32]. The expression of ACE-2 in cholangiocytes is considerably higher (about 60%) than that in hepatocytes (about 3%)[31,33]. The direct viral injury to bile duct epithelial cells could result from COVID-19-caused liver injury, which is recognized to significantly diminish the immune response and liver regeneration[34]. Moreover, it could be clarified by the fact that cholangiocytes have a crucial role in inflammation, liver regeneration capacity, and immune response. The loss of cholangiocytes leads to hepatocellular damage. However, the cytopathic effect of COVID-19 might not be the major reason for liver damage[34,35].

In liver biopsies from two infected individuals with COVID-19 who died, the particles of typical coronavirus were recognized in the cytoplasm of the hepatocytes; therefore, the cytopathic damage could be distinguished through endoplasmic reticulum dilatation, glycogen granule, and mitochondrial swelling[36].



DOI: 10.13105/wjma.v11.i1.5

Figure 1 The proposed mechanisms of liver injury with coronavirus disease 2019. ACE-2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; TNF: Tumor necrosis factor.

Cholangiopathy is another mechanism to describe COVID-19-related liver injury. There is a broad domain of hepatic-biliary symptoms with COVID-19, including cholangiopathy's chronic and infrequent symptoms. It has been illustrated that the bile duct structure mimics secondary sclerosing cholangitis. It is ambiguous at this phase if these hepatic-biliary symptoms were an outcome of direct infection of the biliary tract and liver or if these demonstrated alterations of biliary tree ischemia. The complete recovery in COVID-19 patients was not reported with the increased concentrations of serum alkaline phosphatase (ALP) and bilirubin[37,38].

Drug-induced liver injury is also probable. COVID-19 requires drugs such as antiviral and antibody agents (protease inhibitors, azithromycin, receptor antagonist, and anti-interleukin IL-6 monoclonal antibody); such agents could cause hepatic injury. For example, remdesivir is a drug confirmed by the US Food and Drug Administration as a cause of liver injury[39]. The COVID-19-associated liver injury might also occur secondary to the potentially hepatoxic effects of different drugs, such as antivirals, acetaminophen, corticosteroids, immune modulators, and antibiotics, among others. The presence of liver inflammation and microvesicular steatosis characterized by small intracytoplasmic fat vacuoles (liposomes) which accumulate within hepatocytes in the liver biopsies of individuals with COVID-19 might also be drug-associated[27].

The interaction between drugs and cytochrome P-450 can demonstrate a few hepatic toxicities secondary to such medicines as acetaminophen, lopinavir/ritonavir, azithromycin, and hydroxychloroquine[26]. In the systematic review by Kulkarni *et al*[40], which included 20874 patients (107 articles), about a quarter of COVID-19 patients suffered drug-induced liver injury.

The histopathological analysis for liver biopsy samples from COVID-19 patients recorded nominal lobular and portal activity, simple micro-vesicular steatosis, mitosis, as well as hepatocellular necrosis in the liver tissue, and no viral inclusion bodies. The abnormality of histopathological results may be due to COVID-19-caused liver damage or drug-induced liver injury[41].

Hyper-inflammatory cytokine storm may also cause hepatic injury. The concentrations of inflammatory cytokines, including tumor necrosis factor (TNF), IL-1, and IL-6, were observed to be increased in COVID-19 patients by around 20%, resulting in a cytokine storm. Hepatocytes could be oversensitive to hypoxic hepatic injury during severe COVID-19; the further deterioration of hepatocytes occurs due to immune overreaction resulting in significantly abnormal liver biochemical tests[42]. COVID-19 patients with multiorgan failure in the intensive care unit (ICU) might be associated with severe liver

dysfunction[43]. In addition, patients infected with SARS-CoV-2 with raised AST also have increased ferritin, IL-6, C-reactive protein, and lactate dehydrogenase compared to subjects with normal AST[44].

The over-activation of the immune system, which is correlated with COVID-19, might induce liver injury. A significant increase in the serum concentrations of inflammatory cytokines, including interferon-γ, IL-1β, IL-10, IL-6, TNF, and soluble IL-2 receptor, exists in subjects with SARS-CoV-2, particularly in those patients with severe pneumonia[45,46]. The result of that is liver injury mediated by the immune system through the stimulation of intrahepatic CD4+ and CD8+ cells, Kupffer cells, and T cells leading to dysregulated innate immune response[30,47]. This manifestation has also been characterized in infections caused by other viruses such as SARS-CoV and herpes simplex virus, Epstein-Barr virus, cytomegalovirus, adenovirus, and parvovirus. These viruses target the upper respiratory tract [47].

Patients infected with SARS-CoV-2 might have chronic liver diseases (CLD), for example, non-alcoholic fatty liver disease (NAFLD), HBV or HCV infection, and cirrhosis. In COVID-19 patients with a previous history of HBV or HCV infection and liver cirrhosis, there might be a synergistic effect between the drugs used for these diseases with the drugs used for the COVID-19 treatment. As a consequence, acute hepatitis happens[48].

All previous findings contribute to the hypothesis of COVID-19-associated liver damage. Another study has reported from post-mortem liver histopathology that microvesicular steatosis could occur with the overactivation of T cells, assuming that the liver injury is mediated through the immune system[49]. Endothelitites could be generated due to COVID-19, and damage the liver[50]. The involvement of endothelial cells in hepatic ischemia-reperfusion damage leads to the stimulation of oxidative stress *via* the reaction between the derivatives of nitric oxide and oxygen species[51].

SARS-CoV-2 RNA has been discovered in feces. It appears sensible that the inflammatory mediators and virus are present in the gut lumen, reaching the liver *via* portal circulation. The viral particles could be removed by Kupffer cells, thus resulting in a rising inflammatory response[26,50]. The cholangiocyte-related enzymes are gamma-glutamyl transferase (GGT) and ALP. However, the abnormal concentration of GGT might contribute to acute inflammatory stress since it is known as a biomarker for raised inflammation and oxidative stress[52].

In the case of chronic hepatitis B or C related to COVID-19, the counts of the white blood cells and monocytes significantly diminished compared to those in patients with COVID-19 alone, while the level of $CD8^+$ T cells greatly increased, and HBV-infected patients with COVID-19 had a greater danger of thrombocytopenia[53]. In addition, the HCV and active infection of HCV have a weak relationship with COVID-19. Mangia and his colleagues have reported that HCV-infected patients have a lower risk of being infected with COVID-19. They suggested that antibodies to HCV could protect against COVID-19 [54].

The metabolic syndrome NAFLD, which is the most frequent CLD, carries a highly raised risk for severe COVID-19. It was estimated in a meta-analysis of epidemiological studies that NAFLD was associated with a 5.2-fold increased risk of severe COVID-19[55]. A recent study by Jiuling and his colleagues has reported that a significant association was recorded between NAFLD and severe COVID-19; however, this association disappeared when the demographic (age and gender) and comorbid factors like obesity were adjusted, while the other metabolic perturbations (diabetes mellitus and hypertension) does not have an association with severe COVID-19[56]. CRP, D-dimer, and ferritin levels as well as lymphocyte and neutrophil counts are similar for both NAFLD and non-NAFLD patients. The liver parameters such as serum albumin, ALP, and serum bilirubin levels are comparable across both groups. In contrast, increased concentrations of alanine transaminase (ALT), AST, and GGT have been observed in NAFLD patients compared to non-NAFLD patients. The mortality and hospitalization stays have not increased in COVID-19 patients with NAFLD based on increased liver parameters[57].

A study by Pan *et al*[58] has illustrated liver injury for COVID-19 patients with NAFLD; it has found that liver injury happened in 50% and 75% of infected persons upon admission and during staying in the hospital, respectively. These findings are due to the increased expression of the ACE-2 receptor as well as chronic inflammation of the liver in NAFLD, which leads to liver injury. In addition, the degree of liver fibrosis in NAFLD may affect the consequence of SARS-CoV-2 infection, and the high or intermediate score of FIB4 has been associated with severe SARS-CoV-2 illness among patients with MAFLD[59].

USEFULNESS OF LIVER FUNCTION TESTS IN ASSESSMENT OF COVID-19 SEVERITY

Liver injury often cause the changes in liver function tests above normal ranges; AST > 40 U/L, ALT > 40 U/L (higher than 3 times the upper limit unit of normal (ULN), ALP > 130 U/L (2 × ULN), bilirubin > 1.1 mg/dL, and GGT > 48 U/L (2 × ULN) were monitored in patients with asymptomatic-to-severe/critical COVID-19. Despite that the accurate impact of SARS-CoV-2 on the liver is unclear, abnormal liver enzymes are present in around 15%-65% of COVID-19 patients. Liver function is normally impaired in patients with COVID-19 due to abnormal liver biochemical markers, which lead to an increase in the danger of progressing to severe disease during staying in the hospital with cholestasis hepatocellular injury[60,61]. A retrospective study by Lei and his colleagues documented the liver

function tests regardless of COVID-19 severity; AST was elevated, followed by an elevation in ALT with a variant concentration in bilirubin. The mortality risk was significantly related to the levels of AST[62].

In the Singhai study, among 600 COVID-19 patients, 416 had mild COVID-19, 23 had moderate COVID-19, and 161 had severe COVID-19. The severity of COVID-19 could be classified as asymptomatic, mild, moderate, and severe/critical. Mild COVID-19 patients have no pneumonia and minor symptoms; moderate COVID-19 patients have respiratory tract symptoms, and fever, and show pneumonia without respiratory distress on imaging; the average hospitalization is 6.98 d. Severe COVID-19 patients have an arterial blood partial pressure/O_2 concentration of less than 300 mmHg, and more than 50% have lung involvement on radiological imaging, hypoxia (oxygen saturation < 93%), or respiratory distress. Critical COVID-19 involved respiratory failure, shock, and multiorgan failure (5%) or death (2.3%); the average hospitalization is 11.41 d. The levels of AST and ALT are highest in moderate COVID-19, ALP is highest in mild COVID-19, and there are no different values in bilirubin between these groups[7,61,63].

The biomarker to diagnose the injury of cholangiocytes is GGT, but it is not raised in most patients. ALP is still at the normal level. The indices of albumin and total protein are diminished at admission, indicating that COVID-19 may directly damage the liver. At the same time, the indices of total bilirubin, direct bilirubin, indirect bilirubin, ALT, and AST levels are increased during admission, during treatment, as well as during hospitalization. Previous observations recorded that the aggravated liver dysfunction (increased levels of AST and ALT) during the COVID-19 course, was significantly associated with COVID-19 severity[12,64,65]. CRP level is greatly increased during admission in COVID-19 patients and returned to the normal range before discharge[64].

Liver injury in severe cases was more severe than that in patients with mild and non-severe COVID-19. Severe infection was more likely to cause severe hepatic injury compared to a mild infection. Patients with hypertension or diabetes generally have an increase in liver enzymes, bilirubin, and ALP and a decrease in albumin (2.6–3 g/dL). It could be detected for early severe COVID-19 through the abnormality of the liver test[66-68]. Liver injury with COVID-19 was more frequently found among severe patients compared to non-severe patients and mild COVID-19 (about 45% for severe patients, 15% for mild COVID-19, and 10% for non-severe COVID-19)[69,70]. Pneumonia developed during COVID-19 is associated with a high level of CRP, mildly elevated levels of bilirubin and AST, and a low level of serum albumin, which leads to COVID-19-induced liver dysfunction[64]. Liver abnormalities might occur due to tissue hypoxemia and sepsis. The concentration of CRP is elevated in severe patients [71].

A significant correlation was observed between the elevation of AST, ALT, and bilirubin and the critical illness of COVID-19, and their concentrations are higher in critical COVID-19 compared to severe or mild COVID-19. Serum albumin decreased in the critical illness of COVID-19, and it is lower than that in severe COVID-19[72].

EFFECTS OF COVID-19 THERAPEUTIC AGENTS ON THE LIVER

Several therapeutic agents are utilized to treat patients with COVID-19 and associated manifestations. There is no particular medication for COVID-19 at present, and antiviral drugs account for the significant treatment. These medications consist of antivirals (ritonavir, remdesivir, favipiravir, and lopinavir), antimalarials (chloroquine and hydroxychloroquine), some monoclonal antibody products, acetaminophen, steroids, antipyretics, immune-modulators, and corticosteroids. Since the liver metabolizes these drugs, they can lead to hepatotoxicity[73]. Paracetamol and acetaminophen are medicines used to block some complications of COVID-19[74]. The use of acetaminophen used as an antipyretic drug causes sudden hepatic failure at high doses, and the treatment doses utilized to heal SARS-CoV-2 may cause abnormal levels of ALT and AST and lead to mild liver injury[75].

The safety and effectiveness of ritonavir and lopinavir medicines were examined to treat COVID-19. They are accounted as human immunodeficiency virus protease inhibitors to inhibit viral replication *via* inhibiting the proteolytic cleavage of the polyprotein of virus polymerase[76]. Another study has demonstrated that ritonavir and lopinavir treatment caused increased concentrations of AST, ALT, and total bilirubin in a few infected persons[77].

Remdesivir inhibits viral replication through intracellular transformation to inhibit viral RNA polymerase[78]. The antiviral drug remdesivir antagonizes RNA polymerase. It has been utilized to treat patients with Marburg virus infection, Ebola virus disease, and hepatitis. Remdesivir has reported *in vitro* efficacy against COVID-19 and is partially metabolized through the cytochrome P450 enzymes [79]. A study by Lee *et al*[80] reported that remdesivir has safety and efficacy properties in about 80 COVID-19 patients with severe disease; the clinical effectiveness has been reported on hospitalized patients with a mean duration of oxygen therapy of about 10 d, and a time of staying in hospital of 10 d. A study by Van Laar and colleagues has demonstrated that remdesivir therapy causes hepatotoxic effects. In about 100 SARS-CoV-2 patients, 25 individuals had elevated ALT, and 35 had increased AST concentrations[81].

These agents have anti-inflammatory and antimalarial properties, and with the appearance of the SARS-CoV-2 pandemic, they have a potential therapeutic indicator for patients with COVID-19[82]. The appropriate mechanism of impact of hydroxychloroquine on the resistance of COVID-19 is by inhibiting the attachment of the spike protein of COVID-19 to the receptor of ACE-2, thus blocking the viral elements and the fusion of the cell membranes of the target cells. This might reduce the key processes which result from COVID-19, including proteolytic activity, lysosome activity, and autophagy in the host cells; hydroxychloroquine has an immunomodulatory effect by diminishing cytokine production [83]. A systematic review and randomized, parallel and clinical trial by Hernandez *et al*[84] consisting of about 80 patients with COVID-19 demonstrated no relationship between abnormality of hepatic function test and hydroxychloroquine therapy.

The therapeutic agent tocilizumab (IL-6 receptor monoclonal antibody) prevents the signal transduction of the cytokines pathway and blocks the pro-inflammatory actions[85]. Tocilizumab has many adverse effects, such as dizziness, sore throats, fungal infection, hypertension, and headache[86]. In the case of utilizing tocilizumab to treat severe COVID-19 patients, IL-6 is significantly elevated due to cytokine storm which worsens the COVID-19 course[87]. The inflammatory markers, for example, D-dimer and CRP, have also diminished when utilizing tocilizumab in around 50 patients with severe COVID-19, although the reduction in these markers has not greatly influenced the outcome[88]. Tocilizumab administration damaged the liver after 2 wk *via* the development of liver injury induced by the drug in around 90 patients with COVID-19. However, close monitoring should be done during and after giving tocilizumab to COVID-19 patients[89].

The antimicrobial therapeutic medicine azithromycin is utilized to heal bacterial infections, which has the ability to reduce severe lower respiratory tract infections[90]. Azithromycin binds to the ACE-2 receptor-COVD-19 spike protein complex, leading to a reduction in the downstream signaling. As a result, the effect of the virus is inhibited[91]. In COVID-19, azithromycin is used to prevent the first step of virus replication. The outcomes of clinical trials suggest that it should be given alone or with hydroxychloroquine[92]. The transaminase concentrations have significantly increased more than five times when using azithromycin in combination with ritonavir, hydroxychloroquine, and lopinavir to treat COVID-19 in patients with no prior history of hepatic disease[93].

COVID-19 VACCINES AND THE LIVER

SARS-CoV-2-infected patients could recover without specific medicines. So far, the impact of COVID-19 vaccination on CLD is still unknown. The early vaccination for COVID-19 is valuable for the proliferative responses of T lymphocytes and antibody production, resulting in diminished danger of COVID-19 severity. COVID-19 vaccination is necessary for those with liver diseases such as liver cirrhosis and those with liver transplant (LT). The acquisition of immunity following COVID-19 vaccination in patients with liver transplant is low in comparison with normal individuals. The neutralizing antibodies can be observed in approximately 48% of LT patients[94]. A study by Ruether *et al*[95] illustrated that the rates of T-cell response and serum conversion in the second COVID-19 vaccination were 36.6% and 63%, respectively. The percentage of serum conversion for patients with hepatic cirrhosis could reach 100% after the second vaccination.

A study demonstrated that SARS-CoV-19 infection was diagnosed after a single dose of vaccine in 62% and after a couple of doses in 38%. It is reported that COVID-19 vaccination reduced the infection by SARS-CoV-2, and as a result, the consequences of infection with CLD were improved (*e.g.*, respiratory symptoms, hospitalization, invasive ventilation, ICU admission, and death)[96]. In patients with prior LT as well as cirrhosis, it is recommended to fully vaccinate to reduce the cases of severe infection. The immunity against COVID-19 begins after 2 wk of the first dose of the vaccine and elevates extra after the second dose[97].

To increase immunity and decrease COVID-19 cases, it is interesting to provide a booster dose of COVID-19 vaccination (3rd and 4th doses). The antibody titers were elevated after the third dose of COVID-19 vaccination in LT recipients who had negative antibody titers[98,99].

It is well-known that COVID-19 vaccines have local (like local injection site pain) or systemic adverse effects (like smell and taste abnormalities). Local side effects are more common in occurrence than systemic ones. Autoimmune hepatitis and HCV reactivation are examples of liver involvement following COVID-19 vaccination[100-102]. These conditions were reported on rare occasions as case reports. Even though they are identified as rare complications, one should consider them in determining the future safety of these vaccines.

PROGNOSIS

Despite COVID-19 principally causing respiratory manifestations, it also could lead to extrapulmonary diseases as comorbidities, such as hyperglycemia and ketosis, thrombotic complications, cerebrovascular disease, acute kidney failure, neurologic illnesses, diabetes mellitus, gastrointestinal symptoms,

hypertension, hepatocellular injury, and dermatologic manifestations. These symptoms could happen in infected subjects without a recognized preexisting organic disease[64,103].

COVID-19 patients with CLD, particularly those with cirrhosis, have various forms of immune dysfunction which result in an increased risk of infection and abnormal inflammatory response during infection. Cirrhosis-associated immune dysfunction consists of decreased macrophage activation, combinations of the complement system, upregulation of Toll-like receptors, intestinal dysbiosis, and impaired neutrophil and lymphocyte function[104]. Individuals with pre-exciting CLD and cirrhosis are more likely to be infected by SARS-CoV-2. The etiology of hepatic disease could impact clinical outcomes in SARS-CoV-2 infection. In general, advanced age, diabetes, and obesity are risk factors for SARS-CoV-2 mortality and morbidity[105]. Nevertheless, such patients are not diagnosed with NAFLD because liver steatosis was not reported or alcohol use was not determined. Many contradictions throughout the literature have been illustrated in the case of the impact of NAFLD on the SARS-CoV-2 course. The contradiction might be correlated to difficulty in distinguishing the influence of NAFLD from different metabolic comorbidities; this could be due to the effect of virus-induced steatosis or different diagnostic criteria. A retrospective study of 202 patients with COVID-19 recognized NAFLD as a dangerous aspect for longer viral shedding times, abnormal concentrations of liver enzymes, and progressive COVID-19[49]. However, a study of 70 subjects with SARS-CoV-2 infection and autoimmune hepatitis revealed that there is an equivalent result to subjects with other causes of CLD and propensity score-matched controls despite the use of baseline immunosuppression in 86% of patients[106]. The major reason for death is CLD liver-correlated mortality preceded by SARS-CoV-2-induced pulmonary disease[107].

Of note, if individuals are infected with COVID-19 and have preexisting CLD, the increase in mortality and morbidity has occurred with the rising severity of cirrhosis. An increase in mortality was found for individuals who required intensive care, and only 10% of patients who underwent mechanical ventilation survived. However, a significant relationship has been illustrated between SARS-CoV-2-related mortality and preexisting severe liver cirrhosis, which results in a rise in the mortality percentage[107]. SARS-CoV-2, similar to influenza, could lead to acute-on-chronic liver failure (ACLF); ACLF could be caused by viral illness or bacterial infection, and ACLF is noticed through the increasing severity of the disease and liver decompensation[108].

Gut microbiota composition has the function of regulating the severity of COVID-19 by modulating the immune responses of the host; alterations to the gut microbiota composition are caused by cirrhosis and intestinal permeability. The changes in the gut-liver axis may participate in the course of severe COVID-19 noticed in the patient group[109].

It is worth mentioning that the main reason for deaths in individuals with COVID-19 and cirrhosis is respiratory failure, despite that the accurate path of this observation is still unclear. It is reasonable that the hallmark of severe SARS-CoV-2 infection, pulmonary thromboembolic disease, has a participatory role in the hypercoagulable case related to cirrhosis. Thromboprophylaxis is recommended during the period that COVID-19 patients stay in the hospital[110]. Given together, the relationship and coexistence of coagulopathy with both COVID-19 and cirrhosis are leading to a cumulative danger of thrombotic complications[111]. Moreover, research has reported with 40 patients that the use of thromboprophylaxis in individuals with COVID-19 and cirrhosis yielded no risk of hemorrhagic complications[112].

CONCLUSION

Abnormal liver function tests are common at the presentation and increased during the COVID-19 course. There are six proposed pathophysiological mechanisms of liver involvement: Hypoxia, direct viral effect, drug-induced liver injury, cytokine storm, elevated hepatic chemistry tests, and preexisting CLD. Various liver involvements occur, which include, but are not exclusive to, elevated AST and ALT, hyperbilirubinemia, prolonged prothrombin time, elevated ALP, GGT elevation, and low serum albumin level. Hepatic involvements determine the severity of COVID-19. Abnormal liver function tests are more in non-survivors than in survivors. Great care is highly recommended to avoid liver injury in COVID-19 patients by modulation of therapeutic agents and regular measurement of the liver function tests, particularly in patients with a history of CLD. COVID-19 vaccines have adverse effects on the liver, for example, resulting in autoimmune hepatitis. However, complete COVID-19 vaccination for patients with a history of CLD or those who were subjected to LT is highly recommended to avoid the occurrence of the disease and further hepatic destruction.

FOOTNOTES

Author contributions: Al-Ani RM designed the study, wrote the abstract, core tip, introduction, and conclusion, formatted the references, edited the draft, and prepared the final version of the manuscript; Al-Rawi TSS collected the references and wrote the majority of the manuscript; both authors revised and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors declare that there is no conflict of interest to disclose.

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S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Liu JH

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World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 January 12; 11(1): 18-28

DOI: 10.13105/wjma.v11.i1.18

ISSN 2308-3840 (online)

MINIREVIEWS

Cancer risk stratification system and classification of gastritis: Perspectives

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Muguruma N, Japan; Quach DT, Viet Nam

Received: October 26, 2022
Peer-review started: October 26, 2022
First decision: November 16, 2022
Revised: November 17, 2022
Accepted: December 27, 2022
Article in press: December 27, 2022
Published online: January 12, 2023

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Abstract

Kyoto global consensus reports that the current ICD-10 classification for gastritis is obsolete. The Kyoto classification of gastritis states that severe mucosal atrophy has a high risk of gastric cancer, while mild to moderate atrophy has a low risk. The updated Kimura-Takemoto classification of atrophic gastritis considers five histological types of multifocal corpus atrophic gastritis according to stages C2 to O3. This method of morphological diagnosis of atrophic gastritis increases sensitivity by 2.4 times for severe atrophy compared to the updated Sydney system. This advantage should be considered when stratifying the high risk of gastric cancer. The updated Kimura-Takemoto classification of atrophic gastritis should be used as a reference standard (gold standard) in studies of morpho-functional relationships to identify serological markers of atrophic gastritis with evidence-based effectiveness. The use of artificial intelligence in the serological screening of atrophic gastritis makes it possible to screen a large number of the population. During serological screening of atrophic gastritis and risk stratification of gastric cancer, it is advisable to use the Kyoto classification of gastritis with updated Kimura-Takemoto classification of atrophic gastritis.

Key Words: Atrophic gastritis; Cancer risk stratification; Gastric cancer prevention; Classification of gastritis

Core Tip: Prevention of gastric cancer is an actual challenge of modern oncology. Its implementation is possible by means of serological screening of atrophic gastritis with accurate morphological diagnostics within the framework of the Kyoto classification of gastritis. If the Kyoto classification of gastritis is supplemented with the updated classification of Kimura-Takemoto atrophic gastritis, then it will be easier to estimate the risk of developing stomach cancer. The new system of gastric cancer risk stratification has the prospect of practical application in any population. For gastric cancer prevention at the level of large populations, we suggest using computer programs. The authors' computer program is given in this manuscript.

Citation: Kotelevets SM, Chekh SA, Chukov SZ. Cancer risk stratification system and classification of gastritis: Perspectives. *World J Meta-Anal* 2023; 11(1): 18-28
URL: https://www.wjgnet.com/2308-3840/full/v11/i1/18.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i1.18

INTRODUCTION

The statement that *Helicobacter pylori* (*H. pylori*) is the main cause of gastritis, atrophic gastritis, and gastric and duodenal ulcers belongs to the Kyoto global consensus. "Question of the hour" of gastroenterology is whether the current ICD-10 classification for gastritis is appropriate for use. Kyoto global consensus reports that the current ICD-10 classification for gastritis is obsolete[1]. At the present time, the complete classification of atrophic gastritis is absent. Lahner *et al*[2] mention autoimmune atrophic gastritis other than *H. pylori*-induced atrophic gastritis. There are very few modern publications on the topic of reflux-induced atrophic gastritis. Gad Elhak *et al*[3] revealed that after cholecystectomy, the incidence of reflux-induced atrophic gastritis increases, and the incidence of *H. pylori*-associated gastritis decreases. Nishidoi *et al*[4] found a relationship between resection of the stomach of male Wistar rats and the incidence of remnant stomach carcinoma. Moreover, the larger part of the stomach was removed, the more often carcinoma of the stomach remnant developed. The pathway of carcinogenesis in this case is considered duodeno-gastric reflux, especially bile acid reflux. Histologic examination of the gastric mucosa revealed atrophic gastritis. Bile acid reflux contributes to the development of atrophic gastritis and increases the incidence of intestinal metaplasia of the gastric mucosa[5].

Japanese authors Toyoshima *et al*[6] proposed an integral system for stratification of the risk of gastric cancer development, including the Kyoto classification of gastritis and neutrophil activity which was scored according to the updated Sydney System using biopsy samples obtained from the greater curvature of the corpus and the antrum. The Kyoto classification is based on the following scoring criteria: Atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness ranging from 0 to 8. This is a visual endoscopic rating. The morphological assessment is restricted only by neutrophil activity scoring in a small number of biopsy specimens taken by means of the Sydney system. Histological evaluation of the mucosal atrophy and intestinal metaplasia is absent.

The integrated assessment of the risk of developing stomach cancer using the updated Kimura-Takemoto classification of atrophic gastritis has many possibilities because biopsy specimens are available in optimal numbers. There are five biopsy specimens for the gastric corpus and one for the antrum. Each biopsy specimen represents the stage of gastric mucosal atrophy from C1 to O2[7]. The Kyoto global consensus states that severe mucosal atrophy has a high risk of gastric cancer, while mild to moderate atrophy has a low risk[1]. The updated Sydney system takes into account two types of multifocal atrophic gastritis: Antral atrophic gastritis and corpus atrophic gastritis[8-13]. The updated Kimura-Takemoto classification of atrophic gastritis considers five histological types of multifocal corpus atrophic gastritis according to stages C2 to O3. This method of morphological diagnosis of atrophic gastritis increases sensitivity by 2.4 times for severe atrophy compared to the updated Sydney system. This advantage should be considered when stratifying the high risk of gastric cancer[7].

NON-INVASIVE SEROLOGICAL SCREENING FOR MULTIFOCAL ATROPHIC GASTRITIS

Endoscopic and morphological diagnosis of atrophic gastritis cannot be used for a large number of the population. Non-invasive serological screening for atrophic gastritis is essential at the first step in the prevention of gastric cancer. The search for effective serological markers of gastric mucosal atrophy is a very long process. Modern methods for the detection of atrophic gastritis and risk of gastric cancer using gastrin-17 (G-17), pepsinogen-I (PG-I), and the ratio of PG-I/PG-II are not perfect. Development of markers for atrophic gastritis and risk of gastric cancer continues[9,14-20]. Uniform criteria for assessing the concentration levels of the markers G17, PG1, PG2, and PG1/PG2 ratio are not defined when using by various authors. The location of gastric mucosal atrophy (antral atrophic gastritis, corpus

atrophic gastritis, and multifocal atrophic gastritis) is not taken into account when using serological levels and other criteria to assess the severity of atrophy. The updated Sydney system was used in all morpho-functional studies as a reference method. At the same time, it does not have sufficient sensitivity to detect multifocal atrophic gastritis[7,21-28].

USE OF COMPUTER DATA PROCESSING TO RISK STRATIFICATION OF GASTRIC CANCER

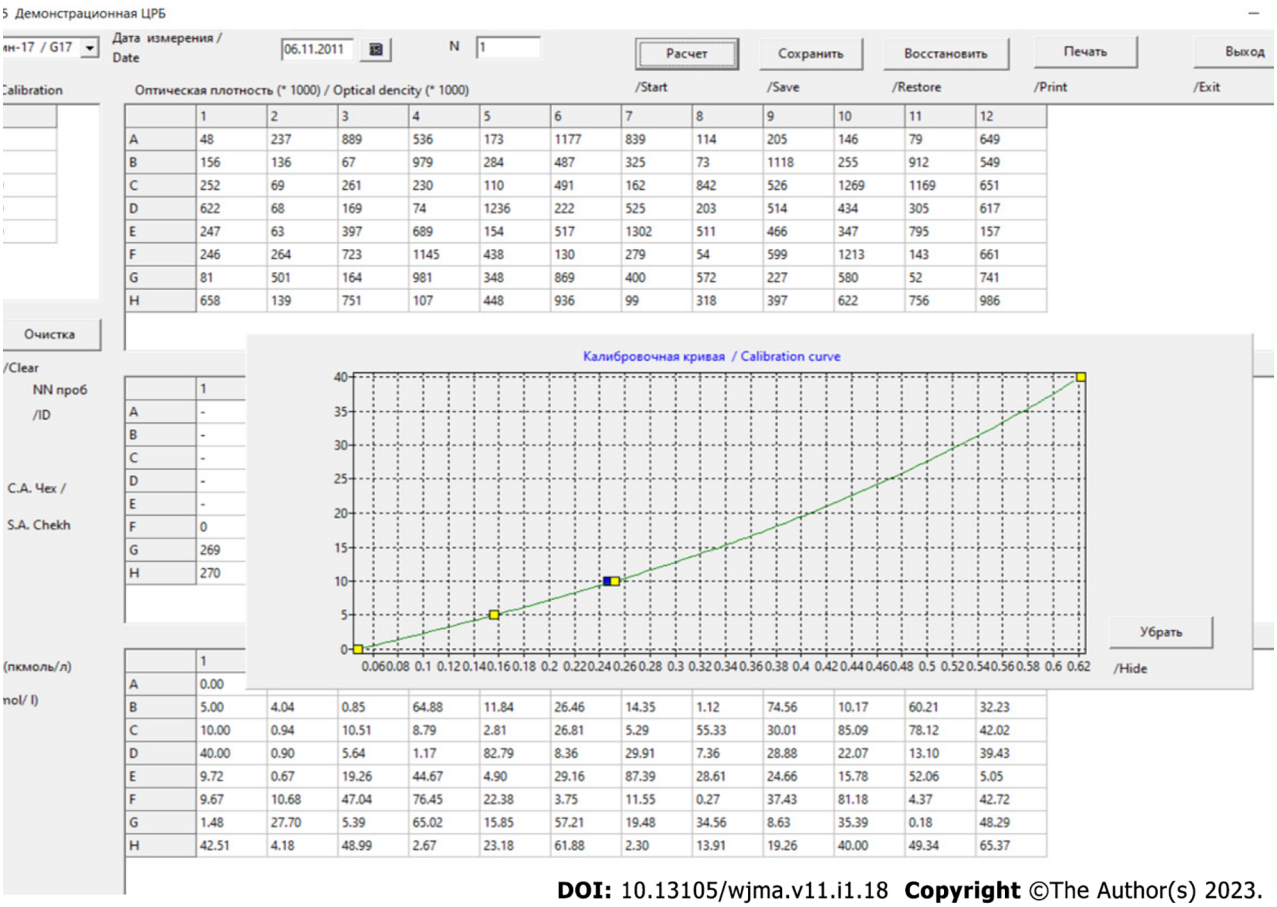
The use of machine processing can improve the efficiency of finding markers. Kotelevets CM and Chekh SA selected three markers of gastric mucosal atrophy from 47 factors associated with atrophy using computer data processing in 360 patients. In addition, serological criteria for mild, moderate, and severe atrophy were determined for the gastric antrum and corpus. These criteria were used for screening of about 5000 patients. Patient data, including personal data, were recorded in the registry after obtaining informed consent. Then, depersonalized referrals for serological testing were issued to the patient. Blood samples are stored at low temperature (-20 degrees Celsius). The analysis is performed on an enzyme immunoassay analyzer, which has 96 cells. Five of them are used for calibration samples, and the rest are used for patient samples. The optical density values are entered into the program, where the concentration values are calculated taking into account the calibration samples. Concentration values can be entered directly if the instrument used provides calibration (Figure 1). The time for obtaining optical densities on an enzyme immunoassay analyzer is 3.5 h. The researcher enters the year of birth and gender for each patient, and receives recommendations from the program (adjust them if necessary). The results are given to the patient in printed form, indicating the patient's full name, and affixing a signature and seal (Figures 2 and 3). This screening technique was presented in detail at the Third Congress of Therapists of the North Caucasian Federal District (Stavropol, May 19, 2016). This approach allowed to save the lives of patients with precancerous gastric disease[29,30]. Machine processing allows to reduce the fuzziness and randomness in data handling and thus can serve as the primary choice for obtaining results and big data analysis to make informed decisions. Artificial intelligence and Bidirectional Deep Neural Networks (BiDEN) are increasingly used for stratification of risk of gastric cancer development. Modern information technologies make it possible to obtain numerous multiomics data during screening of atrophic gastritis[29-33]. They are also used to evaluate data obtained from endoscopic and histological findings from initial endoscopy, barium double-contrast radiography of the upper gastrointestinal tract, and endoscopic three-dimensional (3D) reconstruction of the mucosal surface[34-36].

PERSPECTIVE FOR SEROLOGICAL SCREENING FOR ATROPHIC GASTRITIS

Due to the limitations of the endoscopic method of examining the stomach, a full-fledged endoscopic screening for atrophic gastritis and precancerous changes in the gastric mucosa in the population is not possible[37]. The Kyoto global consensus states that serological tests are useful for risk stratification of gastric cancer[1]. Therefore, it seems useful to include a section on serological screening for atrophic gastritis in the Kyoto classification of gastritis. For many years, the best markers of atrophic gastritis, precancerous changes, and the risk of gastric cancer have been PG-1, PG-2, G-17, the ratio of PG-1/PG-2, and antibodies to *Helicobacter pylori* (*H. pylori*). This has been confirmed by numerous multicenter studies and meta-analyses[37-46]. The current analysis is carried out, first of all, regarding the economics of serological screening for atrophic gastritis and precancerous changes in the gastric mucosa and determining the risk of gastric cancer. The main requirement for any screening is the availability of implementation in a large population. The cost should be low and the method should be non-invasive. These conditions are met by serological screening using markers PG-1, PG-2, G-17, the ratio of PG-1/PG-2, and anti-*H. pylori* IgG[47-49]. The effectiveness of serological screening of atrophic gastritis is significantly increased if serological markers are used that allow to differentiate between mild, moderate, and severe mucosal atrophy. The use of such markers by means of computer data processing made it possible to save more than four lives within seven years in a group of 2220 people[28,29].

PATHOLOGICAL ASPECTS OF USE OF CLASSIFICATIONS OF GASTRITIS

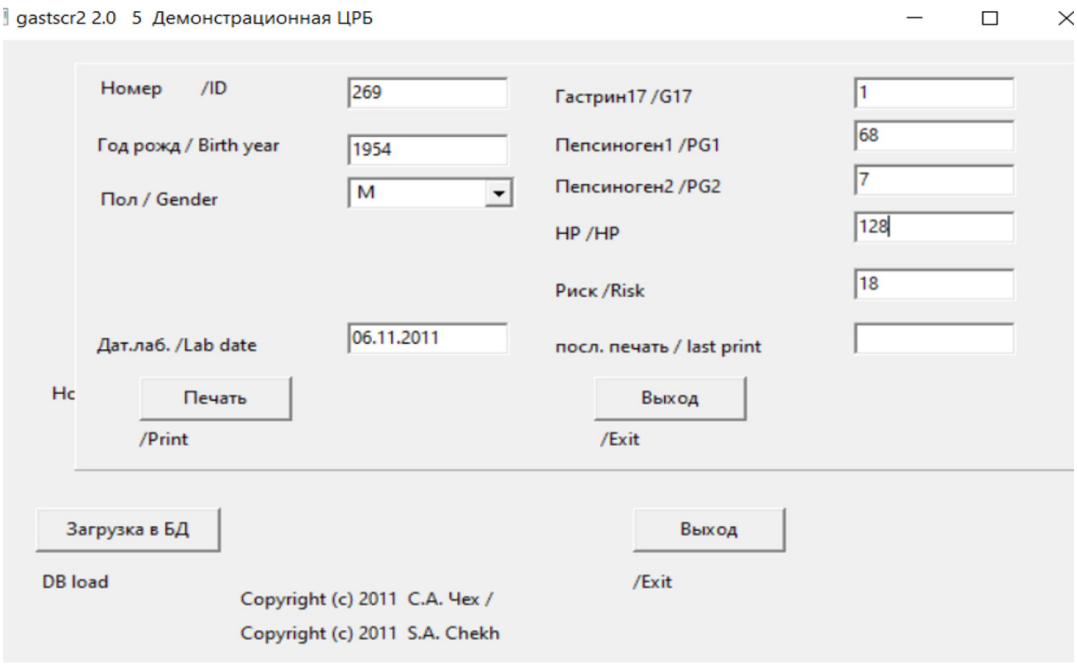
Accurate diagnosis of chronic atrophic gastritis is of critical importance in monitoring stomach cancer, which remains the leading cause of death of cancer patients worldwide. According to the International Agency for Research on Cancer (IARC) GLOBOCAN project, worldwide, there were 1033701 new cases of gastric cancer (representing 5.7% of all cancer cases diagnosed)[50]. Gastric carcinogenesis is a complex multifactorial process. Currently, obvious evidence has been obtained about the main role of *H. pylori* in the development of gastric cancer[51]. *H. pylori* was declared a class 1 carcinogen by the World



DOI: 10.13105/wjma.v11.i1.18

Figure 1 Calculation of laboratory parameters by optical density.

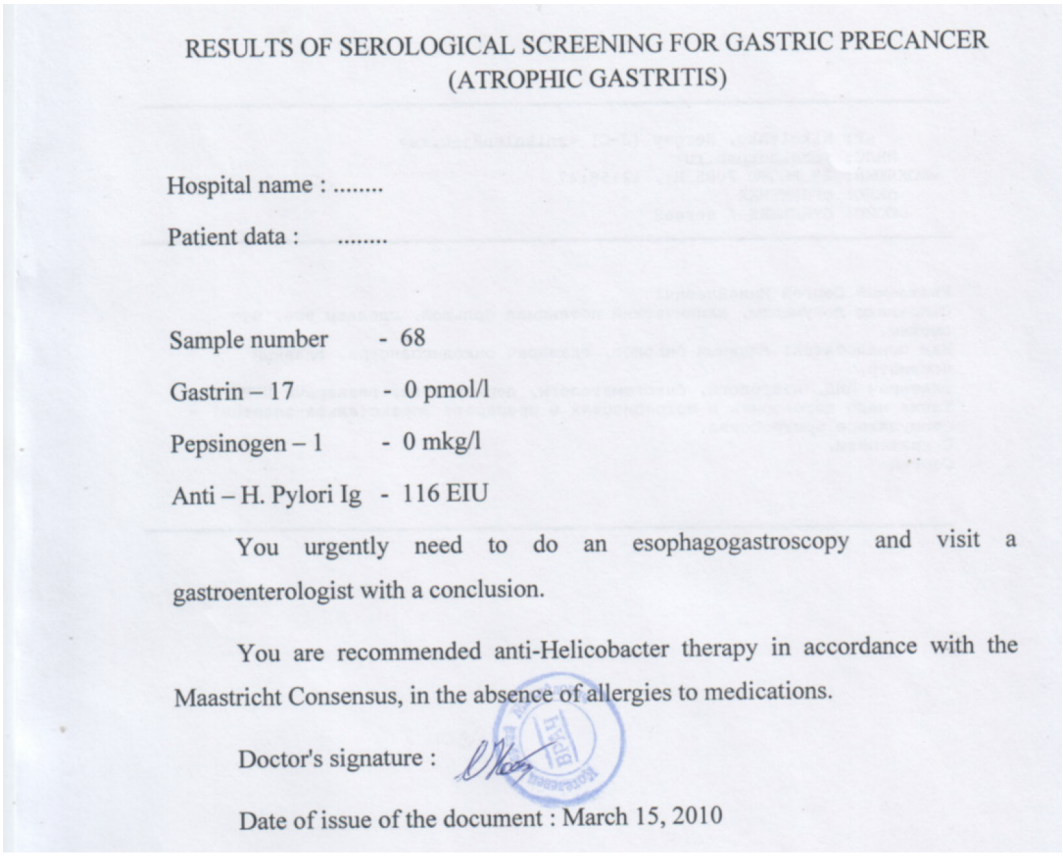
Health Organization committee of experts, even though the final mechanism of *H. pylori*-associated carcinogenesis has to be studied[52]. The main events in the pathogenesis of gastric cancer include the interaction of *H. pylori* virulent factors, environmental factors, and genetically determined sensitivity of the patient's organism. At least 70% of cases of non-cardiac gastric cancer are associated with the consequences of *H. pylori* infection[53]. It is also known that the risk of developing gastric cancer in *H. pylori*-infected subjects is significantly (from 6 to 25 times or more) higher than that in uninfected[54]. Gastric cancer is divided into two main types according to the Lauren classification – intestinal and diffuse. Intestinal gastric cancer, in accordance with the Correa paradigm[55], occurs through the sequential development of a cascade of pathological changes, starting with gastritis, followed by the appearance of atrophy, intestinal metaplasia, dysplasia, and finally, adenocarcinoma. Diffuse gastric cancer occurs *de novo*, without obvious previous histological changes in the gastric mucosa[56]. Both types of gastric cancer are characterized by the clear association with *H. pylori* infection[57]. *H. pylori* infection usually occurs in early childhood, and there is global interest to determine the age period from which it makes sense to carry out *H. pylori* eradication as a preventive measure for the development of gastric cancer – the so-called "point of no return" of precancerous changes in the gastric mucosa. An increased risk of developing gastric cancer in chronic *H. pylori* infection is associated with increased proliferation of gastric epithelial stem cells, and this increase occurs in two ways: As a response to damage to the gastric mucosa requiring intensive regeneration, and as a direct consequence of activation of intraepithelial signaling pathways associated with accelerated cell division. Studies of the surgical material of resected stomachs carried out in the first half of the last century showed that in cases of gastric cancer, there was always detected chronic gastritis of greater severity than in cases of peptic ulcer disease[58]. The researchers also noted that the foci of adenocarcinoma were more often found in areas of chronic inflammation, especially in atrophic gastritis. The advantage and necessity of histological examination are that it reveals causative relationships in the pathogenesis of *H. pylori*-associated gastric mucosal injury, establishing the presence of bacteria and the consequences of an inflammatory response to the infection as a cascade of changes, starting with acute inflammation, followed by transformation into a chronic course, with further disruption of regeneration processes in the form of atrophy, metaplasia, dysplasia, and finally, tumor growth. This defines the histological examination of gastric specimens as diagnostic "gold standard"[59-61]. At the same time, the problems of histological examination remain, such as sampling (the number and site of biopsies), the staining



DOI: 10.13105/wjma.v11.i1.18

Figure 2 Linking serological screening results to a specific patient.

methods, and the pathologist's experience[61-64]. Although atrophy and intestinal metaplasia (IM) are independent stages of the Correa cascade, they are often detected simultaneously. Atrophy is defined by most pathologists as the loss of specialized glandular tissue (for example, the loss of the main gastric glands in the stomach corpus mucosa)[65]. Atrophy is usually detected in the form of a multifocal or diffuse process, and in the cases of atrophy of the oxyntic mucosa, one can reveal the appearance of mucous glands characteristic of the antral mucosa - the so-called pseudopiloric metaplasia (PM)[58]. IM is the replacement of the original gastric glands with intestinal crypts lined with absorbent and goblet cells, in combination with inflammatory infiltration of the mucosal lamina propria[65]. According to studies, PM correlates more closely with the presence of gastric cancer than IM, and may be a precursor of neoplastic changes[66]. One of the possible explanations for the relationship between the loss of parietal cells in atrophic gastritis and the development of metaplastic changes is the fact that the loss of parietal cells is associated with a decrease in the levels of signaling molecules modulating the growth and differentiation of stem cells of the gastric mucosa, which leads to increased proliferation and accumulation of undifferentiated progenitor cells[67]. Among such signaling molecules, there is a family of Sonic hedgehog (SHH) proteins, which are considered one of the key regulators of growth and differentiation of a wide range of tissues during embryogenesis. Immunohistochemical studies have shown that SHH is expressed by parietal cells[68], and SHH levels are reduced in patients with atrophic gastritis[69]. Experimental studies have shown that SHH-deficient mice developed IM in the gastric mucosa[70]. In acute pharmacological ablation of parietal cells, rapid and reversible development of PM was observed[71]. There are three categories of IM based on the structure of the crypts formed and the type of mucin. Type I (or complete type of) IM resembles a small intestinal mucosa in structure, while enterocytes, Paneth cells and goblet cells containing sialomucins are detected in direct crypts. Type III IM resembles a large intestinal mucosa: Columnar epithelial cells containing sulfomucins are found in the convoluted crypts. Type II is an incomplete small intestinal metaplasia without Paneth cells, or there can be the mixture of the first and third types. Type III IM is considered to be more precancerous. Thus, in a prospective study of 1281 patients, Filipe *et al*[72] found that with the development of type III IM, the risk of developing gastric cancer is increased by 3.8 times compared to type I IM. Despite the fact that atrophy and IM often accompany each other in patients with chronic gastritis, these conditions represent two different processes. The mechanisms of development of these two conditions continue to be studied. It is important that the pathologists separately evaluate the severity of gastric atrophy and IM, with the interpretation of the degree of their progression. The mechanism of IM development is caused in general by an impairment of differentiation of gastric mucosal proliferating stem cells. In particular, the differentiation of these cells is regulated by the homeobox genes, Hox and ParaHox clusters containing the Pdx1, Cdx1, and Cdx2 genes. The latter seem to be the most important in the expression of the small-intestinal phenotype, unlike Cdh1 genes, whose expression is realized in the direction of the large-intestinal phenotype[73]. The Cdx2 protein is not found in the normal gastric mucosa, but is expressed in the IM sites, as well as in the cases of Barrett's esophagus. The mechanism of induction of Cdx2 gene expression in chronic gastritis has to be elucidated. After the development of



RESULTS OF SEROLOGICAL SCREENING FOR GASTRIC PRECANCER (ATROPHIC GASTRITIS)

Hospital name : .....

Patient data : .....

Sample number - 68

Gastrin – 17 - 0 pmol/l

Pepsinogen – 1 - 0 mkg/l

Anti – H. Pylori Ig - 116 EIU

You urgently need to do an esophagogastroscopy and visit a gastroenterologist with a conclusion.

You are recommended anti-Helicobacter therapy in accordance with the Maastricht Consensus, in the absence of allergies to medications.

Doctor's signature :

Date of issue of the document : March 15, 2010

DOI: 10.13105/wjma.v11.i1.18

Figure 3 The conclusion of the patient after serological screening.

IM, according to the Correa cascade, dysplasia develops in the gastric mucosa, and the mechanism of this transition also remains unclear. The concept proposed by Correa in 1975[74] is generally accepted, according to which the metaplastic epithelium itself is a precursor of neoplasia. An alternative hypothesis suggests that IM is nothing more than an adaptive process in response to chronic damage. IM foci may be surrounded by areas of enhanced apoptosis, while apoptosis in the IM foci is reduced [75]. This is due to the expression of trefoil peptides that reduce apoptosis and stimulate differentiation in the direction of IM. The progression of gastric carcinogenesis is stimulated by the accumulation of genetic changes, which, in particular, manifest themselves at the chromosomal level. The molecular changes underlying these precursor processes require further study. The increased risk of developing gastric cancer may also be due to other factors that occur during the development of atrophic gastritis. These factors may include constantly enhanced cellular renewal in the atrophic mucosa, enhanced mutagenesis due to high levels of nitrites, and reduced levels of ascorbic acid in the gastric juice of these patients. Another proposed mechanism is based on the hypothesis that hydrochloric acid production may have a protective effect against gastric carcinogenesis. In the atrophic mucosa, a decrease in hydrochloric acid production leads to a decrease in purification from anaplastic cells in areas of micro-injury and the development of carcinoma *in situ*[76]. The unification of the assessment of inflammatory damage, atrophy, and IM in *H. pylori*-associated gastritis by means of a visual-analog scale was carried out in the Sydney system and its Houston modification[77]; however, it did not allow assessing the prognosis of damage and seemed to some researchers too weighty for use in routine diagnostics. In April 2005, in Parma, an international group of researchers, including gastroenterologists and pathologists [Operative Link for Gastritis Assessment (OLGA)], made a critical revision of the modified Sydney system[78]. OLGA experts concluded that since the risk of developing gastric cancer is directly related to the prevalence of gastritis and atrophy of the gastric mucosa, it is necessary to develop a system for assessing the stage of atrophic gastritis, which would ensure the determination of the prognosis and possibly, the tactics of the gastroenterologist. The proposed staging system combines indicators of atrophy in the stomach corpus and antrum, by using a visually analog scale of the modified Sydney system. Such a scheme will allow the clinician to get an idea of the prevalence of damage to the gastric mucosa and the degree of risk of developing gastric cancer in the specific patient. Also, very reliable associations can be obtained in the diagnosis of atrophic gastritis by endoscopy using the Kimura-Takemoto system, the results of which also correlate quite satisfactorily with histological data. The accuracy of endoscopic diagnosis of atrophic gastritis by means of the Kimura-Takemoto system was proven by many research groups, and we also established high levels of its sensitivity and

specificity in our studies[7]. Finally, in 2013, the Japan Gastroenterological Endoscopy Society advocated the Kyoto classification, a new grading system for endoscopic gastritis. The classification is described above in this article. Ongoing studies indicate the usefulness of the Kyoto classification. For example, Toyoshima *et al*[79] accessed the association between the Kyoto classification and updated Sydney system score by comparison of endoscopic and pathologic (histologic) data. All endoscopic findings in the Kyoto classification for gastritis were associated with high scores of pathological inflammation (*i.e.*, neutrophil activity and chronic inflammation) in both the corpus and antrum. Endoscopic atrophy and intestinal metaplasia were associated with high scores of pathological atrophy and intestinal metaplasia in both the corpus and antrum. Nodularity was associated with a low score of pathological intestinal metaplasia in the antrum. Thus, endoscopy by means of the Kyoto classification is very close to the real state of affairs, and yet, it is strongly recommended to be accompanied with histology of the gastric mucosa in patients with chronic atrophic gastritis, especially when the precancerous changes are revealed by endoscopy. It should be noted that the histological assessment of the gastric mucosa both by the modified Sydney system and by OLGA (Operational Link for Gastritis Assessment), or by Kimura-Takemoto classification is significantly limited by the number of biopsies and by the site of the biopsy. All three classifications use the same standard for taking a biopsy. Three biopsies (including incisura angularis) allow to characterize and evaluate the antral mucosa (the lesser functional part of the stomach), which reflects the morphological state of only the initial stage of the atrophic process according to Kimura-Takemoto – C1. Only two biopsies from the Sydney system remain to assess the stage of the atrophic process in the largest functional part of the stomach - the body, analogous to the respective grades of Kimura-Takemoto visual endoscopic classification (C2, C3, O1, O2, and O3). The updated Kimura-Takemoto classification of atrophic gastritis has much greater diagnostic capabilities and possibilities for stratifying the risk of gastric cancer. According to this technique, it is necessary to take six biopsies in accordance with C1 to O3 grades. Each biopsy allows stratifying the risk of gastric cancer from low to high at each stage: C1 – O3, according to the degree of histological atrophy from mild to severe[7].

CONCLUSION

The practical significance of the classification of stomach diseases is the prevention of stomach cancer, since this malignancy is the third most common cause of cancer death (782685 cases in 2018) among all oncological diseases[80]. The main advantage of the Kyoto classification is that it contains a detailed section on the etiology of gastritis. In the section of chronic atrophic gastritis, only mild to moderate atrophy of the stomach and severe atrophy of the stomach are distinguished[1]. This is not enough to effectively stratify the risk of stomach cancer. For effective practical use of the Kyoto classification of gastritis, it is advisably to supplement it with at least three more sections.

At the initial stage of gastric cancer risk stratification, serological screening for atrophic gastritis should be used. When using serological markers of atrophic gastritis, it is necessary to take into account the serological criteria for mild, moderate, and severe atrophy of the antrum mucosa and the stomach body[28].

At the second stage, it is necessary to carry out endoscopic screening among patients with atrophic gastritis who were identified at the stage of serological screening. Since the Kyoto classification of gastritis based on endoscopy and the pathological topographic distribution of neutrophil infiltration correlate with the risk of stomach cancer, endoscopic screening should be carried out taking into account the Kyoto endoscopic classification scale[6].

At the final diagnostic stage, it is necessary to carry out histological diagnosis of multifocal atrophic gastritis in accordance with the updated Kimura-Takemoto classification of atrophic gastritis[7].

Only the integral approach to creating an effective classification of gastric pathology based on morphology will allow to achieve the overall goal of preventing stomach cancer by means of more accurate identification and morphological monitoring of severe atrophic gastritis (stomach precancerous condition).

FOOTNOTES

Author contributions: Kotelevets SM wrote the first part of the paper; Chekh SA wrote the second part of the paper; Chukov SZ wrote the third part of the paper.

Conflict-of-interest statement: All the author declare no conflict of interests for this article.

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S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Liu JH

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World J Meta-Anal 2023 January 12; 11(1): 29-37

DOI: 10.13105/wjma.v11.i1.29

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Post-COVID-19 cholangiopathy: A systematic review

Maddalena Zippi, Sirio Fiorino, Wandong Hong, Dario de Biase, Claudio Giuseppe Gallo, Alfonso Grottesi, Annamaria Centorame, Pietro Crispino

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Mahmoud MZ, Saudi Arabia; Shariati MBH, Iran

Received: August 25, 2022
Peer-review started: August 25, 2022
First decision: October 4, 2022
Revised: October 13, 2022
Accepted: November 23, 2022
Article in press: November 23, 2022
Published online: January 12, 2023

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Abstract

BACKGROUND

The recent and still ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entailed various long-term complications, including post-infectious cholangiopathy.

AIM

To identify the available studies concerning post-coronavirus disease 2019 (COVID-19) cholangiopathy.

METHODS

An extensive bibliographical search was carried out in PubMed and in Cochrane Library to identify the articles (retrospective and prospective studies, cohort studies, case series and case reports) published between January 1, 2020 and August 22, 2022, using both MeSH terms and free-language keywords: cholan-

giopathy; COVID-19; post-COVID-19 cholangiopathy; SARS-CoV-2.

RESULTS
Thirteen studies fulfilled the inclusion criteria, which included 64 patients suffering from this condition. The patients were male in 82.8% of cases. Liver transplant was executed in 6 patients and scheduled in 7 patients, while 2 patients refused the surgical approach. Therefore in 23.4% of the cases, performing this procedure appeared to be necessary.

CONCLUSION
This review has revealed that generally the involvement of the liver in the course of SARS-CoV-2 infection is mild and transient, inducing cholestasis of cholangiocytes but can also be severe enough to cause organ failure in some cases.

Key Words: Cholangiopathy; COVID-19; Post-COVID-19 cholangiopathy; SARS-CoV-2; Transplantation

Core Tip: As severe acute respiratory syndrome coronavirus 2 infection keeps spreading, its long-term complications, like cholangiopathy, will manifest. Post-coronavirus disease 2019 (COVID-19) cholangiopathy is most commonly identified in patients hospitalized in the intensive care unit and shows histological characteristics reminiscent of secondary sclerosing cholangitis. Post-COVID-19 cholangiopathy represents a serious complication that may evolve into liver failure, even requiring transplant.

Citation: Zippi M, Fiorino S, Hong W, de Biase D, Gallo CG, Grottesi A, Centorame A, Crispino P. Post-COVID-19 cholangiopathy: A systematic review. *World J Meta-Anal* 2023; 11(1): 29-37
URL: https://www.wjgnet.com/2308-3840/full/v11/i1/29.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i1.29

INTRODUCTION

It is well known that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the disease named coronavirus disease 2019 (COVID-19), can induce liver damage in addition to the prevailing respiratory diseases[1]. This pathogen determines gastrointestinal symptoms, especially hepatic, with a multifactorial modality: direct damage, intestinal translocation, drug hepatotoxicity and immune-mediated inflammation secondary to the "cytokine storm"[2-4].

The first mechanism described is due to the presence of angiotensin converting enzyme-2 (ACE-2) receptors expressed on the liver cells, in particular on the epithelial cells of cholangiocytes[5,6]. To the best of our knowledge, the first pathological description of the liver was reported in 2020 by Xu *et al*[7], who described a mild lobular and portal inflammation, thus exhibiting direct liver damage sustained by this virus. The reported incidence of liver injury ranges between 14.8% and 53.0% of infected patients, of which 2%-11% are suffering from known hepatic pathologies (nonalcoholic fatty liver disease, chronic viral hepatitis, immune-mediated liver disease and alcoholic hepatitis)[7,8]. The hepatic symptoms characterized by an increase of the transaminases and/or of the cholestasis indices are widely described in the literature and tend to appear during the course of the infection and decrease at the end of the disease course[9].

In particular, an increase in serum gamma-glutamyl transferase (GGT) levels has been present in 27.9% of severe forms of COVID-19, suggesting an ongoing damage to the cholangiocytes[7,10]. Cholestasis is induced by high simultaneous values of GGT and alkaline phosphatase (ALP)[9]. In 2021, Roth *et al*[11] described a new hepatic manifestation characterized by severe cholestasis developed during the recovery phase in patients with the critical form of COVID-19, named "post-COVID-19 cholangiopathy"[12]. Several mechanisms inducing the cholangiocyte damage have been proposed by researchers and will be briefly described below.

Mechanisms of cholangiocytic damage

SARS-CoV-2 may infect the intestine, the liver, the kidneys and the brain cells. This variety of clinical manifestations is detectable not only during the acute phase of the disease but also in the recovery process[13]. The entry of the virus into the cell is preceded by the interaction of the pathogen with the ACE-2 receptor. The interaction is widely distributed in all the human tissues and easily observable in the liver and in the biliary tract[14,15]. In particular, increased mitotic activity of swollen hepatocytes, an enhanced rate of apoptosis visible in cells obtained from liver biopsies of COVID-19 patients as well

as the abundance of the ACE-2 receptor in the different types of liver cells, provide evidence that SARS-CoV-2 exhibits a substantial affinity for these hepatic cells[16]. Therefore, cholangiocytes, hepatocytes and bile duct cells represent an ideal reservoir for SARS-CoV-2[17].

A high expression of ACE-2 receptors and transmembrane serine protease 2 (TMPRSS2) has been reported in enteric neurons and in glial cells of the small and large intestines[18]. A recent study has shown that this enteric nervous system allows SARS-CoV-2 to reach the biliary tract of the liver by exploiting the well-known gut-liver axis[17]. ACE-2 receptors in cholangiocytes support a retrograde mode of liver damage after the virus has entered the biliary tree cells[19,20]. Liver biopsies confirm the presence of viral RNA in the liver tissues. Atypical signs of hepatocyte damage, such as cellular apoptosis along with swelling, acidophilic bodies and lobular inflammation, have been observed too, characterized by the mechanism of direct viral damage[21]. Some pathogenetic mechanisms have been correlated with tissue damage in these individuals, including ACE-2-mediated direct viral infection of hepatocytes. The virus could even infect cholangiocytes and dysregulate the functions of both the biliary tract cells and the entire hepatic gland, causing a direct liver injury[22-24] owing to the generation of organelles damage[10,22].

Acute and persistent lobular inflammatory damage may occur in the liver of patients with COVID-19. This process is characterized by: (1) Elevated levels of circulating proinflammatory cytokines/chemokines and other mediators, eventually triggering a cytokine storm and inducing liver dysfunction, as observed in a series of viral infections[22,25-27]; (2) A close association between liver injury and inflammatory responses whilst in SARS-CoV-2 infection[27], as patients with COVID-19 may incur hepatocellular damage, ranging from mild injuries to liver failure; and (3) Hepatotoxicity of drugs[22].

SARS-CoV-2 virions have been isolated in the bronchoalveolar fluid, in the sputum and in the blood samples of patients with COVID-19. However, recent evidence suggests the gastrointestinal tract represents a potential route of infection and transmission of this pathogen. Viable viral particles and RNA of SARS-CoV-2 have also been found in the feces of people suffering from COVID-19[28], meaning they may also represent a potential route of transmission. In synthesis, available studies show that: (1) It is possible a fecal-oral route of SARS-CoV-2 transmission in the gastrointestinal system and the virus replicates in the mucosa of the intestinal epithelial cells[29]; (2) A high expression of receptors and candidate coreceptors/auxiliary proteins can be identified in the gastrointestinal tract with an affinity for SARS-CoV-2; (3) An elevated expression of TMPRSS2 of the host is detectable in the cells of the gastrointestinal tract; (4) Following COVID-19 infection, the stool test for viral SARS-CoV-2 RNA gives a positive result for a considerable time in approximately 64% of patients with negative nasopharyngeal swab[30,31]; and (5) SARS-CoV-2 mRNA and its intracellular nucleocapsid protein can be observed in gastric, duodenal and rectal epithelia[32].

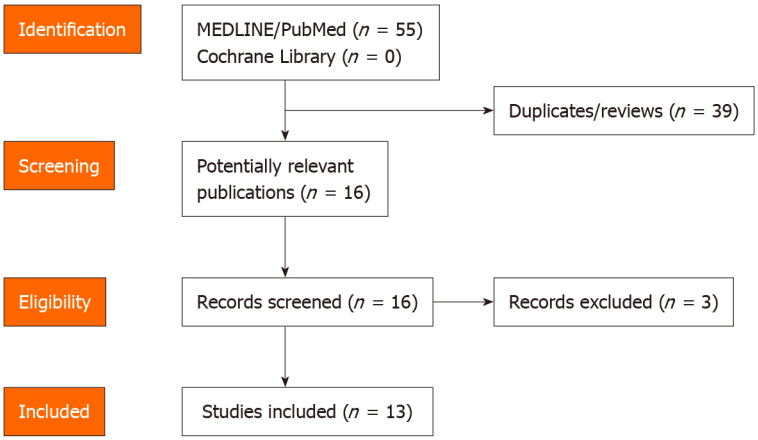
In order to pursue the objective of this research, we performed an extensive bibliographic search of the published works available in the literature concerning post-COVID-19 cholangiopathy. Then we conducted a systematic review of this topic.

MATERIALS AND METHODS

A systematic computer-based search of articles available in the literature was conducted through two electronic databases (MEDLINE/PubMed and Cochrane Library) with the aim of identifying relevant papers about post-COVID-19 cholangiopathy published between January 1, 2020 and August 22, 2022. Articles in all languages were considered. The MeSH terms and the keywords used were: "cholangiopathy," "COVID-19," "post-COVID-19 cholangiopathy" and "SARS-CoV-2." The authors used the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to it[33]. Two of the authors (de Biase D and Gallo CG) independently and in parallel carried out the literature search and identified the relevant articles based on the title and/or the abstract. The inclusion criteria considered in our analysis were: retrospective and prospective studies, cohort studies, case series and case reports. Two additional authors (Hong W and Grottesi A) independently extracted and tabulated all the relevant data from the selected studies. Fiorino S controlled the accuracy of the data extracted. When an inconsistency of the results emerged between the selected papers, a consensus among all the authors was required. To avoid possible duplicates, we looked for the first author's name, the place and the period of the enrollment of the subjects. The identified studies are depicted in Figure 1. In addition, we conducted a relevant search to supplement latest research results by Reference Citation Analysis (https://www.referencecitationanalysis.com/) when revising the manuscript.

Statistical analysis

The heterogeneity of data as well as the small size limited the ability to perform a comparative statistical analysis or a meta-analysis**.** Only a descriptive analysis with percentages has been carried out, not using any specific software.



DOI: 10.13105/wjma.v11.i1.29

Figure 1 Summary of study identification and selection.

RESULTS

Available studies

A total of 16 articles have been identified describing patients with post-COVID-19 cholangiopathy. Three were excluded for the following reasons: two papers described the cholestasis caused by intravenous ketamine used for the sedation of patients with acute respiratory distress syndrome (ARDS) [[34,35]; and the third concerned a retrospective study of 72 cholestatic patients observed as early as 28 d after admission[36]. The included studies are summarized in Table 1.

Taking into account the descriptive analysis of these 13 studies[11,37-48], the following data have been obtained: (1) 64 patients were examined, with a prevalence (82.8%) of males (53 males *vs* 11 females); (2) The average peak of ALP values was 75.5 d; (3) A liver biopsy was performed in 24 of the 64 patients (37.5%); (4) A total of 17 endoscopic retrograde cholangiopancreatography (ERCPs) were carried out, mainly to extract sludge and stones. During an examination, cholangioscopy was used to directly view the stenosed intrahepatic segment[43]; and (5) 6 patients received a liver transplant, while 7 patients have been scheduled for surgery. Two patients refused liver transplant. A total of 15 patients (23.4%) were eligible for a liver transplant.

DISCUSSION

Secondary sclerosing cholangitis in critically ill patients is a rare cholestatic condition encountered in patients developing sepsis or ARDS during a prolonged stay in the intensive care unit. This pathology rapidly induces cirrhosis, leading to liver failure. Its prognosis is poor, and the only option consists of a liver transplant. Some risk factors for post-COVID-19 cholangiopathy have been identified: mechanical ventilation, prone position and excess intraperitoneal fat[49]. Its pathogenesis is complex and is suggestive of a damage of ischemic origin that may involve the biliary tract until its stenosis and at the end a subsequent over infection caused by multidrug-resistant bacteria[49].

Roth *et al*[11] first noticed that the histological characteristics were similar to secondary sclerosing cholangitis in critically ill patients occurring in their patients, with severe damage to cholangiocytes. The injury of the cells has been characterized by a marked cytoplasmic vacuolization and by intrahepatic microangiopathy. This recognized pattern highly suggests a direct liver damage induced by SARS-CoV-2[11]. These findings have been the very first observations of secondary sclerosing cholangitis post-COVID-19. Hence, the authors suggested that post-infectious cholestasis could be due to an overlap of secondary sclerosing cholangitis in critically ill patients. This assumption is supported by a higher elevation of serum ALP levels registered in correlation with direct hepatic damage[11].

In a recent prospective cohort study, 461 patients with COVID-19 underwent liver function tests both during hospitalization and at 1, 3, 6 and 12 mo after their discharge[50]. The results showed that they markedly improved over time, with only 13.2% of tests altered at 12 mo compared to 25.1% in the 1st month[50]. Unfortunately, this study considered only GGT levels as a cholestasis index, with corresponding median values of 27 U/L (range: 18-40 U/L) in the 1st month of follow-up and 20 U/L (range: 13-29) after 1 year, without having tested and serum bilirubin levels[50].

In these subjects, the presence of a persistent cholestatic condition combined with jaundice requires diagnostic radiological integration. An intravenous contrast computed tomography scan of the abdomen may show both dilation of the intrahepatic bile ducts and of the common bile duct with hyperpotentiation of their walls[51]. A magnetic resonance cholangiopancreatography can provide

Table 1 Characteristics of patients with post-coronavirus disease 2019 cholangiopathy

Ref.	SARS-CoV-2 patient age, sex	Known liver diseases	ICU, mechanical ventilation	Time peak of ALP since COVID-19 diagnosis	Liver biopsy (time)	ERCP (time)	LT
Edwards *et al* [37], 2020	59 yr, male	No	Yes	79 d	Planned	Sludge clearance (2 procedures)	Planned for LT
Roth *et al*[11], 2021	38 yr, male	No	Yes	139 d	Yes (day 151)	Sludge extraction (day 180)	No
	25 yr, male	No	Yes	103 d	Yes (day 96)	Sludge and stones extraction (day 89 and 100)	No
	40 yr, female	No	Yes	172 d	Yes (day 178)	Not performed	No
Durazo *et al* [38], 2021	47 yr, male	No	Yes	81 d	Yes	Stone extraction and findings of SSC (day 73 and 81)	Yes
Lee *et al*[39], 2021	64 yr, male	No	Yes	60 d	No	Stone, extraction, insertion of 8.5 Fr biliary stent and findings of SSC (day 52 and day 150)	Yes
Faruqui *et al* [40], 2021	12 patients, mean age 58 yr (11 males, 1 females)	No	Yes	118 d	4 patients	4 patients	1 patient and 1 planned for LT, 2 patients declined
Rojas *et al* [41], 2021	29 yr, female	No	Yes	69 d	Yes	Negative	No
Bütikofer *et al* [42], 2021	11 patients with mild cholestasis (9 males, 2 females), 59 yr (range: 52-70)	No	Yes	1.7 d (range: 1.2-2.0 d)	4/9 patients (44%)	Not performed	1 planned for LT
	9 patients with severe cholestasis (7 males, 2 females), 59 yr (range: 53-68)	No	Yes	5.4 d (range: 2.5-7.4 d)	No	Not performed	No
Franzini *et al* [43], 2022	65 yr, male	No	Yes	63 d	No	Biliary casts removal	No
Santisteban Arenas *et al* [44], 2002	55 yr, male	No	Yes	74 d	Yes (in three patients)	Stones extraction in 1 patient	No
	54 yr, male	No	Yes	34 d			No
	62 yr, male	No	Yes	88 d			No
	56 yr, female	No	Yes	39 d			No
	73 yr, female	No	Yes	82 d			No
	34 yr, male	Hepatic hemangiomas	Yes	95 d			No
Ludwig *et al* [45], 2022	69 yr, male	Not known	Not known	Not known	Not known	Diffuse beading and stricturing of the intrahepatic bile ducts	Yes
Rela *et al*[46], 2022	50 yr, male	No	Yes	42 d (serum bilirubin)	Yes	Not performed	Yes
Kulkarni *et al* [47], 2022	8 patients unvaccinated, 59 yr (range: 24-67), all males	Fatty liver (2 patients)	7 patients (87.5%)	571.5 d (range: 368-1058 d)	5 patients	Not performed	2 patients and 4 patients planned for LT
	7 patients vaccinated, 52 yr (range: 29-67), 5 males and 2 females	Fatty liver (4 patients)	4 patients (57.1%)	312 d (range: 239-517 d)	2 patients	Not performed	No
Roda *et al* [48], 2022	63 yr with bilateral lung transplant, male	No	Yes	90 d	Cholangiopathy confirmed post-mortem	Not performed	No

ALP: Alkaline phosphatase; COVID-19: Coronavirus disease 2019; ERCP: Endoscopic retrograde cholangiopancreatography; ICU: Intensive care unit; LT: Liver transplant; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SSC: Secondary sclerosing cholangitis.

other additional details, including the presence of diffuse periductal edema[52]. Finally, an invasive and therapeutic examination (ERCP), as we have observed in the works listed in Table 1, can show tortuosity of intrahepatic bile ducts[53].

The drugs used for the treatment of this infection include antivirals, antibiotics, antipyretics and immune modulators that often provoke transient hepatotoxicity[54,55]. With specific regard to its medical therapy, in most examined works it is reported that drugs such as ursodeoxycholic acid and obeticholic acid have been used, with the aim of not resolving the disease but only slowing down the liver damage produced by the accumulation of bile acids that were not excreted[56].

We are of the opinion that post-COVID-19 cholangiopathy represents a topic of interest that could entail future developments. Unfortunately, the low number of available studies and the small cases of enrolled patients constitute a current limit to our evaluation. In the near future, further investigations focused on this new emerging pathology based on a greater sample of subjects should be undertaken in order to better identify the best treatment.

CONCLUSION

Liver involvement during SARS-CoV-2 infection is mild and transient, as reported in the literature. Unfortunately, some cases of severe liver damage can occur, leading to the failure of the organ. According to the data emerged by reviewing the previous works, it can be asserted that post-COVID-19 cholangiopathy may represent a clinicopathological condition needing strict control owing to the high risk of developing progressive liver damage that might need a transplant. This research is quite innovative and shows interesting results, but because of its recent discoveries it meets some limitations, such as the low number of published studies and patients enrolled. Further investigations including a larger sample size could help in a better comprehension of the pathogenesis and of the development of this disease, preventing or at least mitigating its clinical course and improving its treatment.

ARTICLE HIGHLIGHTS

Research background

Post-coronavirus disease 2019 (COVID-19) cholangiopathy is a recently identified clinical entity that develops during the recovery phase from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Research motivation

Early recognition of this complication is critical to ensure prompt and adequate management, which could affect the prognosis of these patients.

Research objectives

The main objectives of this review were to identify the available data contained in the studies accessible from the literature concerning post-COVID-19 cholangiopathy.

Research methods

We have searched within two electronic databases (PubMed and the Cochrane Library) works on this topic, published between January 1, 2020 to August 22, 2022, using MeSH terms and free-language keywords: cholangiopathy; COVID-19; post-COVID-19 cholangiopathy; SARS-CoV-2.

Research results

Thirteen studies were included in this descriptive review, which included 64 patients suffering from this condition.

Research conclusions

This review analyzed the possible causes and the clinical course of post-COVID-19 cholangiopathy, aiming to understand both its possible causes and its consequent clinical evolution.

Research perspectives

Cholangiopathy is a medium-to-long-term complication of this virus, in which biliary damage is

generally progressive up to liver failure. Researchers should focus on both early recognition and timely treatment of this complication.

ACKNOWLEDGEMENTS

The authors thank Dr. de Vito S, Italian Medicines Agency, Rome, Italy for English revision of the manuscript.

FOOTNOTES

Author contributions: Zippi M, Fiorino S and Crispino P made substantial contributions to study conception and design; Hong W, de Biase D, Gallo CG, Centorame A and Grottesi A were involved in acquisition, analysis and interpretation of data; Zippi M, Fiorino S and Crispino P were involved in drafting the article, revising it critically for important intellectual content and gave the final approval of the version to be published.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Zhang H

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World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 January 12; 11(1): 38-46

DOI: 10.13105/wjma.v11.i1.38

ISSN 2308-3840 (online)

META-ANALYSIS

Cap-assisted endoscopy for esophageal foreign bodies: A meta-analysis

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Okasha H, Egypt; Zhang JW, China

Received: October 15, 2022
Peer-review started: October 15, 2022
First decision: October 31, 2022
Revised: November 11, 2022
Accepted: December 21, 2022
Article in press: December 21, 2022
Published online: January 12, 2023

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Abstract

BACKGROUND

Esophageal foreign bodies are common around the world. Newer approaches, such as cap-assisted endoscopy, have been introduced as an alternative to conventional methods. Therefore, we performed a meta-analysis ono cap-assisted endoscopy versus conventional endoscopy for removal of esophageal foreign bodies.

AIM

To investigated the effectiveness of cap-assisted endoscopy with conventional endoscopy.

METHODS

An extensive literature search was performed (December 2021). For esophageal foreign body removal, cap-assisted endoscopy was compared to conventional endoscopy for procedure time, technical success of the procedure, time of foreign body retrieval, *en bloc* removal, and adverse event rate using odds ratio and mean difference.

RESULTS

Six studies met the inclusion criteria (n = 1305). Higher odds of technical success (P = 0.002) and *en bloc* removal (P < 0.01) and lower odds of adverse events (P = 0.02) and foreign body removal time (P < 0.01) were observed with cap-assisted endoscopy as compared to conventional techniques.

CONCLUSION
For esophageal foreign bodies, the technique of cap-assisted endoscopy demonstrated increased *en bloc* removal and technical success with decreased time and adverse events as compared to conventional techniques.

Key Words: Esophageal foreign body; Food bolus; Endoscopy; Snares; Forceps; Assisted devices; Cap-assisted endoscopy

Core Tip: Esophageal foreign body impaction is very common worldwide. Many techniques have been used to treat these impactions. A newer technique of using a cap on the endoscope to assist the removal of the foreign body has been introduced. Therefore, we performed a meta-analysis. This meta-analysis showed that cap-assisted endoscopy has higher odds of technical success and *en bloc* removal as well as lower odds of adverse events and reduced procedure time for removal of impacted esophageal foreign bodies as compared to conventional techniques. With this information, cap-assisted endoscopy should be highly considered in removal of esophageal foreign bodies.

Citation: Tarar ZI, Farooq U, Bechtold ML, Ghouri YA. Cap-assisted endoscopy for esophageal foreign bodies: A meta-analysis. *World J Meta-Anal* 2023; 11(1): 38-46
URL: https://www.wjgnet.com/2308-3840/full/v11/i1/38.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i1.38

INTRODUCTION

Foreign body (FB) ingestion is a common gastroenterological emergency with an annual incidence of 120000 cases in the United States[1]. About 86.9% of ingested foreign bodies are lodged in the esophagus and, if left unresolved, it has been linked with the highest adverse event rate when compared to foreign bodies lodged in other parts of the gastrointestinal tract[2-4]. In majority of cases, the FB is ingested accidentally in adults while eating food, this includes impacted food bolus. In other cases, non-consumable objects are mainly ingested by individuals with an underline psychiatric disorder, social or developmental issues, alcohol abuse, or digestive diseases[5,6]. In many cases, when sharp foreign bodies, food boluses, or batteries are ingested, they may lead to complete esophageal obstruction and severe complications such as aspiration, perforation, or hemorrhage. In these cases, emergent assessment and management is warranted[2,7].

About 80%-90% of gastrointestinal foreign bodies pass spontaneously, while 10%-20% require endoscopic management and less than 1% of cases require surgery. Endoscopy has gained popularity as the preferred modality because it is not only effective in FB removal, it is also minimally invasive with low risk of adverse events[8]. Furthermore, endoscopy provides the added benefit of diagnosing other underlying gastrointestinal pathologies and obviates the need for surgical intervention[9].

A push technique can be used to mobilize an impacted FB and preferably push it distally into the stomach. Alternatively, endoscopy-assisted retrieval of the FB can be performed using special devices. Some of these devices include biopsy forceps, grasping forceps (rat-toothed or alligator type), Dormia baskets, snares, tripod graspers and retrieval nets (Roth's type). However, more recently, endoscopic mucosal resection cap has been added to endoscopes to help remove esophageal foreign bodies more effectively[10-12]. Traditional endoscopic techniques sometime encounter poor esophageal visualization due to its narrow lumen and contrary to this, studies have reported growing evidence of better visualization of esophagus with cap-assisted endoscopy as well higher technical success and shorter procedure time[13,14].

We performed a meta-analysis of published studies comparing the technical success rate of conventional endoscopy (snares, tripod graspers, forceps, Dormia baskets, retrieval nets) *vs* cap-assisted endoscopy in which a cap has been used in addition to the conventional devices mentioned above. Furthermore, we investigated the FB retrieval time, adverse events rate and *en bloc* removal rates in both groups.

MATERIALS AND METHODS

Data search and screening

We comprehensively performed an electronic literature search of MEDLINE/PubMed, EMBASE, Scopus, Reference Citation Analysis, and Web of Science databases; from inception to December 10, 2021. The meta-analysis was conducted in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. The search terms were (esophageal foreign body impaction or food impaction or gastrointestinal foreign body ingestion, dysphagia or throat pain or soreness or foreign body sensation) and (endoscopy or endoscopic management of esophageal foreign body or use of assisted device in retrieval of foreign bodies or conventional endoscopic technique or cap-assisted endoscopy or push technique for foreign body management, use of forceps or use of basket). We also manually searched the bibliographies of the included articles to find any studies that we may have missed during our initial literature search.

Study selection

Study selection was performed by two reviewers (ZIT and UF). They independently screened the abstracts, titles, and full manuscripts to identify the studies eligible for inclusion. Any conflict was resolved through discussion between the two reviewers. We included the studies published only in English, comparing the effectiveness of cap-assisted endoscopy to conventional endoscopy for management of esophageal FB in adult patients (age ≥ 18 years). Outcomes of interest were FB retrieval time, technical success of the procedure, adverse events, and *en bloc* removal rate.

Data extraction

Data was extracted by two reviewers (ZIT and UF). We extracted information about study design, country of study, study cohort characteristics, procedure performed, type of foreign bodies, rate of adverse events, time required for FB removal, difference in procedure timings, and procedure success rate. Once data was extracted, two reviewers (YG and MB) independently reviewed the extracted data sheet and final data sheet was prepared after discussion between the four reviewers.

Quality assessment

Quality was assessed for non-randomized studies[4,14-16] using Cochrane risk of bias tool (Robin -I)[17] and randomized studies using Cochrane tool for risk of bias assessment[12,18,19].

Statistical analysis

We used RevMan 5.3 (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) for statistical analysis. We calculated the mean difference and corresponding 95% confidence interval (CI) for continuous outcomes and pooled odds ratio (OR) with corresponding 95%CI for dichotomous outcomes. Random effects model was used to calculate the pooled odds ratio with 95%CI and P value < 0.05 was deemed statistically significant. The I^2 statistics and Cochran's Q test was used for heterogeneity and variance. Publication bias was assessed by funnel plots.

RESULTS

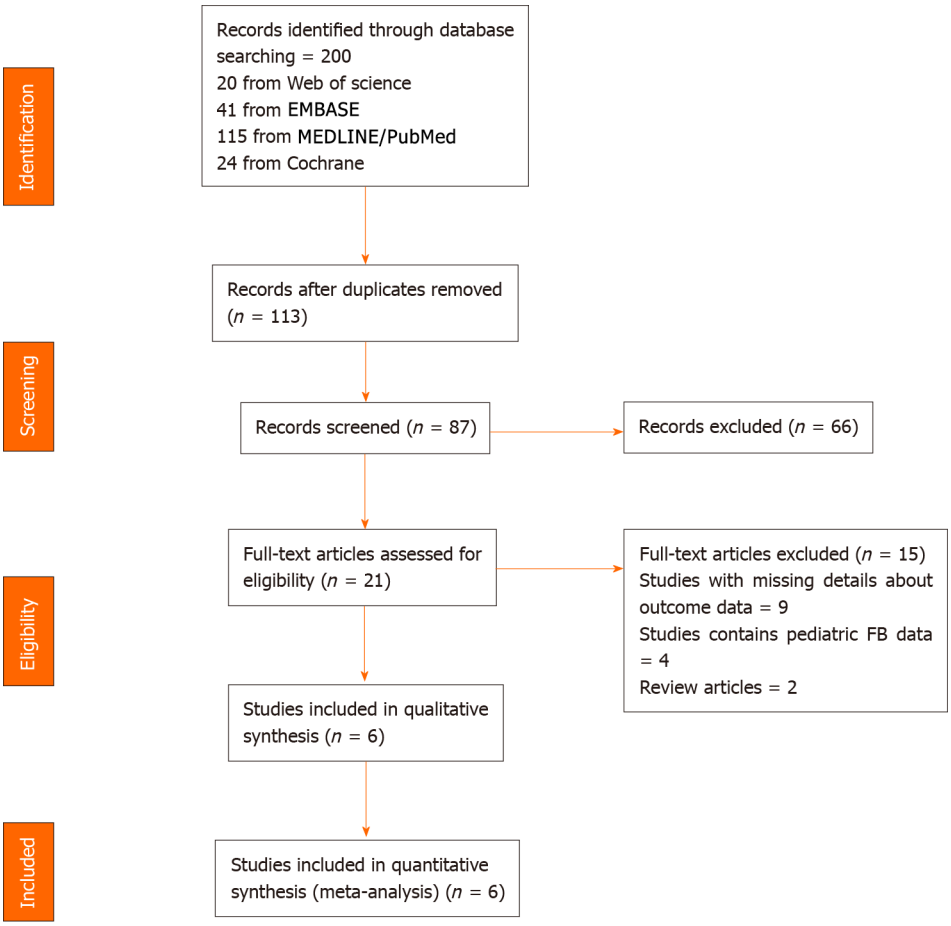
Study selection and exclusion

On initial literature search, we shortlisted 200 studies, of which 113 were excluded due to overlap or duplication. On further assessment, 66 studies were excluded after reviewing their respective titles and abstracts. Twenty-one papers were considered potentially relevant for our analysis, so we reviewed them in detail, out of which six[4,12,14-16,19] were included in the final meta-analysis (Figure 1). We also searched the bibliographies of the reviewed full text articles but did not find any additional study that qualified for inclusion. All the six studies included in the final analysis were retrospective, comprising of 1305 patients (636 underwent cap-assisted endoscopy, 669 underwent conventional endoscopy) (Table 1). Three studies only included the patients with food bolus impaction while the other three studies reported patients with any type of esophageal FB. The type of cap utilized differed between the studies. Three studies used an 18.1 mm diameter cap attached to the endoscope with sticky tape[4,12,16], two studies used a 11.3 mm band ligation cap[14,15], and one study used an Olympus cap but did not specify the size[19]. The technique differed slightly between the studies as well. For food bolus impactions, the cap-assisted technique used on only suction with very rare use of any additional equipment (forceps, snare, or net). For foreign bodies, especially sharp bones, the cap-assisted technique often used forceps or snares in addition to suction. Lastly, although food bolus impactions were the most studied type of impaction, other impactions such as fish/chicken bones, jujube pits, and sharp objects (keys, wire, *etc.*) were also included in some studies.

Table 1 Characteristics of the included studies

Ref.	Study type	Location	# of patients	Male %	Mean age conventional endoscopy	Mean age cap-assisted endoscopy	Type of FBs
Ooi *et al*[12], 2021	RCT	Australia	342	70.5	53.6 ± 14.7	54.7 ± 15.2	Food bolus
Fang *et al* [4], 2020	Retrospective Cohort	China	448	55.4	62.4 ± 18.2	62.8 ± 16.7	Jujube pit, fish bones, poultry bones, food bolus, other sharp objects
Wahba *et al* [15], 2019	Prospective Cohort	Egypt	216	46.2	52.9	51.7	Food bolus
Ooi *et al*[16], 2018	Retrospective Cohort	Australia	199	69.8	60.8 ± 19.8	57.5 ± 20.2	Food bolus
Zhang *et al* [19], 2013	RCT	China	70	58.6	48.9 (23-74)	47.6 (19-73)	Fish bone, chicken bones
Zhang *et al* [14], 2010	Retrospective cohort	China	30	NA	NA	NA	Fish bone, jujube pit, food bolus, coin or metal

RCT: Randomised controlled trial; FB: Foreign body; NA: Not available.

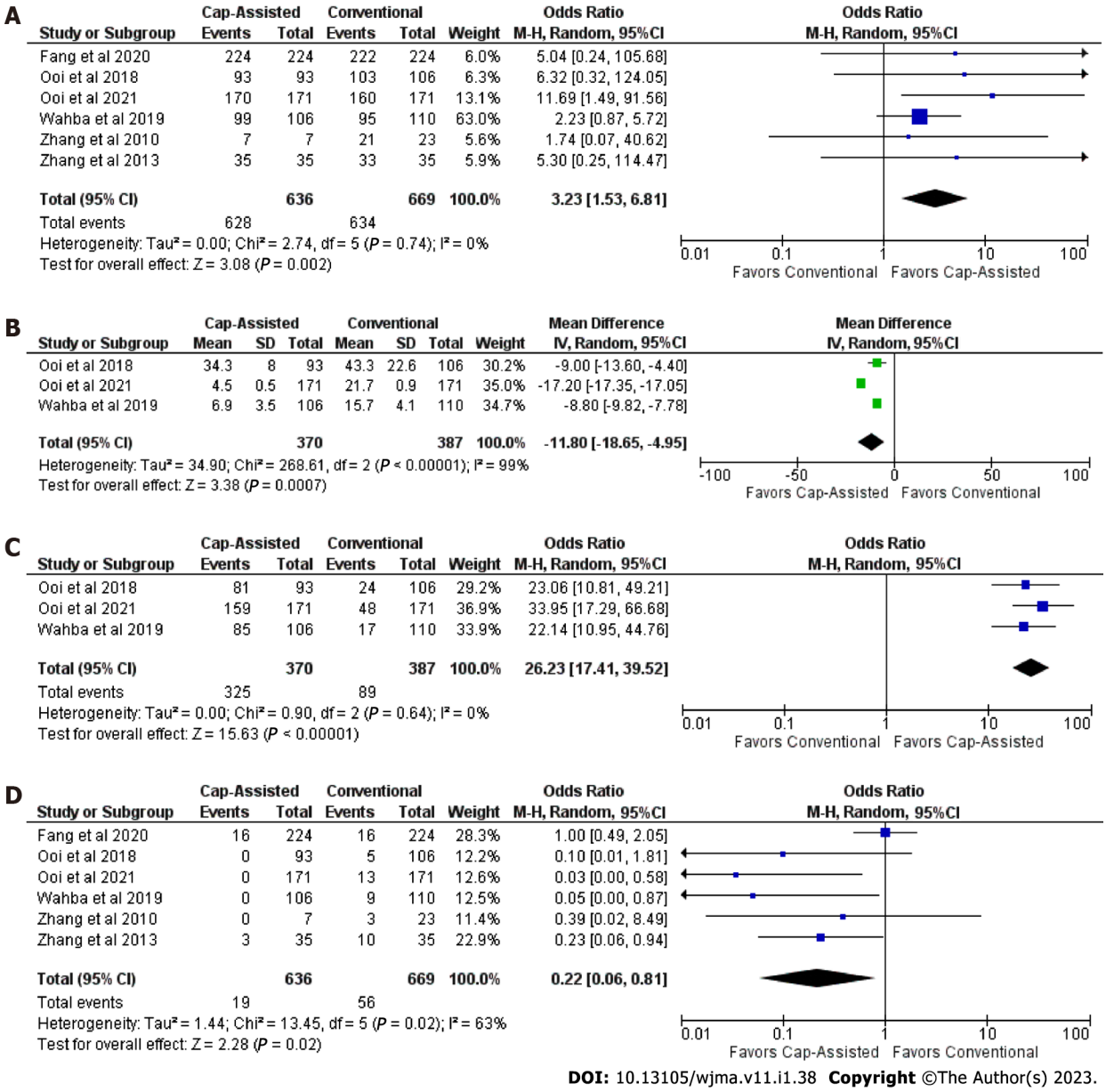


DOI: 10.13105/wjma.v11.i1.38

Figure 1 Flowchart showing details on the article search and selection. FB: Foreign body.

Outcomes

Technical success: Six studies (n = 1305) examined the technical success between cap-assisted endoscopy *vs* conventional endoscopy for esophageal FB removal[4,12,14-16,19]. Technical success was found in 628 of 636 with cap-assisted endoscopy but only in 634 of 669 with conventional endoscopy. Cap-assisted endoscopy demonstrated higher odds of technical success compared to conventional



DOI: 10.13105/wjma.v11.i1.38

Figure 2 Forest plot. A: Forest plot showing the technical success of cap-assisted endoscopy *vs* conventional endoscopy for esophageal foreign body removal; B: Forest plot showing the foreign body retrieval time of cap-assisted endoscopy *vs* conventional endoscopy for esophageal foreign body removal; C: Forest plot showing the *en bloc* removal of cap-assisted endoscopy *vs* conventional endoscopy for esophageal foreign body removal; D: Forest plot showing the adverse events of cap-assisted endoscopy *vs* conventional endoscopy for esophageal foreign body removal.

endoscopy (OR 3.23; 95%CI: 1.53-6.81; P = 0.002; I^2 = 0%) (Figure 2A).

Foreign body retrieval time: Three studies (n = 757) provided the information about mean difference in FB retrieval time[12,15,16]. Foreign body retrieval time was significantly lower in cap-assisted endoscopy (MD -11.80 min; 95%CI: -18.65 to -4.95); P < 0.01; I^2 = 99%) (Figure 2B).

***En bloc* removal:** Three studies (n = 757) examined *en bloc* removal of esophageal FBs[12,15,16]. Cap-assisted endoscopy (325 of 370) was more effective in removing the FB as a single piece compared to conventional endoscopy (89 of 387). Cap-assisted endoscopy had a significantly higher pooled rate of removing FB in *en bloc* fashion as compared to conventional endoscopy (OR 26.23; 95%CI: 17.41-39.52; P < 0.01; I^2 = 0%) (Figure 2).

Adverse events: Six studies (n = 1305) reported adverse events between the two groups[4,12,14-16,19]. Cap-assisted endoscopy demonstrated adverse events in 19 of 636 and conventional endoscopy in 56 of 669 procedures. The odds for adverse events were found to be less in cases of cap-assisted endoscopy *vs* conventional endoscopy (OR 0.22; 95%CI: 0.06-0.81; P = 0.02 I^2 = 63% (Figure 2D).

Publication bias

Using funnel plots, no publication bias was deemed significant in any of the outcomes (Figure 3).

Quality assessment

Using Cochrane risk of bias tool, all studies were determined to have low risk of bias (Tables 2 and 3).

DISCUSSION

In the current analysis, we found that addition of a cap to the end of the endoscope in cases of esophageal foreign body impaction demonstrated significantly higher rates of technical success and *en bloc* removal with reduction in adverse events and time of foreign body retrieval as compared to conventional techniques. This is the first meta-analysis performed to compare the effectiveness of cap-assisted endoscopy when compared to conventional endoscopy.

In cases of esophageal foreign body impaction, 1 out of 5 requires endoscopic management[20]. Current European Society of Gastrointestinal Endoscopy recommendations are to apply gentle push technique initially to push FB into the stomach; however; if resistance is felt during pushing, a pull technique should be considered to extract the foreign body[7]. Traditionally, various endoscopic devices has been utilized, such as snares, forceps, tripod graspers, and net retrievers to remove FBs, but these methods are often time-consuming and, in most cases, the FB requires fragmentation before extraction [15]. Contrary to this, the addition of a cap allows better visualization of the narrow esophageal lumen and helps in *en bloc* removal of the FB by enlarging the suction area[14,21].

We found that cap-assisted endoscopy demonstrated better results for esophageal FB removal when compared to conventional endoscopy for all outcomes. Technical success of cap-assisted endoscopy was successful in 98.7% (628/636) of cases while conventional group was successful in only 94.76% (634/669) of cases. Ooi *et al*[12] postulated that the likely explanation for the lower success rate in conventional techniques was the failure to extract the esophageal FB in an *en bloc* manner which results in longer procedure times. Procedure times (recorded from the time of starting esophageal assessment with endoscopy to the extraction of FB) is shorter with the application of cap to the endoscope, likely due to the ability to remove the FB in *en bloc* fashion, which also causes less trauma to the surrounding tissue. Furthermore, with conventional techniques, the maneuver requires repeated removal and insertion of the attached device or endoscope which not only increases the retrieval time, but also leads to trauma of the surrounding tissue[14,16,19]. Cap-assisted endoscopy was successful in *en bloc* removal in 87.8% (325/370) of cases compared to 23% (89/387) of cases when conventional endoscopy was performed. *En bloc* retrieval is a major advantage of cap-assisted endoscopy due to strong suction applied to esophageal FB, which not only shortens the procedure time but also decreases the complication risk. Finally, adverse events in cap-assisted endoscopy were 2.98% (19/636), consisting of minor events such as mucosal tears and bleeding, while the conventional endoscopy were 8.37% (56/669). The risk of increased mucosal trauma and minor bleeding in conventional endoscopy group was likely due to the inability to remove the esophageal FB in *en bloc* fashion, which results in fragmentation and repeated insertion of the device.

This meta-analysis has several strengths. First, this is the first systematic review and meta-analysis that compares the efficacy of cap-assisted endoscopy with conventional endoscopy methods for esophageal FBs. Second, a thorough literature search was conducted and good quality studies were selected after establishing well-defined inclusion and exclusion criteria. Third, half of the outcomes (technical success and *en bloc* removal) demonstrated 0% heterogeneity. Fourth, no publication bias was identified. However, some limitations do exist. Firstly, only two of the studies were randomized controlled trials. Ideally, meta-analysis of randomized controlled trials is desired; however, the literature to-date lacks in this aspect. Furthermore, despite including retrospective studies, the quality assessment demonstrated low risk of bias. Secondly, half of the outcomes (FB retrieval time and adverse events) demonstrated significant heterogeneity. An exclusion sensitivity analysis was performed to evaluate the effect of heterogeneity on the results of these two outcomes. For FB retrieval, if Ooi *et al*[12] was removed, then the results were similar without heterogeneity (MD -8.81 min; 95%CI: -9.8 to -7.82; $P < 0.01$; $I^2 = 0\%$). For adverse events, if Fang *et al*[4] was excluded, then the results were similar without heterogeneity (OR 0.14; 95%CI: 0.05-0.4; $P < 0.01$; $I^2 = 0\%$). Therefore, heterogeneity seems to have minimal impact on the overall results.

CONCLUSION

In conclusion, our study has many clinical implications. Cap-assisted endoscopy for esophageal FB removal demonstrates higher odds of technical success and *en bloc* removal while reducing procedure times and adverse events. Therefore, cap-assisted endoscopy should be considered for removal of impacted esophageal foreign bodies.

Table 2 Quality assessment using cochrane risk of bias tool for non-randomized studies

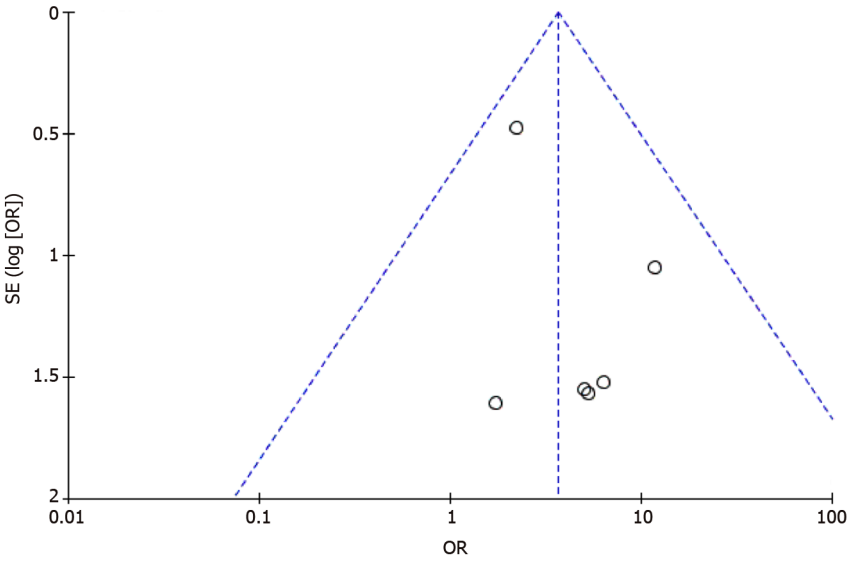
Non-randomized studies								
Ref.	Confounding	Selection of participants	Classification of interventions	Deviation from interventions	Missing outcome data	Measurement of outcome	Selection of reported results	Overall
Zhang *et al*[14], 2010	1	1	1	1	1	1	1	Low
Ooi *et al* [16], 2018	1	1	1	1	1	1	1	Low
Wahba *et al*[15], 2019	1	1	1	1	1	1	1	Low
Fang *et al* [4], 2020	1	1	1	1	1	1	1	Low

Risk of bias assessment: 0: No information; 1: Low; 2: Moderate; 3: Serious; 4: Critical.

Table 3 Quality assessment using cochrane risk of bias tool for randomized studies

Randomized controlled trials							
Ref.	Random sequence generation	Allocation concealment	Blinding	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Zhang *et al* [19], 2013	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Ooi *et al*[12], 2021	Low	Low	High	Unclear	Low	Low	low

Risk of bias assessment: 0: No information; 1: Low; 2: Moderate; 3: Serious; 4: Critical.



DOI: 10.13105/wjma.v11.i1.38

Figure 3 Funnel plot showing no publication bias.

ARTICLE HIGHLIGHTS

Research background

Cap-assisted endoscopy for removal of esophageal foreign bodies is a new technique.

Research motivation

With any new technique, studies need to be performed to truly evaluate the effectiveness and adverse events.

Research objectives

This meta-analysis examines cap-assisted endoscopy *vs* conventional endoscopy for removal of esophageal foreign bodies.

Research methods

An extensive literature search was conducted using multiple databases. Studies that compared cap-assisted endoscopy to conventional endoscopy for the removal of esophageal foreign bodies were included. Odds ratio or mean difference was used to analyze outcomes.

Research results

Cap-assisted endoscopy demonstrated higher odds of technical success ($P = 0.002$) and *en bloc* removal ($P < 0.01$) as compared to conventional techniques. Furthermore, cap-assisted endoscopy showed decreased odds of adverse events ($P = 0.02$) and mean time of foreign body removal ($P < 0.01$) as compared to conventional techniques.

Research conclusions

Cap-assisted endoscopy should be considered as a potential first-line option for impacted esophageal foreign bodies.

Research perspectives

Endoscopists may utilize cap-assisted endoscopy for removal of esophageal foreign bodies.

FOOTNOTES

Author contributions: Tarar Z and Bechtold ML designed the meta-analysis; Tarar Z, Farooq U, and Bechtold ML acquired the data; Tarar Z, Bechtold ML, and Ghouri YA analyzed and interpreted the data; Tarar Z and Farooq U drafted the manuscript; Bechtold ML and Ghouri YA critically revised the manuscript; and Bechtold ML provided statistical expertise.

Conflict-of-interest statement: All the authors have no conflicts of interest for this manuscript.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Liu JH
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