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EDITORIAL

Importance of well-designed meta-analyses in assessing medical and surgical treatments

Sunny Chi Lik Au

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Abstract

When evaluating the efficacy of medical or surgical treatments, the most robust study design is often considered to be the high-quality randomized clinical trial (RCT). However, the true answer lies in the meta-analysis of high-quality RCTs. While RCTs have their merits, meta-analyses possess two crucial qualities that make them superior: Generalizability and the ability to verify replicability across different trials. A well-designed meta-analysis, defined here as a systematic review that pools data, holds significant advantages over individual RCTs. Retrospective and observational surgical research is prone to biases that are not mutually offsetting; instead, they accumulate. Selection bias, transfer bias, and assessment bias all taint retrospective studies more than randomized trials, making the novel treatment appear more effective than it truly is. Pooling studies suffering from these limitations in a meta-analysis amplifies these biases, causing an overestimation of treatment benefits. This becomes particularly concerning when the treatment itself carries substantial risks, as is often the case in surgical journals. The consequences can result in harm or even death for patients. While a well-designed meta-analysis is the best tool for assessing medical and surgical treatments, a weak meta-analysis amplifies biases and promotes flawed data. Thoughtful readers must become proficient in honing their methodological toolkits, delving deeper into topics like heterogeneity and publication bias. It is essential to avoid wasting time on meta-analyses drawing data from retrospective or observational research regarding surgical treatments.

Key Words: Meta-analysis; Systematic review; Methodology; Research; Journal; Academic

Core Tip: It is crucial to differentiate between well-designed and poorly designed meta-analyses. Not all meta-analyses are conducted equally, and identifying their quality is vital to avoid misleading conclusions that can potentially harm patients. Meta-analyses concerning medical or surgical treatment outcomes should ideally include only randomized, controlled trials or high-quality prospective studies as source material. While reputable journals adhere to this research ethics, caution must be exercised when exploring studies that pool data without maintaining strict criteria.

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INTRODUCTION

Dear Editor, When evaluating the efficacy of medical or surgical treatments, the most robust study design is often considered to be the high-quality randomized clinical trial (RCT)[1]. However, the true answer lies in the meta-analysis of high-quality RCTs[2]. While RCTs have their merits, meta-analyses possess two crucial qualities that make them superior: generalizability and replicability[3,4].

The limitation of relying solely on individual RCT is that what works at one institution may not necessarily work in others[5]. By pooling data from multiple high-quality RCTs, a meta-analysis provides a broader perspective, enhancing generalizability. This is essential as treatments that prove effective in prestigious institutions may not yield similar results elsewhere. Furthermore, a meta-analysis verifies the replicability of the findings observed in the source trials. These factors contribute to the credibility and reliability of the conclusions drawn from a meta-analysis.

META-ANALYSES AND SYSTEMATIC REVIEWS

It is crucial to differentiate between well-designed and poorly designed meta-analyses. Not all meta-analyses are conducted equally, and identifying their quality is vital to avoid misleading conclusions that can potentially harm patients[6]. Good meta-analysis involves several key elements: Clear research objective, precise research questions, comprehensive literature search *via* different scientific databases as well as the reference lists of included articles, well-defined inclusion and exclusion criteria, objective quality assessment with standard tools (*e.g.* Cochrane Risk of Bias Tool or the Newcastle-Ottawa Scale), meticulous data extraction and statistical analysis, and thoughtful consideration of publication bias. These elements are actually defined in the widely recognized PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[7]. It plays a vital role in promoting transparency, consistency, and quality in the development of meta-analyses. However, it is important to acknowledge that adherence to these guidelines does not guarantee the quality or validity of a meta-analysis. Proper implementation and interpretation of these guidelines rest on the expertise and judgment of the researchers involved.

Meta-analyses concerning medical or surgical treatment outcomes should ideally include only randomized, controlled trials or high-quality prospective studies as source material. While reputable journals adhere to this research ethics[8,9], caution must be exercised when exploring studies that pool data without maintaining strict criteria[10]. Such practices can lead to severe discrepancies and mislead both readers and those affected by the treatments under scrutiny.

Retrospective and observational surgical research is prone to biases that are not mutually offsetting[11,12]; in contrast, they accumulate. Selection bias, transfer bias, and assessment bias all taint retrospective studies more than randomized trials[13,14], making the novel treatment appear more effective than it truly is. Pooling studies suffering from these limitations in a meta-analysis amplifies these biases, causing an overestimation of treatment benefits. This becomes particularly alarming when the treatment itself carries substantial risks, as is often the case in surgical journals. The consequences can result in harm or even mortality for patients.

Meta-analyses hold significant influence in subsequent research and are cited more frequently than any other study design across scientific research[15,16]. Consequently, the repercussions of a poorly designed observational study are overshadowed by those of a sloppy meta-analysis. Therefore, it is imperative to exercise caution and delve deeper into methodology to avoid being misled. Topics such as heterogeneity and publication bias are essential components of understanding meta-analyses comprehensively[17-19]. While they may seem intimidating at first, learning about these issues is crucial in critically evaluating the reliability and validity of meta-analyses.

It is important to distinguish between systematic reviews and meta-analyses[20]. Systematic reviews utilize reproducible approaches to search available evidence and explicitly outline parameters that determine which papers are included or excluded[21,22]. Unlike meta-analyses, systematic reviews do not pool data, resulting in more qualitative conclusions[23]. While well-done retrospective work may be included to provide a snapshot of existing knowledge, its source material is not as strong as that of meta-analyses, thus necessitating careful interpretation. Occasionally, meta-analyses may focus on complications, risk factors, or unusual endpoints that cannot be randomized[24]. Journals should exercise caution when presenting such information, always providing suitable caveats.

CONCLUSION

"Garbage in, garbage out"[25]. In conclusion, while a well-designed meta-analysis is the best tool for assessing medical and surgical treatments, a weak meta-analysis amplifies biases and promotes flawed data. Researchers and scientists should be proficient in honing their methodological toolkits.

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REVIEW

Post-transplant malignancy: Focusing on virus-associated etiologies, pathogenesis, evidence-based management algorithms, present status of adoptive immunotherapy and future directions

Rahul Yadav, Mohsen El Kossi, Dawlat Belal, Ajay Sharma, Ahmed Halawa

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Abstract

Modern immunosuppression has led to a decrease in rejection rates and improved survival rates after solid organ transplantation. Increasing the potency of immunosuppression promotes post-transplant viral infections and associated cancers by impairing immune response against viruses and cancer immunoediting. This review reflects the magnitude, etiology and immunological characteristics of various virus-related post-transplant malignancies, emphasizing the need for future research. A multidisciplinary and strategic approach may serve best but overall literature evidence targeting it is sparse. However, the authors attempted to provide a more detailed update of the literature consensus for the prevention, diagnosis, management and surveillance of post-transplant viral infections and associated malignancies, with a focus on the current role of adoptive immunotherapy and the way forward. In order to achieve long-term patient and graft survival as well as superior post-transplant outcomes, collaborative research on

holistic care of organ recipients is imperative.

Key Words: Post-transplant malignancy management; Post-transplant virus-associated malignancy; Cancer; Kidney transplantation; Solid organ transplantation; Virus

Core Tip: Post-transplant malignancy poses a serious threat with increased risk in organ recipients, varying with the intensity of net immunosuppression. Various virus infections are either causative or associative or promote the development of post-transplant malignancies. It is crucial to be aware of different viral infections so as to pre-emptively screen viral infections and survey for post-transplant cancers, helping early diagnosis, thereby favoring improved outcomes and graft survival. Transplant clinicians must be up to date on current management strategies with the vital role of immunosuppression reduction and options like antivirals, rituximab, chemotherapy, adoptive immunotherapy, topical therapy and surgery based on individual case characteristics.

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INTRODUCTION

Post-transplant infections and malignancies are on the rise with increasing efficacy of immunosuppression[1,2]. Several population-based registries found a 2–5-fold increase in cancer risk after transplantation[3-7].

Although multifactorial, most of these cancers are attributed to a viral cause (known or suspected) and immunosuppression plays a significant role, as it suppresses the immune response to oncoviruses and impairs cancer immunosurveillance[3,8]. Eight to ten percent of kidney transplant recipients' deaths are due to post-transplant cancers, the third leading cause of mortality after cardiovascular disease and infection in organ recipients[9,10].

Diverse types of malignancies can develop after transplantation, with some incurring a significant increase in incidence (lymphoma, non-melanoma skin cancer, lung, colon and liver) and others are not (ovarian, brain, breast, prostate and cervical malignancy) as mentioned in Table 1[9,11,12]. Table 2 emphasizes the burden of cancer, especially related to viral infections during the post-transplant period.

Currently, there is varied agreement regarding the prevention, diagnosis, treatment and surveillance of post-transplant cancers, especially in relation to viral infections. Additionally, the introduction of adoptive immunotherapy (AI) has resulted in the dilemma of treatment management alternatives.

This article focuses on the up-to-date information of the various post-transplant virus-associated etiologies and their pathogenetic differences compared to the general population with respect to post-transplant malignancy. It also mentions in detail about comprehensive consensus regarding the management of post-transplant malignancy, pertaining to viral infections, in light of recent research findings, including the role of AI. Furthermore, this article highlights the need of future research with the purpose of developing a tailored therapeutic strategy for each patient based on existing risk factors and diagnostic techniques.

VARIOUS VIRAL INFECTIONS THAT MAY INDUCE/PROMOTE/ASSOCIATED WITH POST-TRANSPLANT MALIGNANCY

Various viruses that have been associated with causing[13-17] or promoting[18-19] post-transplant malignancies as given in Table 3.

Skin cancers (commonly found post-transplant and those related with viral infections)

The commonest cancer following kidney transplantation is skin cancer, which is more aggressive than in the general population and nearly affects 50% of post-transplant patients[20]. Non-melanoma skin cancers (NMSCs) are the most common type, reported in up to 82% of patients within 20 years of transplantation[21,22]. Ninety percent of all NMSCs are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)[23,24]. Post-transplant recipients in comparison to the general population, have a 65–250-fold and 10-fold increased risk of developing SCC and BCC, respectively[20]. Various studies have reported that the ratio of BCC to SCC in the general population (5:1) is reversed in organ recipients (1:4 to 1:5)[23,24]. BCC, SCC, Kaposi's sarcoma (KS) and malignant melanoma constitute up to 90%–95% of all skin cancers in

Table 1 Post-transplant cancers standardized incidence ratio compared to general population[12]

Standardized incidence ratio compared to general population	Post-transplant cancers
> 5	NMSC, PTLD, lip, RCC and KS
2-5	Melanoma, thyroid cancer, leukemia and multiple myeloma
< 2	Breast, brain, lung and prostate cancer

NMSC: Non-melanomatous skin cancers; PTLD: Post-transplant lymphoproliferative disorders; RCC: Renal cell carcinoma; KS: Kaposi's sarcoma.

Table 2 Post-transplant malignancy meta-analysis standardized incidence ratio in relation to viral infections[2,140]

Cancers associated with post-transplant viral infections	Meta-analysis SIR
EBV-associated	
Hodgkin's lymphoma	3.89 (2.42-6.26)
NHL	8.07 (6.40-10.2)
HHV8-associated	
Kaposi's sarcoma	208 (114-369)
HBV/HCV-associated	
Hepatocellular	2.13 (1.16-3.91)
HPV-associated	
Cervical	2.13 (1.37-3.30)
Vulva & vagina	22.8 (15.8-32.7)
Penis	15.8 (5.79-34.4)
Anus	4.85 (1.36-17.3)
Oropharynx	3.23 (2.4-4.35)
Non-melanocytic skin cancer	28.6 (9.39-87.2)

EBV: Epstein–Barr virus; SIR: Standardized incidence ratio; NHL: Non-Hodgkin's lymphoma; HHV8: Human herpes virus 8; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPV: Human papilloma virus.

transplant recipients[25,26]. Rare skin cancers include cutaneous lymphoma, Merkel cell carcinoma, vascular cutaneous tumor (angiosarcoma), mesenchymal cutaneous tumors and adnexal gland carcinoma.

Even though human papilloma virus (HPV) is frequently detected in warts, hair follicles, and keratotic lesions, both in patients with and without skin tumors, there is no conclusive evidence linking HPV to skin tumor development in transplanted patients[27,28]. Oncogenic (HPV types 16 and 18) and non-oncogenic (HPV types 6 and 11) HPV DNA is found in 65%–90% of SCC in organ recipients, but its carcinogenic role is still unclear[27].

Novel polyoma virus has been identified in human Merkel cell carcinoma (hence the name Merkel cell virus or MCV) with possible causation[29].

The skin cancers of organ recipients tend to be more aggressive, present at a younger age, and involve multiple primary sites as opposed to those of the general population.

Multiple factors contribute to the etiology of skin cancer, including immunosuppression, intensity of immunosuppression, UV radiation exposure, white race, older age, a history of skin cancer, human herpes virus (HHV) 8 and possibly HPV 16/18 and MCV[30].

Epstein–Barr virus/HHV 4

Epstein–Barr virus (EBV) is a member of the gamma herpesvirus family, and is an encapsulated single-stranded DNA virus and ubiquitous. There are two strains infecting humans, EBV-1 and 2 (previously called EBV A and B). In the USA and Europe, EBV-1 predominates, whereas in Africa and New Guinea, both EBV strains are equally prevalent[31]. EBV spreads *via* saliva (and possible transmission through sexual intercourse), before spreading to circulating B cells through infection of the oropharyngeal epithelium[32]. EBV seroprevalence is 100% by age 4 years and 89% by 19 years in developing and developed nations and varies with socioeconomic status[33,34].

Kidney transplant recipients are susceptible to acute infection or reactivation of a latent virus, with clinical manifestations ranging from non-neoplastic viral replication (asymptomatic viremia, infectious mononucleosis) to neoplastic viral proliferations, like post-transplant lymphoproliferative disorder (PTLD) and smooth muscle tumors[35,36].

Table 3 Different viruses associated/related to post-kidney transplant tumours/cancers

Virus	Associated/related post-kidney transplant tumours/cancers
EBV	PTLD, smooth muscle tumours
HPV	Squamous cell carcinoma
HHV8	Kaposi's sarcoma, multiple myeloma
HIV	Plasmablastic lymphoma, Merkel cell carcinoma
HBV/HCV	Hepatocellular carcinoma
BK polyomavirus	Urothelial, renal cell and collecting duct carcinoma
CMV	Gastrointestinal tumours, nephrogenic adenoma

EBV: Epstein–Barr virus; PTLD: Post-transplant lymphoproliferative disorders; HPV: Human papilloma virus; HHV8: Human herpes virus 8; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CMV: Cytomegalovirus.

Table 4 Risk factors associated with post-transplant lymphoproliferative disorders [35,45,52,141,142]

Risk factors of PTLD in KT	Likely cause/association
Recipient age < 10 yr	A greater likelihood of being seronegative for EBV
Recipient age > 60 yr	Associated finding in various studies
EBV seropositive donor to EBV seronegative negative recipient (EBV D+/R-)	90% are donor derived and 10–76-fold higher incidence of early PTLD
Bimodal peak	First peak (with higher incidence) in first 2 years and 2nd peak between 5 to 10 years post-transplant
Intensity of immunosuppression and use of T cell depleting antibodies (ATG and/or OKT3), belatacept	Reduction in cancer immunosurveillance
Treated acute rejection within first year after transplantation with depleting antibodies	Reduction in cancer immunosurveillance
Simultaneous pancreas–kidney transplantation	Association
HLA mismatches (especially HLA B and DR mismatches)	Likely, due to higher associated risk of rejection and use of increased net immunosuppression

PTLD: Post-transplant lymphoproliferative disorders; KT: Kidney transplantation; EBV: Epstein–Barr virus; HLA: Human leukocyte antigen; ATG: Antithymocyte globulin; OKT3: Trade name of Monomurab CD3 (a murine monoclonal antibody reacting with CD3 molecule on human T lymphocyte).

Asymptomatic low-level, high-level, or the absence of viremia may exhibit no distinguishable symptoms and usually detected through screening with EBV polymerase chain reaction[37]. In a few studies, renal dysfunction, patient and graft survival are no different between groups (absent, low or high viral loads), whereas others report a higher incidence of opportunistic infections with increasing viral loads[37,38]. EBV seronegative at transplantation, prior history of PTLD and non-Caucasians are risk factors for EBV viremia[37].

Other manifestation of EBV includes EBV-associated Guillain–Barre syndrome[39], gastric carcinoma[40], smooth muscle tumors[41], hemophagocytic syndrome[42] and autoimmune hemolytic anemia[43].

EBV-related PTLD, is the most serious sequel in organ recipients by the virus and cumulative incidence varies with 1%–5%, 2%–10% and 5%-20% in kidney, heart and lung and intestinal and multivisceral transplant recipients[44]. Other manifestations include an 11.8-fold increased risk of non-Hodgkin's lymphoma in kidney transplant recipient compared to the age-matched non-transplant group[45].

PTLDs, mostly (65%–80%) present as extranodal masses and vary histologically as infectious mononucleosis-like, plasmacytic hyperplasia, florid follicular hyperplasia, polymorphic, monomorphic PTLD (B- and T-/NK-cell types) or classical Hodgkin's lymphoma PTLD[46]. Risk factors associated with PTLD in kidney transplantation are listed in Table 4. Early PTLD (< 1 year post-transplant) is usually seen in EBV-seronegative recipients, polymorphic, with graft involvement (in 57%) and responds to reduction in immunosuppression (RIS). Late PTLD is usually monomorphic, disseminated and extranodal (graft involvement - only 10%) and resistant to RIS[47-50].

The most common sites of PTLD involvement are the gastrointestinal tract (15%–30%), lungs, skin (5%–10%), liver, central nervous system (CNS) (20%–25%, usually late PTLD) , and the allograft (20%–25%, often culminating in allograft loss)[50]. CNS PTLD often has poor prognosis, and has the highest incidence in kidney transplant recipients[35,51,52].

HPV

HPV is a double-stranded DNA virus that can infect the keratinized skin (basal epithelium), mucous membranes, and the cervical transformation zone and spread *via* direct contact transmission (person to person). HPV types 6, 11, 16 and 18 are implicated in low- and high-grade neoplasia[28,53-55]. HPV has been linked to precancerous lesions (cervical intraepithelial neoplasia and anal intraepithelial neoplasia), lesions with low malignant potential like cutaneous, anogenital warts and certain cancers [cervical, anal, vulvar/vaginal/penile squamous cell cancers, rarely oropharyngeal (head and neck) cancers][56].

There is higher risk of HPV-associated malignancies, extensive and treatment-refractory warts on the cutaneous and anogenital areas in transplanted patients (reactivation of old or new infection) compared to age matched non-transplant individuals[3,57].

HPV rarely causes viremia (in immunocompetent as well as immunodeficiency states) but lack of cell-mediated immunity at infected sites, especially in transplant recipients, leads to its persistence, extensive warts that are not responsive to treatment, and increased probability of cancers[58,59].

Persistent infection with HPV 16 and 18 is associated with premalignant and malignant lesions of the cervix, anus, vulva, penis or scrotum. Lesions are typically asymptomatic, may present with abnormal bleeding, ulcer/nodule/wart-like features, local pruritus, pelvic pain, and dyspareunia in some cases[60-62].

There has been links of HPV association with oropharyngeal and lung SCC but with conflicting results[3,63,64].

HHV8 or KS herpesvirus

HHV8, a DNA gamma-herpes virus, has four variants: sporadic or classic (first description by Kaposi), endemic (in sub-Saharan Africa), epidemic (associated with HIV), and iatrogenic (in immunosuppressed transplant recipients)[65].

Virus can be transmitted *via* saliva (primarily), sexually (semen/vaginal secretion), vertically (breast milk), intravenously (drug use or blood products) or through transplantation.

Like EBV[66], HHV8 invades B cells, macrophages, lymphoepithelial cells and epithelium, can persist lifelong in a latent form, or reactivate when immunosuppressed to enter a lytic form leading to viremia[67,68]. In organ transplant recipients, lytic reactivation of virus due to immunosuppression (iatrogenic) may lead to uncontrolled monoclonal/oligoclonal proliferation of latently infected lymphoepithelial cells or proliferation of post-germinal center where B cell maturation happens.[67,68].

Lymphatic-endothelium-derived cells infected with HHV8 form multicentric neoplasm classically known as KS[69,70]. HHV8 induced neoplastic and non-neoplastic manifestation post-transplant can be derived from latent virus, seroconversion from positive donor to seronegative recipient[71], proliferation of seeded HHV8$^+$ cells[72,73] or KS tumor in transplanted organs[74] while in an immunosuppressed state.

HHV8 is not ubiquitous like EBV, but seroprevalence is higher than 50% in some endemic regions (sub-Saharan Africa, Caribbean, Latin America, Mediterranean, and Middle East) and matches post-transplant KS (PT-KS) herpesvirus-associated pathologies in such regions[75].

KS risk is low in transplant recipients but 200–500-fold higher than in the general population[76,77]. Besides the key risk factor of HHV8 seropositivity, other factors include ethnicity (higher in seroprevalent geographic regions), receipt of lymphocyte depleting agents, HLA-B mismatch, older age and lung transplantation[76,78-82].

PT-KS has a higher incidence in kidney transplant compared to other solid organ transplantations (SOTs) (liver and heart) and rare in hematopoietic stem cell transplantation (HSCT). This condition usually manifests early after transplantation (median 2.5 years) as cutaneous or mucosal lesions, but 25%–50% have visceral manifestations[82] with mortality ranging from 8% to 14%. Disseminated disease is associated with thrombocytopenia, anemia, and abnormalities of bone marrow progenitor cells and widespread involvement (cutaneous, mucosal and visceral). Al-Khader *et al*[83] proposed clinical staging of PT-KS that assesses extent of disease and guides treatment. Few studies have shown that cytomegalovirus (CMV) infection can reactivate HHV8, and initiate onset and/or recurrence of KS[83,84].

Post-transplantation, HHV8 can also cause other lymphoproliferative disease such as primary effusion lymphoma, multicentric Castleman disease[85,86] and other non-malignant complications like plasmacytic B-cell proliferation, bone marrow failure and hepatitis[82,87].

HIV

Observations concerning the impact of HIV infection post-transplantation have been largely based on the experiences of recipients who previously had HIV infection and underwent transplantation. Transplant outcomes in HIV-positive recipients are almost similar to those in non-HIV-positive recipients with few differences[88,89].

KS prevalence in HIV-positive patients on antiretroviral therapy (ART) is 0.18%–0.46%, while it increases to 0.50%–0.66% in transplanted patients[90].

People with HIV [Standardized incidence ratio (SIR) = 4.95%] and organ recipients (SIR = 3.28%) had a greater risk of developing new cancers compared to general population[91].

SOT in HIV-positive patients carries a low risk of recurrence or *de novo* cancer. HPV-associated neoplasia (cervical, anal and atypia) had a higher risk in a few studies, however, this requires confirmation in future studies[92].

EBV-associated PTLD/lymphoma has similar prevalence in organ recipients with HIV[89].

Compared to non-HIV recipients, incidence of tuberculosis and fungal infections appears to be greater in HIV-infected recipients during the post-transplant period[93].

Hepatocellular carcinoma related to hepatitis B and hepatitis C viruses

In a United States registry data (223 660 recipients, 1987–2005), *de novo* hepatocellular carcinoma (HCC) post-

transplantation was evaluated among non-liver (kidney, heart and lung) and liver transplant recipients[94].

In non-liver recipients, the study reported *de novo* post-transplant HCC incidence of 6.5 per 100 000 person-years. Hepatitis B surface antigenemia [hazard ratio (HR): 9.7], hepatitis C virus (HCV) infection (HR: 6.9), and diabetes mellitus (DM) (HR: 2.8) are risk factors independently linked with HCC incidence. Incidence of HCC was greater in those with HCV (SIR = 3.4) or hepatitis B surface antigenemia (SIR = 6.5), but comparable with general population (SIR = 0.8).

In liver recipients, *de novo* post-transplant HCC incidence was 25 per 100 000 person-years. Advancing age, male sex (HR: 4.6), HCV infection (HR: 3.1), and DM (HR: 2.7) were independently associated risk factors. Overall, the incidence of HCC was higher (SIR = 3.4), but particularly among individuals with HCV (SIR = 5.0) or DM (SIR = 6.2).

Due to the high endemic prevalence of hepatitis B virus (HBV) infection in Taiwan, HCC is a major malignancy in general as well as in the post-transplant population, favoring hepatitis virus antigenemia as a potential causative factor [95]. HCV infection is also related to post-transplant cirrhosis and thereby increasing the risk of post-transplant HCC[96].

Various other studies of different ethnicities also found that HBV and HCV infection post-kidney transplantation was a significant risk factor for HCC[97,98].

Polyomavirus

The polyomavirus (BKV) is a ubiquitous polyoma virus that causes asymptomatic infection in childhood and has a seroprevalence of 70%–80% in adults. It develops latency in organs such as the kidneys, ureters, spleen or brain[99]. Its non-oncological manifestations in kidney recipients are ureteral stenosis, vasculopathy, tubulopathy, hemorrhagic cystitis, and interstitial nephritis[100,101]. BKV-related malignancies in kidney recipients include urothelial carcinoma of the renal pelvis, renal cell carcinoma, and collecting duct cancer [99,102-105].

CMV

Rarely, CMV has been associated with *de novo* gastrointestinal tumors and nephrogenic adenoma following renal transplantation. Its causal role is unclear[106,107].

PATHOGENESIS OF POST-TRANSPLANT MALIGNANCIES

Pathogenesis and transplant specific risk factors for post-transplant malignancies are multifactorial but mainly include immunosuppression and decreased immunosurveillance.

Cancer immunoediting involves three phases (Figure 1)[108-110]: Elimination phase (cancer immunosurveillance); equilibrium phase (cancer persistence/dormancy); and escape phase (cancer progression). Immunosuppression has an impact on all phases.

In post-transplant patients exposed to viral infections, UV radiation, carcinogens or chronic inflammation, some healthy cells transform into highly immunogenic tumor/transformed cells. These tumor cells may revert to normal tissue *via* a mechanism of intrinsic tumor suppression (repair, apoptosis or senescence), which may become weak due to the effects of modern era immunosuppression.

As soon as these highly immunogenic transformed cells evade the intrinsic tumor suppression mechanism, they enter the elimination phase (cancer immunosurveillance). During the elimination phase, innate and adaptive immunity (NK and T cells) offers protection against the development of cancer (known as extrinsic tumor suppression). If the phase of elimination concludes successfully, the body restores healthy tissue but is weakened by immunosuppression.

When transformed cells escape the elimination phase, they enter an equilibrium state (cancer persistence/dormancy), in which adaptive immunity (T cells, interleukin-2, interferon-) works to maintain such cells in a dormant state. In the event that dormancy occurs efficiently, it prevents outgrowth of transformed cells or occult tumors/cancers throughout life and represents the end stage of cancer immunoediting but is altered by immunosuppression. Tumor immunogenicity is edited during the elimination phase by constant immune selection. Antigen loss variants, flaws in antigen processing or presentation, immune effector cell resistance, and the generation of an immunosuppressive microenvironment within the tumor are some of the editing mechanisms. Genetic instability and tumor heterogeneity increase as editing proceeds, and highly immunogenic tumor cells become less immunogenic and immunoevasive tumor cells.

These less immunogenic and immunoevasive tumor cells escape immunosurveillance and progress to clinically apparent cancer. This phase is designated as the escape phase (cancer progression).

Specific carcinogenic mechanisms of various viral infections post-transplant are listed in Table 5[111].

Multidrug immunosuppression in the transplant setting impacts cancer immune editing by a number of mechanisms, as shown in Table 6.

Multifactorial pathogenesis associated with post-transplant malignancy due to decrease immunosurveillance following exposure to viral infections, UV radiation and carcinogens including other related risk factors is summarized in Figure 2 [108].

DIFFERENCES BETWEEN MALIGNANCIES IN ORGAN RECIPIENTS COMPARED TO THE GENERAL POPULATION

Interaction with a healthy immune system (as in general population) selects tumors devoid of tumor-specific antigens, meaning poorly immunogenic or immunoevasive tumors.

Table 5 Viruses and their specific carcinogenic mechanisms

Virus	Carcinogenic mechanisms
EBV	EBV-infected cells generates more interleukin-6, which promotes the proliferation of B-cells, and interleukin-10, an immunosuppressive cytokine that promotes tumour development
HPV	E6 and E7 proteins expressed by HPV suppress p53-mediated apoptosis and increase malignant growth in infected cells
HHV8	Viral proteins encoded by HHV8 inhibit the activation of pro-caspase-8, promotes Ras-PI3K-Akt survival pathway and enhances antiapoptotic Bcl-2 (B-cell lymphoma 2) expression, thereby inhibiting apoptosis and promoting uncontrolled proliferation of infected and endothelial cells
HBV	HBx proteins produced by virus activate the Ras-PI3K-Akt survival pathway and change EGFR signalling. In addition, it modifies the transcriptional activity of c-Myc, c-Fos, and c-Jun and promotes the expression of angiogenic factors, including VEGF and angiopoietin-1. Consequently, this stimulates proliferation and angiogenesis
HCV	Virus-produced non-structural proteins (NS3 and NS5A) promote the Ras-PI3K-Akt survival pathway. NS5A also modulates the signalling mediated by. Consequently, this stimulates proliferation and angiogenesis

EBV: Epstein–Barr virus; HPV: Human papilloma virus; HHV8: Human herpes virus 8; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor.

Table 6 Immunosuppressive agents, mechanisms of carcinogenesis and cancer risk [9,108,140]

Immuno-suppressive agents	Mechanisms in carcinogenesis	Cancer risk
Polyclonal lymphocyte depleting agents (OKT3/rATG)	Interfere with T-cells, B-cells, NK and DC functions[143-145]	Increased risk of PTLD
Alemtuzumab	Depletes B and T cells	Increased risk[146]
		NHL (2.5-fold rise)
		Colorectal cancer (2.5-fold rise)
		Thyroid cancer (3-fold rise)
		Mixed results with PTLD association[147,148]
Cyclosporine A	Downregulate T-bet dependent immunosurveillance[149]	Suppress immune response against melanomas
	Inhibit antigen presentation by DC[150]	Impairs elimination of oncogenic viruses and overall increased risk of cancer[151]
Tacrolimus	Inhibit antigen presentation by DC[150]	Impairs elimination of oncogenic viruses
		Overall increase risk of PTLD and reduced trough levels substantially decline the risk[152]
Azathioprine	selectively depletion of memory T-cells[153]	Linked to late SCC (of skin) and myelodysplastic syndrome [154]
Mycophenolate (MMF/MPA)	Antiproliferative and antioncogenic potential [155]	Protective and reduce the risk of PTLD
mTOR inhibitors	Promotion of $CD8^+$ central memory T cells[156]	Enhance antiviral immunity
	Upregulate transcription factor T-bet[157]	T-bet regulates cross-talk of innate and adaptive immune cells and has tumour-suppressive activities[158]
	Antioncogenic and antiproliferative role	Overall cancer risk reduction and even regress KS[159]
Belatacept	Inhibitor of T cell proliferation	Unclear though postulated as slight increased risk of oncogenicity[160]

OKT3: Trade name of Monomurab CD3 (a murine monoclonal antibody reacting with CD3 molecule on human T lymphocyte); rATG: Recombinant antithymocyte globulin; NK cells: Natural killer cells, DC: Dendritic cell; PTLD: Post-transplant lymphoproliferative disorders; NHL: Non-Hodgkin's lymphoma; SCC: Squamous cell carcinomas; KS: Kaposi sarcoma.

Tumors formed in immunosuppressed hosts are more immunogenic than in the general population (immunocompetent host) as *de novo* malignancies arise due to permissive effect of immunosuppression by inhibiting cancer immunosurveillance and immunoediting[109,110,112]. RIS and immunotherapy (*i.e.*, adoptive/checkpoint inhibitors) may facilitate immune reconstitution, which can help by clearing immunogenic cancer cells but can raise risk of rejection[113].

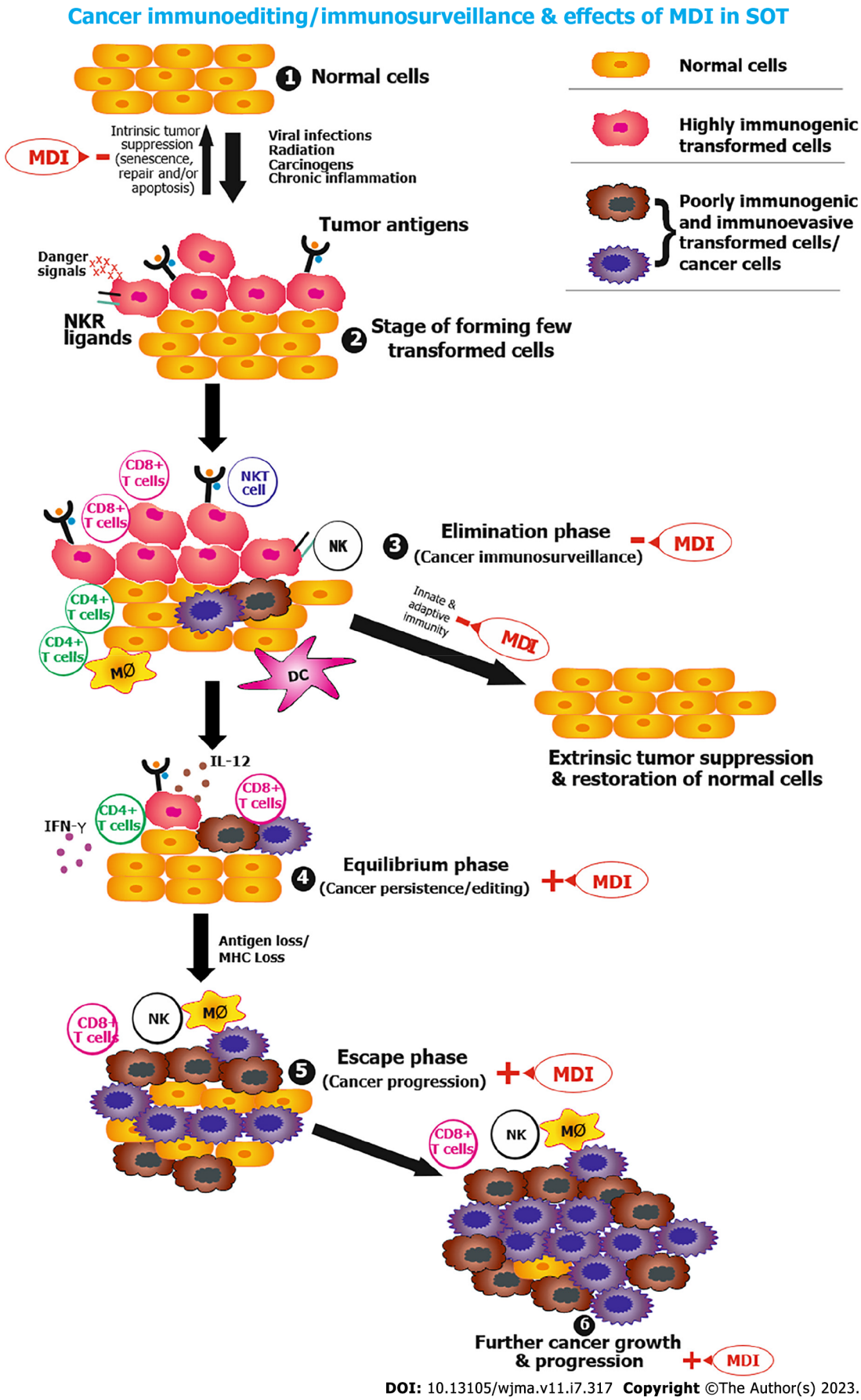

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Figure 1 Cancer immunoediting and influence of immunosuppression after transplantation. +: Promote; –: Inhibit; MDI: Multidrug immunosuppression; MHC: Major histocompatibility complex; NK: Natural killer cell; NKR: Natural killer cell receptor; SOT: Solid organ transplant.

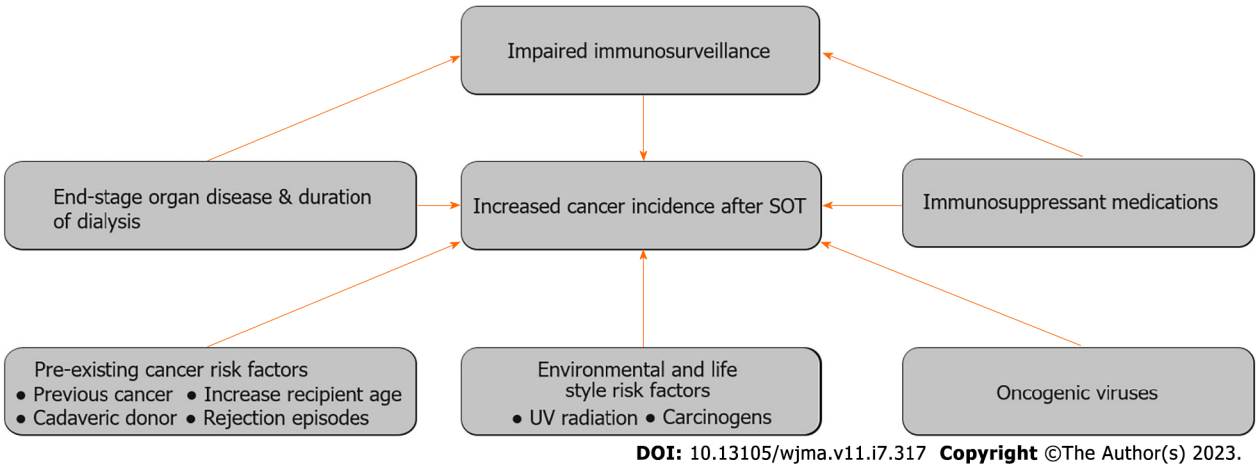

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Figure 2 Summary of etiology of increased cancer incidence after transplantation. SOT: Solid organ transplant; UV: Ultraviolet.

SCREENING, DIAGNOSIS, AND TREATMENT OF POST-TRANSPLANT VIRAL INFECTIONS RELATED WITH THE POTENTIAL TO DEVELOP MALIGNANCY

Viral etiology is well known and accepted as a probable association or causation (either promoting or inducing) of a wide variety of post-transplant malignancies. Table 7 highlights screening, diagnosis and treatment of post-transplant viral infections.

DIAGNOSIS OF VARIOUS POST-TRANSPLANT VIRUS-ASSOCIATED MALIGNANCIES

Susceptibility of viral infections post-transplant is proportional to the degree of net immunosuppression and varies greatly due to inherent limitations in the available data. The availability of population registry data for specific viral infections related to the type of organ transplant is insufficient, differs with immunosuppression regimen and geographical distribution, and is, in general, weak worldwide.

After a thorough literature research, we could only find EBV-associated PTLD and HHV8-associated KS risk with different types of organ transplantation as mentioned below. PTLD risk is highest for intestine and multi-organ transplants (12%–17%), followed by lung (6%–10%), heart (3%–5%), liver (2%–3%), and kidney (1.5%–2.5%), being the least[114].

KS incidence varies with organ transplant and is reported as per 100 000 person-years. It was reported as 95.79 [95% confidence interval (95%CI): 42.81–214.31] in kidney, 44.25 (95%CI: 4.78–409.20) in liver, 49.25 (95%CI: 2.48–977.84) in heart and 10.97 (95%CI: 4.12–29.23) in lung [115].

An in-depth detail to diagnose various post-transplant virus associated cancers is outlined in Table 8.

TREATMENT & PREVENTION OF POST-TRANSPLANT MALIGNANCIES

The literature lacks evidence on how many years of immunosuppression post-transplant increases the risk of cancer. Despite uncertainties, the literature consistently indicates that the overall duration and intensity of immunosuppression, rather than individual drugs in the immunosuppressive regimen, lead to an increased risk of cancer. Table 9 describes treatment and prevention of post-transplant cancers.

SURVEILLANCE PROTOCOLS FOR POST-TRANSPLANT MALIGNANCY

Due to the rise in the risk of malignancy, monitoring organ recipients post-transplant is vital. Current data suggest that the liver is an immunologically favorable organ and immunosuppression withdrawal is reported in selected patients who underwent liver transplantation (*i.e.* up to 40% of adults and 60% of pediatric liver recipients)[116]. As data have not been specified in most clinical studies, the usefulness of immunosuppression withdrawal in carefully selected liver transplant recipients has not demonstrated a significant clinical benefit on *de novo* malignancies post-transplantation[116]. Hence, there is risk of carcinogenesis. The surveillance protocol is provided in Table 10.

Table 7 Viral infections post-transplant (associated with the potential to develop a malignancy): Screening, diagnosis, and treatment

Post-transplant virus infections	Screening	Diagnosis	Treatment
HPV anogenital/cutaneous manifestation[28,161]	All 9–26-yr: Before transplant, receive 3 doses of HPV vaccine [nine-valent or quadrivalent vaccine (Gardasil 9 or Gardasil; Merck, Whitehouse Station, New Jersey)] or HPV-bivalent vaccine (Cervarix; GlaxoSmithKline, Rixensart, Belgium) in women	Examination and biopsy of atypical lesions	Cutaneous warts: Topicals (patient applied): Salicylic/lactic acid/imiquimod or cryotherapy (provider-applied)
	Males and females (up to age 45 yr): May also be vaccinated with 3 doses of HPV vaccine (nine-valent)	Anogenital, perianal warts/history of receptive anal intercourse warts: colposcopy/anoscopy	Anogenital warts: topicals (patient applied): podofilox/5% imiquimod cream or cryotherapy/TCA /BCA/podophyllin resin (provider-applied)
	Organ recipient's (15–26 yr): Immunize even if they have anogenital warts		Not responding or extensive or resistant warts: refer to dermatologist
	At each visit: bright light skin examination (including feet)		
	Cervical pap smear (with or without HPV PCR co-test): Every 6 mo in first year and then yearly, post-transplant, in females (> 30 yr), irrespective of HPV vaccination status		
	If rejection treated with T cell depleting agents, resume above schedule		
	Follow in all females irrespective of HPV vaccination status		
EBV viremia/disease	Identify high risk recipients (*i.e.* EBV D+/R-): EBV viral load once first week, monthly first 3–6 mo, and every 3 mo until the end of the first post-transplant year; Additionally, after treatment of acute rejection[162]	Quantitative EBV load assay [calibrated to World Health Organization IS for EBV DNA) (EBV NAAT)	Reduce immunosuppression with rising EBV loads in EBV-seronegative patients
	EBV disease precedes detectable or rising EBV loads	Whole blood/lymphocyte samples are preferable to plasma (the EBV viral load is greater and becomes detectable sooner), thereby enhancing sensitivity and early detection/reactivation	
	Watch for signs/symptoms: fever, diarrhoea, lymphadenopathy, and allograft dysfunction	Same sample type, assay and laboratory for assessing rise in EBV loads	
HHV8 viremia	Post-transplantation, HHV8 serologic testing is not routinely recommended globally	Serological assays (IFA ELISA) which detect HHV8 antibodies against latent and lytic viral antigens (both)[163]: Issues with such assays are inadequate standardisation, variable sensitivity and specificity among tests (60%–100%), and poor agreement with a predefined reference standard. It is still preferable when compared with quantitative PCR in identifying "at risk" transplant patients in endemic regions	RIS if quantitative PCR elevated/rising and/or absent HHV antibodies in "at risk" post-transplant patient or with non-neoplastic KS diseases
	Identify "at risk" before transplant, for HHV8 related disease post-transplant, in endemic zone [*i.e.* R+ (HHV8 reactivation) and D+/R- (HHV8 primary infection)][163,164]	Serological assay which detect HHV8 DNA by quantitative PCR: Its role are: (1) Predicts the occurrence of non-neoplastic HHV8 related diseases (in HHV8 primary infections and high viral loads);	Strictly follow and monitor
		(2) Detect active HHV8 replication; and	
		And (3) monitor response to treatment in post-transplant patients with HHV8 related diseases	
		Issue of serological assays in HHV8 diagnosis: Lack of any serological gold standard assay	
		Direct detection of HHV8 (HHV8 immunohisto-chemical staining) from involved site is still gold standard for diagnosis	

		Histopathological confirmation and HHV8 DNAemia confirms the diagnosis	
Plasmacytic B-cell proliferation (HHV8 associated)[82]	Watch for SIS	Biopsy: Shows polyclonal HHV8 B-cell proliferations in lymph nodes/visceral organs	RIS
	Exclude mimickers of signs/symptoms	HHV8 viral load (quantitative PCR)	Rituximab
			Trial of antiviral
Bone marrow failure/HPS (HHV8 associated)[82,165]	Watch for fever, jaundice, severe pancytopenia, plasmacytosis, hepato-splenomegaly, SIS, rash (maculo-papular)	Biopsy confirmation of HHV8 in bone marrow/ lesions	RIS
	Exclude mimickers of signs/symptoms	HHV8 viral load (quantitative PCR)	Rituximab
			Trial of antiviral
Hepatitis (HHV8 associated)	Elevated liver enzymes, SIS, rash (maculopapular).	HHV8 viral load (quantitative PCR)	RIS
	Exclude mimickers of signs/symptoms	Biopsy confirmation of lesion/organ affected	Trial of antivirals

NAAT: Nucleic acid amplification test; RIS: Reduction in immunosuppression; IFA: Indirect immunofluorescence assay; ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction; IHC: Immunohistochemical staining; TCA: Trichloroacetic acid; BCA: Bichloroacetic acid; SIS: Systemic inflammatory symptoms; HPS: Hemophagocytic syndrome; HPV: Human papilloma virus; HHV8: Human herpes virus 8; EBV: Epstein–Barr virus; IS: International Standard.

Table 8 Post-transplant virus associated malignancy and their diagnosis

Post-transplant viral associated malignancy	Diagnosis
CIN and cervical cancer and (HPV- associated)	Abnormal cervical Pap test/cytology on screening: Colposcopy biopsy of any suspicious lesion[28,161]
AIN and anal cancer (HPV-associated)	Abnormal anal Pap test/cytology on screening: High-resolution anoscopy ± biopsy of any suspicious lesion[28,161]
EBV associated PTLD	Identify "B" symptoms (fever, night sweats and weight-loss)
	Excision biopsy/core biopsy (in allograft PTLD as excision in not practical) is gold standard for diagnosis[46]
	Stage PTLD with CT imaging of the chest, abdomen, and pelvis, as well as MRI brain imaging before initiating treatment as in immunocompetent host[166]
	PET-CT may help in diagnosing occult PTLD, accurate staging in occult cases and sometime evaluating treatment response[167-169]
PT-KS	Examine for cutaneous or mucosal lesions, visceral involvement and haematological manifestations
	Diagnostic gold standard: HHV8 confirmation in biopsy of KS lesions[170]
	HPE characteristic of PT-KS: Spindle-shaped cells and immunostaining confirmation with latency-associated nuclear antigen and CD34 positive staining[171,172]
	Quantitative PCR load of HHV8: Role in supporting diagnosis and monitoring treatment response
	Confirmation of diagnosis by HPE and HHV8 DNAemia
	Depending on site involved, disease staging by imaging and invasive procedures (*e.g.*, bronchoscopy, esophago-gastroduodenoscopy, colonoscopy)[173]
MCD	Watch for lymph node enlargement, systemic inflammatory symptoms
	Gold standard for diagnosis: Lymphnode biopsy confirmation of HHV8[170]
	HPE: HHV8+ plasmablasts in follicular mantle zone and vascular hyperplasia
	Quantitative PCR load of HHV8: Role in supporting diagnosis and monitoring treatment response
	Confirmation of diagnosis by HPE and HHV8 DNAemia
PEL	Watch for effusion (pleural, peritoneal, pericardial)

	Gold standard: Confirmation of HHV8 in pleural/ascitic fluid[170]
	HPE characteristic: HHV8+ plasmablasts displaying immunoblastic and anaplastic characteristics
	Quantitative PCR load of HHV8: Role in supporting diagnosis and monitoring treatment response
	Confirmation of diagnosis by HPE and HHV8 DNAemia

CIN: Cervical intraepithelial neoplasia; HPV: Human papilloma virus; AIN: Anal intraepithelial neoplasia; MCD: Multicentric Castleman disease; PTLD: Post-transplant lymphoproliferative disorders; CT: Computed tomography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computerized tomography; PCR: Polymerase chain reaction; PEL: Primary effusion lymphoma; PT-KS: Post-transplant Kaposi's sarcoma; HHV8: Human herpes virus 8; HPE: Histopathology examination; EBV: Epstein–Barr virus.

Table 9 Post-transplant malignancies: treatment and prevention

Post-transplant malignancy	Treatment	Prevention
CIN (HPV-associated)[28,161]	Loop electrosurgical excision procedure/cryotherapy/cold knife conization of the lesion	Vaccination as mentioned in Table 3 (screening of HPV)
Cervical cancer (HPV-associated)[28,161]	Microinvasive disease (< 3 mm): conization[174]	Known previous history: Assess for anogenital lesion for cervical/anal lesions prior to transplant
	Up to stage IIA: Chemoradiation[175]	Recommend condom use
	Locally advanced: Chemoradiation[176]	During laser surgery for HPV lesions, cover skin surface, mask and eye protection to prevent reimplantation of virus in electrocautery fumes
	Metastatic: Chemoradiation (palliation and symptoms alleviation)[177]	
AIN (HPV-associated)[28,161]	AIN I (< 1 cm^2 at base): Topical 80% TCA[178]/5-fluorouracil[179] or cryotherapy	
	Larger size AIN I, AIN II and III: Infrared coagulation[180,181] or fulguration (anoscopy guided)[181]	
Anal and penile cancer (HPV-associated)[28,161]	Invasive anal carcinoma: Combined-modality therapy [radiotherapy and chemotherapy (5-fluorouracil and mitomycin/cisplatin)][182]	
	Penile cancer: Surgical resection ± chemotherapy (as per stage in immuno-competent)	
PTLD[183]	Differentiate allograft dysfunction from PTLD, before initiating treatment using allograft biopsy	EBV viral load surveillance (for EBV D+/R-) as mentioned in screening of EBV
	RIS: Preferred pre-emptive intervention. Adjust to lowest tolerated immunosuppression, may switch to mTOR inhibitor. Lack of sufficient evidence to suggest any specific RIS protocol or switching to mTOR inhibitor	
	Rituximab monotherapy for progressive disease following RIS and CD20+ PTLD	Patients (EBV D+/R-) with fluctuating immunosuppression, episodes of rejection, or who have not established a viral "set point" will be monitored for a period beyond the first year
	Cytotoxic chemotherapy if progression after rituximab and RIS. R-CHOP 21 regimen: Four sequential cycles of rituximab/ cyclophosphamide, doxorubicin, oncovin, and prednisone every 3 wK[184,185]	
	Children with EBV + PTLD: the low-dose cyclophosphamide and prednisone regimen plus rituximab [186].	EBV viral loads becomes positive 4 to 16 wk prior to development of PTLD[189]
	CD20- Tcell PTLD, B cell, Burkitt and Hodgkin's lymphoma: same chemotherapy regimen as immunocompetent host	
	CNS PTLD: Chemotherapy regimens are same as used to treat primary CNS lymphoma (PCNSL) in general population/ immunocompetent individuals [187,188]. Regimen with systemic rituximab, dexamethasone and antivirals, if unable to tolerate chemotherapy or disease occurring early post-transplant	Monitor viral load in EBV seropositive recipients in re-transplantation after PTLD
	Start pneumocystis jirovecii prophylaxis: If PTLD treatment administered beyond RIS	
KS	RIS (30% complete remission in few reports)[190]	Pre transplant "at risk" in endemic areas (D+/R- or R+ HHV8 status): Frequent viral load monitoring for 3–6 months and physical examination of skin and mucosal surfaces as a routine, post-transplant

	Switch to mTOR if using CNI (mTOR inhibitor is antiangiogenic, inhibit viral replication pathways)[191,192] and helps recovery of HHV-8-specific cytotoxic T cells[78,82] Antivirals (ganciclovir, foscarnet, cidofovir): Not routinely used, as *in vivo* efficacy is not demonstrated If no response or relapse after above: Oncology consultation and chemotherapy (CHT) (L-anthracyclines) If single skin lesion: Surgical excision or intralesional electrocautery or intralesional chemotherapy can be considered	RIS if viral loads rising while monitoring and switching to mTOR inhibitors early
MCD	RIS (limited evidence) and/or switch to mTOR from CNI (if possible) Rituximab[193] If aggressive disease, no response/relapse: chemotherapy [R-CHOP/R-CVP (rituximab- cyclophosphamide, doxorubicin, vincristine, prednisone)][82]	
PCL	Primary therapy is CHT [cyclophosphamide, doxorubicin, vincristine, prednisone(CHOP)][194] RIS (limited evidence) If CHT contraindicated/no response or relapse: Intracavitary antivirals(cidofovir)[82]	

CNS: Central nervous system; CHT: Chemotherapy; MCD: Multicentric Castleman disease; RIS: Reduction in immunosuppression; CIN: Cervical intraepithelial neoplasia; HPV: Human papilloma virus; PTLD: Post-transplant lymphoproliferative disorders; EBV: Epstein–Barr virus; KS: Kaposi's sarcoma; CNI: Calcineurin inhibitor.

AI

Principle

Immunosuppression increases the chance of opportunistic infections in the post-transplant period. Limitations of current pharmacological treatment of viral infections in organ recipients include cost, antiviral toxicity, their variable efficacy and even resistance[117]. Most importantly, pharmacotherapies does not aid in pathogen-specific immune reconstitution, and the repeated risk persists after successful cure or eradication of virus. CMV is one potential example of such a pattern [118].

Spiess *et al*[119] first described the efficacy of AI in murine tumors in 1987, and later demonstrating objective tumor response in metastatic melanoma patients[120].

AI uses pathogen/virus-specific T cells to quickly restore immune responses to infectious pathogens/viruses in organ recipients. Apart from eliciting virus-specific cytotoxic responses, AI has specific advantage over pharmacotherapy by establishing long-term T-cell memory and may help preventing recurrent infections and protects against the organ toxicity/myelosuppression associated with some antivirals.

AI has been explored post-HSCT for CMV, EBV and adenovirus and has weak evidence in SOT. Advancement in immunological techniques has minimized alloreactivity and maximized cytotoxicity with AI, thereby, yielding a targeted approach with good safety profile[121-125].

Likely indications of AI

In EBV-positive PTLD: (1) Failed standard therapy with RIS, rituximab, chemotherapy, and/or radiotherapy[126]; and (2) children failed with RIS and rituximab therapy[127]. Delayed response with AI in such cases is possible due to previous use of rituximab.

In CMV: Refractory and resistant CMV[128-132].

Above indications are inferred from partial/complete response in certain subsets of patients post-transplant after AI therapy when searched within the literature.

Technique of AI

Figure 3 illustrates the steps, isolation, and diverse forms of AI[133-137].

Outcomes of AI

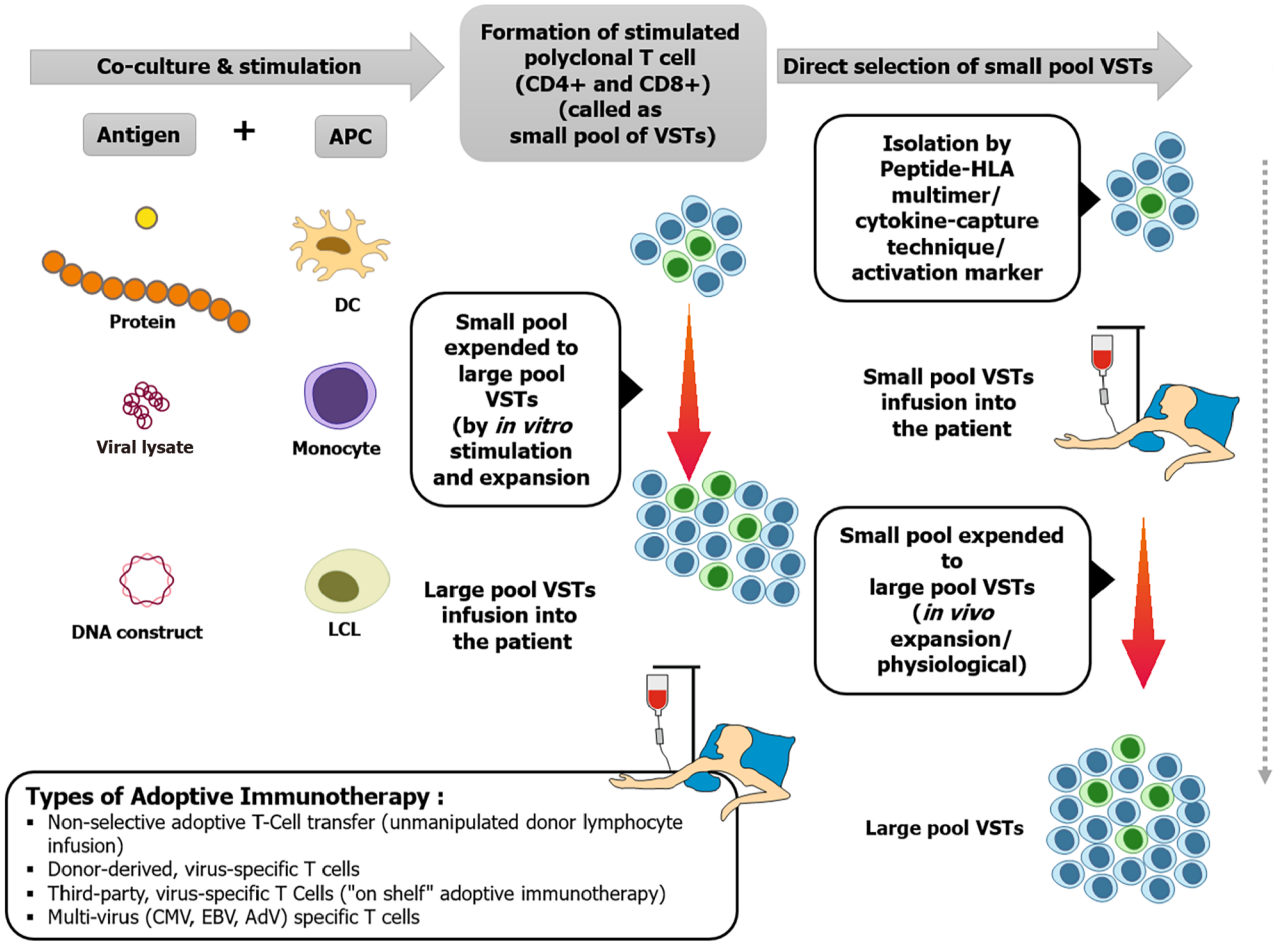
AI has been investigated more in HSCT compared to SOT. Most data have come from the variable success of AI in EBV + PTLD disease. Use of AI in CMV disease is sparse and limited to a few cases in SOT. AI needs more evaluation in controlled trials.

Concerns for the widespread use of AI include limitations such as the need for specialized facilities and a specific time to generate, high costs, questionable durability, long-term overall efficacy and safety, the potential for alloreactivity, and reduced ability to mount adequate response with ongoing immunosuppression.

Table 10 Post-transplant malignancy: surveillance protocols[30]

Cancer	Post-transplant surveillance
Skin	Self-skin examination monthly; examination by dermatologist: 6 to 12 monthly[162] (expert opinion)
PTLD (EBV+)	Routine screening of EBV D+/R- by EBV NAAT: once first week, monthly for next 3–6 mo, and every 3 mo till 1 yr after transplantation [162] (expert opinion)
Cervical	Age 25–74 yr: yearly cervical Pap test and pelvic examination[195]; in higher risk category, more frequent Pap test
Hepatocellular	Every 6 mo screening with USG ± α-fetoprotein in high risk (*i.e.* with cirrhosis) (extrapolation from general population)
Renal	USG screen every 6–12 mo in high risk (*i.e.* acquired cystic kidney)[196]
Breast	Females < 50 yr: individual decision when to start screening; Females 50–74 yr: every 2 yr screening mammography[197]; [extrapolation from immunocompetent (general) population]
Prostate	Men 55–69 yr: individualized screening approach after discussing potential benefits and harm; Men > 70 yr, avoid routine screening[198] [extrapolation from immunocompetent (general) population]
Bowel	All 45–75 yr: stool immunochemical testing every 2 yr, 5-yearly FEGD and sigmoidoscopy, or 5–10-yearly colonoscopy[199]
Lung	All 55–79 yr who have smoked 1 pack/day for 30 yr or its equivalent (2 packs/day for 15 yr, 3 packs/day 10 yr): yearly low dose CT chest [200] [extrapolation from immunocompetent (general) population]

PTLD: Post-transplant lymphoproliferative disorders; EBV: Epstein–Barr virus; NAAT: Nucleic acid amplification test; USG: Ultrasonography; FEGD: Fibreoptic esophago-gastroduodenoscopy; CT: Computed tomography.



DOI: 10.13105/wjma.v11.i7.317

Figure 3 Technique of adoptive immunotherapy (steps, isolation and types of virus-specific T cells). AdV: Adenovirus; APC: Antigen presenting cells; CMV: Cytomegalovirus; DC: Dendritic cells; EBV: Epstein–Barr virus; HLA: Human leukocyte antigen; LCL: Lymphoblastoid cell lines; VSTs: Virus-specific T cells.

FACTORS INFLUENCING THE WAITING PERIOD FOR RE-TRANSPLANTATION AFTER SUCCESSFUL TREATMENT OF THESE MALIGNANCIES

Achievement of complete remission (clinically and radiologically); sustained disease-free status for at least 12–24 mo; presence of seroconversion (virus-specific IgG antibodies); graft nephrectomy in cases of allograft PTLD; and absent or undetectable viral loads after successful treatment of malignancy[50,138,139].

CONCLUSION

Post-transplant malignancy is a considerable risk and cause of significant morbidity and mortality in organ recipients. Strategically reducing immunosuppression is an important step in the management of post-transplant virus-related cancers. Evidence for prevention, treatment and surveillance in post-transplant viral infections and malignancy are extrapolated from findings in the general population. A multidisciplinary team is vital for successful outcome. An individualized approach is the most effective method and treatment to eradicate or cure might not be the ultimate goal in all cases. AI is currently at an initial stage and has inherent logistic problems. Wait time for re-transplantation following the successful treatment of cancer should be assessed on an individual case basis, taking due consideration of the risks associated with renal replacement therapies. Collaborative efforts among all those engaged in the care of post-transplant patients, observing more extensive care studies and multicenter interventional trials, can enrich the evidence base and long-term, quality care of organ recipients.

FOOTNOTES

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MINIREVIEWS

Transient elastography (FibroScan) in critical care: Applications and limitations

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Abstract

FibroScan® is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver *via* the technique of transient elastography. Because fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from the liver hardness. This technique is increasingly being employed to diagnose liver fibrosis, even in critically ill patients. It is now being used not only for diagnosis and staging of liver cirrhosis, but also for outcome prognostication. However, the presence of several confounding factors, especially in critically ill patients, may make interpretation of these results unreliable. Through this review we aim to describe the indications and pitfalls of employing FibroScan in patients admitted to intensive care units.

Key Words: FibroScan; Intensive care unit; Liver dysfunction; Liver stiffness; Transient elastography

Core Tip: Liver dysfunction is common in critically ill patients. For diagnosis, severity assessment, and prognostication of liver fibrosis, liver biopsy is considered the gold standard. However, because of inherent risks associated with the invasive nature of liver biopsy, non-invasive tests may be preferable in intensive care unit patients. Serology markers for liver fibrosis lack specificity and accuracy and hence newer tests like liver stiffness measurement (LSM) are increasingly been used in these patients. Transient elastography using FibroScan is arguably the most commonly employed and validated tool for LSM. FibroScan has been used in the management, prediction of complications, and prognostication of various liver diseases including acute and chronic conditions. However, there are several integral limitations which should be considered while applying this test in critically ill patients.

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INTRODUCTION

Hepatic dysfunction is quite prevalent in critically ill patients, especially among those with multiple organ failure, with a reported incidence of 10%-40%[1,2]. Notably, hepatic dysfunction is linked to a higher mortality rate in critically ill patients, even without pre-existing liver disease. Indeed, the hepatic function is frequently used in clinical multifactorial scoring systems for prognostication in the intensive care unit (ICU) setting, for instance, Acute Physiology and Chronic Health Evaluation II (cirrhosis as an element) or the Sequential Organ Failure Assessment score (serum bilirubin and international normalized ratio as variables)[3]. Still, liver dysfunction and the role of the liver in the pathogenesis of systemic inflammatory response syndrome, sepsis, and multiorgan failure in critically ill patients may be underrated because they are less obvious and less immediately life-threatening compared to respiratory, cardiovascular, or renal dysfunction. Since no single physiologic variable allows for early detection of hepatic dysfunction, current diagnostic criteria are based on laboratory tests, mostly serum bilirubin levels or international normalized ratio. Only a few specialized centers offer sophisticated measurements like the indocyanine green plasma disappearance rate, which reflects liver perfusion and function in critically ill patients[4]. Among other non-invasive tests, the measurement of liver stiffness (LS) by transient elastography (TE) is increasingly used to evaluate hepatic dysfunction in critically ill patients. TE correlates well with liver dysfunction, and increasing stiffness values are also related to increased mortality in the ICU and non-hepatic organ failure patients[5]. Additionally, TE has shown promise in predicting the development of complications such as hepatic encephalopathy and hepatorenal syndrome in critically ill patients[6]. As a non-invasive test, TE can provide valuable information for monitoring liver function in critically ill patients, allowing for early detection and implementing appropriate interventions to prevent further deterioration of liver function and improve patient outcomes. However, even these non-invasive tests are not ideal and are associated with their limitations; hence, it becomes imperative for the practising physician to be aware of any existing limitations before applying and interpreting such tests.

LS MEASUREMENT

Non-invasive tests to evaluate liver fibrosis may be broadly categorised as blood-based tests, tests assessing physical properties of liver tissue, and imaging modalities (Table 1). Serum markers for detecting liver fibrosis are non-specific and have a poor accuracy[7]. Hence, other non-invasive tests, including LS measurement (LSM) and radiological imaging, are generally preferred. LSM can be performed using techniques based on magnetic resonance or ultrasonography. Ultrasound-based elastographic methods have been further classified as per the guidelines by the European Federation of Societies of Ultrasound in Medicine and Biology (Figure 1)[8-10]. Even though LSM using techniques like Acoustic Radiation Force Impulse Elastography with or without the Aixplorer® system (SuperSonic Imagine, France) offers the advantage of providing ultrasound images, FibroScan remains the most widely used and validated tool[7]. TE has been used not only in the management of patients with chronic liver disease but also in acute liver failure (ALF) and those without any underlying liver disease (Table 2).

FIBROSCAN IN PATIENTS WITHOUT PREEXISTING CHRONIC LIVER DISEASE

Acute liver dysfunction in critically ill patients

Hepatic function is often impaired in critically ill patients for several reasons, such as endotoxemia, changes in circulation (cardiac failure), and external factors (such as increased intraabdominal or intrathoracic pressure due to an impending abdominal compartment or mechanical ventilation, respectively). Hypoxic hepatitis occurs with an incidence of 10% in critically ill patients and is associated with an in-hospital mortality rate of 50%[11]. Pro-fibrogenic cells like hepatic stellate cells (HSCs) and myofibroblasts are quickly activated to make extracellular matrix components and hyaluronic

Table 1 Non-invasive tests for diagnosing and staging of liver fibrosis

Categories of test	Clinical application	Clinical tests
Blood-based tests	Serum markers of fibrosis, laboratory variables	Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, platelets, albumin
Methods assessing physical properties of the liver tissue	Liver stiffness	Transient elastography, bidimensional shear wave elastography, magnetic resonance elastography
Imaging methods	Assessing the anatomy of the liver and other abdominal organs	Ultrasound, CT scan, magnetic resonance scans

CT: Computed tomography.

Table 2 Potential clinical applications of transient elastography

	Clinical condition	Clinical applications
Patients without chronic liver disease	Acute liver dysfunction	Diagnosis. Prognostication
	Heart failure	Response to therapy. Prognostication. Prediction of complications like cardiac cirrhosis
	Left ventricular assist device placement	Prognostication. Therapeutic intervention. Prediction of complications like right ventricular failure
	General critically ill	Prognostication marker
	Pregnancy	Prediction of complications like preeclampsia
	Acute liver failure	Differentiate between acute and chronic liver dysfunction. Prognostication. Need for transplantation
Patients with underlying chronic liver disease	Chronic liver failure	Diagnosis of decompensation. Differentiation of aetiology. Severity assessment. Prediction of complications like portal hypertension, variceal bleeding, hepatocellular carcinoma. Response to treatment. Prognostication
	Post liver transplant	Prognostication. Acute transplant rejection

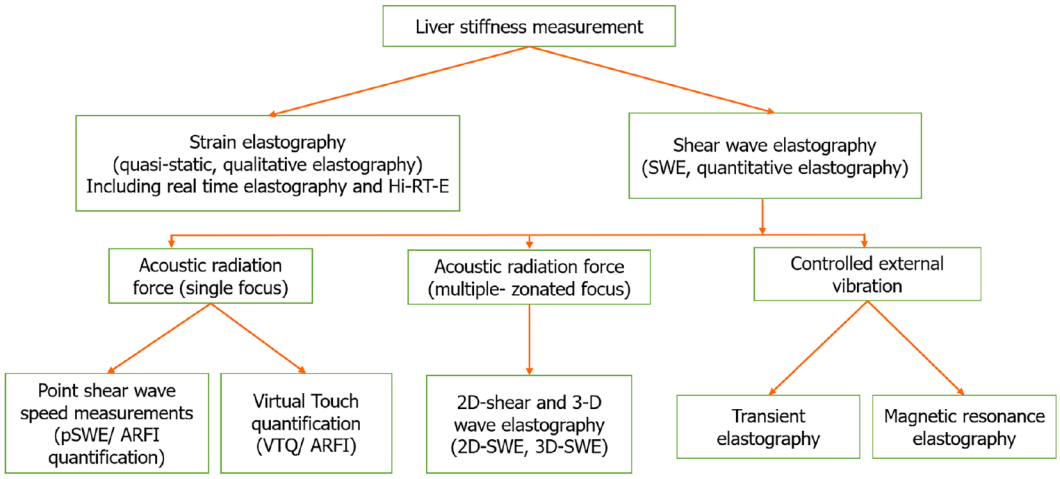

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Figure 1 Classification of ultrasound based elastographic techniques. SWE: Shear wave elastography; pSWE: Point shear wave elastography; APFI: Adolescents' Psychosocial Functioning Inventory; VTQ: Virtual touch quantification.

acid, an indirect sign of collagen formation in the liver. The combination of hepatocyte oedema, bilirubin elevation, and intrahepatic collagen deposition can increase LS. Koch *et al*[12] examined critically ill patients in a medical ICU to assess LS and its clinical impact and predictive power to predict mortality. They measured LS at admission, day 3, day 7, and weekly during the ICU course in critically ill medical patients. ICU patients had a significantly higher LS than standard care patients without liver disease. ICU patients without cirrhosis had median LS values of about 10 kPa, indicative of severe hepatic fibrosis in the general population. Values > 12.5 kPa, which generally indicate established liver cirrhosis, were present in 33% of medical, non-cirrhotic ICU patients at admission. At admission, septic and non-septic patients had similar LS. However, in an extensive subgroup analysis, abdominal sepsis patients had a higher LS than pulmonary

sepsis patients. At admission, septic and non-septic patients had similar LS. However, in an extensive subgroup analysis, abdominal sepsis patients had a higher LS than pulmonary sepsis patients[12].

LSM reflects liver function upon admission to the ICU. On days 3 and 7, LS correlated with kidney, lung, and heart/circulation biomarkers but not with liver biomarkers. High-volume fluid resuscitation, vasopressors, and organ support therapies like mechanical ventilation and continuous veno-venous hemofiltration may change the significance of elevated LS in medical ICU patients, indicating non-hepatic organ failure in follow-up examinations. Also, patients with LS values greater than or equal to 18 kPa had substantially reduced survival rates during ICU treatment and long-term observation [12]. Despite this, there is a dearth of information on TE's ability to predict "challenging end-points" like mortality.

Heart failure

Heart failure (HF) is a complex disease associated with multisystem organ failure and recurrent hospital admission, with 30%-45% of patients hospitalized with acute decompensated HF (ADHF) dying within one year[13]. Congestive hepatopathy (CH) is caused by protracted passive venous congestion as the elevated central venous pressure (CVP) in right-sided HF (RHF) is transmitted to the hepatic veins. ADHF further increases CVP with a resultant increase in hepatic congestion, and this relationship may have prognostic significance[14]. Right heart catheterization (RHC), though a gold standard method, is invasive and costly for assessments in RHF patients, necessitating the search for an accurate, non-invasive test. In HF, increased LS may reflect residual congestion secondary to volume, pressure overload, and/or inadequate liver perfusion with low cardiac output in patients hospitalized with ADHF. LS is reversibly associated with CVP with a direct relationship, increases exponentially with cardiac functional deterioration, and improves dramatically after diuretic therapy (decongestion)[15].

A study that compared LS in people with normal cardiac function, stable left HF (LHF), stable RHF, and ADHF showed that all of the HF groups had a significantly higher LS than the control group. Furthermore, the ADHF group demonstrated notably higher right atrial pressure and LS than the stable LHF group, with a median of 11.2 kPa *vs* 4.7 kPa, respectively (P = 0.01)[16]. Hopper *et al*[17] conducted a cross-sectional investigation whereby they observed a positive correlation between LSM and increased levels of bilirubin, gamma-glutamyl transferase, and alkaline phosphatase in both HF and ADHF groups. Throughout the clinical progression of CH, liver indicators exhibit fluctuations and are generally considered unreliable, even in the presence of substantial changes in body volume. This observation further reinforces that LSM is a more advantageous and superior diagnostic tool in this context. The use of LS may be particularly beneficial when the hemodynamic status cannot be readily assessed at the bedside on physical examination, and the assessment of LS by TE is rapid, simple, and objective. Recent studies have shown that RHC and LSM have a baseline correlation[18].

Additionally, insufficient alleviation of congestion at discharge for ADHF is linked to higher morbidity and mortality. Despite this, a lack of an objective assessment of HF results in the discharge of many patients with residual congestion. Compared to other non-invasive markers for HF, LSM may exhibit more accuracy in illustrating the decongestion process. In a study conducted by Yoshitani *et al*[19], total serum bilirubin, aspartate aminotransferase, alanine transaminase, and gamma-glutamyl transferase were measured before and after diuresis. The results indicated that there was no statistically significant change in these parameters. However, it was seen that body weight, LSM, and brain natriuretic peptide (BNP) all exhibited a substantial drop.

The median LSM at admission was utilized by Saito *et al*[20] to classify patients with ADHF into low LSM (8.8 kPa) and high LSM (8.8 kPa) groups, with mortality, cardiovascular disease, and readmission rates serving as primary outcomes. After a median follow-up period of 153 d, it was observed that the group with high LSM had significantly higher rates of composite events (P = 0.001) and readmission rates (P = 0.022). The only independent risk factor for cardiac events was a high LSM level, not echocardiographic or serologic data. Soloveva *et al*[21] assessed FibroScan-based LSM in patients with HF both during admission and prior to discharge. Their findings revealed a statistically significant increase in the likelihood of unfavorable outcomes when LSM exceeded 13 kPa upon admission and reached or exceeded 5 kPa at the time of discharge. Discharge LSM predicted HF readmission independently and was associated with worse composite endpoints and overall mortality. A recent meta-analysis also suggested that LS may be a novel, independent prognostic marker of cardiovascular outcomes in patients hospitalized with ADHF when assessed without liver disease, supporting LSM as a clinically relevant tool to assess adequate decongestion before discharge. Further, measuring LS may help identify patients at risk of developing cardiac cirrhosis due to HF, as higher systemic venous pressure is well-recognized as a significant risk factor for cardiac cirrhosis. The possibility of cardiac cirrhosis can be excluded if there is complete normalization of LS following the removal of fluid retention. Thus, LS could be a helpful non-invasive surrogate marker for hydrostatic pressure to offer additional prognostic information in patients hospitalized with ADHF and a guiding tool for optimal therapy during ADHF (Table 3).

Left ventricular assist device placement

Left ventricular assist devices (LVADs) are increasingly becoming a common therapy for managing advanced cardiac failure. Secondary right ventricular (RV) failure in LVAD occurs in 5%-44% of patients. The observed phenomenon can be related to the compromised ability of the right heart to adequately manage an increased output from the left side of the heart, resulting in an exaggerated leftward displacement of the interventricular septum and a deterioration in the hemodynamic conditions, leading to the exacerbation of tricuspid regurgitation. This condition generally manifests during a 2-wk period following LVAD insertion and is correlated with increased ICU needs and an unfavorable prognosis. No singular marker or risk algorithm possesses substantial predictive value for problems following LVAD implantation. Nevertheless, other tests, including BNP, CVP, pulmonary artery pulsatility index, RV stroke work index, and the ratio of CVP to pulmonary capillary wedge pressure, are frequently employed to assess the necessity of implanting a RV assist device (RVAD) and performing tricuspid valve replacement prior to surgery.

Table 3 Liver stiffness measurement in heart failure

	Measurement
Indications of FibroScan in HF	(1) Assessment of adequate venous decongestion prior to discharge; (2) prognosis after an acute exacerbation; and (3) risk stratification for determining right ventricular support needs before LVAD placement
The cut-off value of LS in HF	LS < 7 kPa: Normal RV filling pressure and exclusion of RV failure
	LS 7-8 kPa: Gray zone
	LS 8-12.5 kPa: Increased risk of morbidity and mortality from HF or cardiac death; increased risk of RV failure in case of LVAD implantation
	LS > 35 kPa: BiVAD needed due to RV failure

HF: Heart failure; LS: Liver stiffness; LVAD: Left ventricular assist device; BiVAD: BiVACOR biventricular assist device; RV: Right ventricular.

Nishi *et al*[22], using FibroScan to evaluate LVAD candidates, observed that LSM was substantially higher in patients needing RVAD. Based on the receiver operator characteristic analysis, a cut-off of 7.0 kPa was determined for the increased RVAD requirement. Significantly higher LSM was seen in patients who experienced major adverse events (MAEs) than those who did not (22.4 ± 17.4 *vs* 8.0 ± 5 kPa, $P < 0.05$). MAEs were significantly higher in individuals with LSM ≥ 12.5 kPa, with 80% of these patients experiencing MAEs compared to just 25% of patients with LSM less than 12.5 kPa. Various indicators of HF were assessed in this study, such as pre-operative haemodynamic assessments, BNP, and transaminases. However, LSM was the sole risk factor found to be independently associated with MAEs. Although this does not rule out the possibility that liver fibrosis will affect LSM, it does highlight the predictive power of elastography as a separate risk factor for unfavorable events after LVAD implantation and as a tool to supplement current predictors of unfavorable outcomes.

In a study by Kashiyama *et al*[23], the authors examined the LS following LVAD implantation. The results revealed a significant elevation in LS levels among patients experiencing RV failure subsequent to LVAD implantation compared to those without RV failure. Serial measures of LS might provide valuable insights into the perioperative optimization of right-sided filling pressure, even without needing a pulmonary catheter study. This is because LS is known to be immediately influenced by fluctuations in CVP. It is important to mention that cases demonstrating higher LS values, exceeding the expected values based on pre-operative CVP, had a higher probability of experiencing RV failure (RVF) or requiring the insertion of an RVAD following the implantation of a LVAD. This suggests that LSM may serve as an indicator not only of CVP but also of other parameters, such as RVF or RV compliance. In patients with an increased LS, an increased preload might have a more adverse effect on the right ventricle than the advantageous effect of decreased afterload with LVAD support. This observation suggests that a right ventricle with decreased compliance can rapidly elevate RV filling pressure by augmented preload through increased LVAD flow.

General critical care

The most important clinical endpoint for critically ill ICU patients is overall survival. Lindvig *et al*[24] conducted a study in the emergency room to assess initial LSM by elastography to predict 30-d mortality. Increased LS, defined as > 8 kPa, was detected in 22.6% (48/213) of patients. The 30-d mortality rate for patients with TE values > 8 kPa was 20.8%, as opposed to 3.7% for patients with an LS ≤ 8 kPa. Furthermore, it was shown that LS greater than 8 kPa served as a significant independent prognostic factor for mortality. In a separate study, LS was evaluated in a cohort of 108 critically ill patients. LS was measured at admission, day 3, day 7, and weekly during their ICU stay. They noted a substantial increase in LS among critically ill individuals compared to standard-care patients who were matched for sex and age (n = 25). Patients without cirrhosis with LS values greater than 18 kPa upon admission to the ICU exhibited higher death rates in both the ICU and the long term. In a recent meta-analysis by Wang *et al*[25], the relative risk for all-cause mortality was 4.15 for patients with a high LS, which increased by 1.06 for each unit increment of LS. Intriguingly, LS appeared to predict all-cause mortality regardless of the aetiology.

Pregnancy

Twenty-five percent of pregnant women experience an increase in LS, which occurs almost exclusively in the third trimester and quickly returns to normal within a day after giving birth. However, the cause of the increase in LS remains unknown. Since liver inflammation or apoptosis often takes more than a day to resolve, the sudden drop in LS following delivery suggests a mechanical source, such as hemodynamic alterations, including inferior vena compression. Hormonal changes, a rise in the volume of blood, and modifications to the liver's functioning are a few more possibilities for LS elevation during pregnancy[26]. To completely comprehend the underlying mechanisms, more studies are required. Therefore, increased LS during pregnancy should not be confused with liver fibrosis or illness.

On the other hand, LS has a strong correlation with pregnancy-related problems like preeclampsia. A German study looked at two categories of complications: Preeclampsia (n = 22) and intrahepatic cholestasis of pregnancy (ICP) (n = 40). The mean LS values for preeclampsia and ICP were found to be 17.9 kPa and 6.9 kPa, respectively [area under the receiver operating characteristic (AUROC) = 0.82], with both groups showing elevated LS compared to healthy pregnancies in the third trimester. LS and leucocytes were separate predictors of preeclampsia in the multivariate model. Preeclampsia was twice as likely to develop in women with LSM greater than 8 kPa[27]. These findings suggest that LSM

could potentially serve as a valuable biomarker for predicting the development of preeclampsia during pregnancy. Nevertheless, further research is needed to validate these results and determine the underlying mechanisms linking LS to preeclampsia. Additionally, understanding how LS is associated with preeclampsia could provide valuable insights into the pathophysiology of this condition and potentially lead to new therapeutic approaches.

ALF

ALF is a life-threatening clinical illness with a high mortality rate if prompt and advanced intensive care or liver transplantation (LT) is not administered. In the early stages of ALF, accurate mortality prediction continues to pose challenges. The scoring systems of Clichy and King's College are widely acknowledged in the medical field as effective tools for predicting mortality in patients with ALF. However, it is imperative to continue making advancements, as the prognosis is contingent upon a prompt and suitable beginning of treatment. The inclusion of a liver biopsy should be consistently contemplated in individuals presenting with ALF to promptly validate the diagnosis or assess the concentrations of iron or copper. Nevertheless, the diminished coagulation factors resulting from liver failure might provide a constraint for performing biopsies, necessitating reliance only on transjugular alternatives in such circumstances. Therefore, it is imperative to develop alternative approaches for predicting the probability of spontaneous remission or the requirement for LT.

LS elevation in the context of ALF is believed to be attributed to hepatic edema, inflammatory infiltration, and tissue necrosis rather than fibrosis. Nevertheless, HSCs differentiate into contractile myofibroblasts, leading to tissue repair alongside cellular collapse and fibrosis[28]. Dechêne *et al*[29] showed that fibrogenesis is a component of ALF at various stages and can potentially contribute to elevated LS. Fibrosis may potentially work as a mechanism for wound healing, temporarily preserving the structural integrity of the organ until functioning hepatocytes and accessory cells can replace the damaged tissue regions. The resolution of fibrosis is associated with the programmed cell death of activated HSCs. In individuals with short-term liver impairment, such as from poisoning or mycotoxicosis, LS may be decreased. Conversely, LS exhibited an elevation among those experiencing persistent liver damage, such as those afflicted with viral hepatitis. The measurement of LS in individuals diagnosed with ALF can serve as a reliable and timely biomarker for identifying fulminant hepatitis in conjunction with evaluating bilirubin levels, prothrombin time, and platelet count. It correlates with alanine aminotransferase and total bilirubin in acute hepatitis[30]. It is further proposed that a more accurate prognosis assessment can be attained by assessing LS at two distinct time intervals, such as days 0 and 7, following admission to the hospital. This might potentially serve as a tool for prognostic estimation. However, further research is required in order to determine an appropriate threshold for stiffness.

FIBROSCAN IN PATIENTS WITH CHRONIC LIVER DISEASE

Chronic liver disease

Hepatic decompensation: Cirrhosis of the liver is one of the primary causes of death globally. It is characterized by two clinically distinctive conditions: Compensated and decompensated cirrhosis. Decompensation refers to the emergence of pronounced clinical manifestations, such as ascites, haemorrhage, hepatic encephalopathy, hepatorenal syndrome, or jaundice, which are indicative of an unfavorable prognosis.

Therapy aims to prevent clinical decompensation, which has a much worse prognosis than compensated liver cirrhosis. The hepatic venous pressure gradient (HVPG), which is the difference between the pressure in the "wedged" or "occluded" hepatic vein and the pressure in the "free" hepatic vein, is believed to be the most accurate method for measuring the presence and severity of portal hypertension (PH), except in cases such as HF in which HVPG and portal pressure can be different. This technique is relatively costly and unavailable at the bedside and in non-specialized institutions, requires appropriately trained personnel, and may be associated with procedural complications. There is a remarkable correlation between the HVPG and LS below 10 mmHg, with the latter being a reproducible and easy-to-perform non-invasive assay for assessing PH. For HVPG > 10 mmHg, the cut-off of 21 kPa for LSM demonstrated a high specificity (over 90%)[31]. However, the reference standard and LSM relationship diverge for larger values. In addition to the structure-dependent component of LS caused by liver fibrosis, the pressure balance between inflow and outflow from the hepatic sinusoidal system influences LSM, giving it a dynamic element. The 2015 Baveno VI consensus recommended using LS > 20-25 kPa to detect clinically significant PH (CSPH) in untreated hepatitis C or hepatitis B virus-related compensated advanced chronic liver disease (cACLD) patients[32]. In another recent meta-analysis of chronic viral hepatitis patients, LS cut-offs < 13.6 kPa ruled out CSPH [pooled sensitivity: 96%; 95% confidence interval (CI): 93%-97%] and > 22 kPa ruled in CSPH (pooled specificity: 94%; 95%CI: 86%-97%), confirming the Baveno VI agreement.

In a cohort study involving 343 persons diagnosed with chronic liver disease, of whom 60 were diagnosed with liver cirrhosis, it was shown that for each incremental unit in the natural logarithm of LS, there was a 14.7-fold increase in the probability of liver-related events ($P < 0.001$). When the LS value is more than 30 kPa, liver cirrhosis is usually clinically evident, with the ubiquitous presence of ascites and serum markers better predicting mortality within 12 mo. However, in another large meta-analysis with 35249 participants, LS displayed a nonlinear relationship with the risk of liver-related events. These findings suggest a modest increase in the risk of liver-related events and death associated with increased LS. However, further research is needed to develop models that can accurately predict personalized risk stratification based on LS and other variables such as albumin, bilirubin, and prothrombin time.

Differentiation of cirrhotic aetiologies: Disease aetiology significantly affects the liver's response to inflammation. Hepatitis C virus (HCV) patients with identical elevated transaminases and fibrosis stages showed lower LS values than

lobular alcohol liver disease (ALD) patients. Hence, inflammatory localization (portal *vs* lobular) may also determine LS. Also, the liver size to LS ratio between HCV and ALD is significantly different. The liver size in patients with HCV constantly decreases as fibrosis advances, whereas in patients with ALD, it first increases until reaching an LS of 30 kPa, after which it begins to decline. Simultaneous liver-spleen elastography can help distinguish cirrhosis from intrahepatic non-cirrhotic PH. Prehepatic pathologies, such as portal vein thrombosis, are associated with elevated spleen stiffness (SS)/LS ratios. A post-hepatic pathology, such as liver congestion in HF, will result in an SS/LS ratio as low as 0.3. Consequently, the finding of a disproportionate increase in SS *vs* LS in a patient with PH symptoms and the finding of an LS 20 > kPa in a patient suspected of cirrhosis due to PH should prompt further investigations to rule out porto-sinusoidal vascular disease and other causes of non-cirrhotic intrahepatic PH[33]. SS/LS ratios may provide additional non-invasive and valuable information for the differential diagnosis of liver disease.

Moreover, SS can be employed to distinguish between acute and chronic liver injury, as SS values are notably elevated in individuals with chronic liver damage compared to those with acute liver damage, even though LS levels are similar. In terms of predicting esophageal variceal bleeding (EVB), SS exhibited a superior AUROC value than spleen diameter, platelet count, and LS (0.857, 0.746, 0.720, and 0.688, respectively)[34]. Similar SS cut-off values for EVB were found in a recent research by Wang *et al*[35], with SS being superior to LS in predicting EVB (SS = 45.5 kPa and AUROC = 0.923 *vs* LS = 29.6 kPa and AUROC = 0.860). Additional long-term research is necessary to further evaluate the effectiveness of these elastography parameters and their efficacy.

Prediction of complications: Complications may frequently occur in patients with liver cirrhosis, necessitating ICU admission. These complications are associated with increased morbidity and mortality. Hence, identifying patients at risk and early detecting these complications may aid in instituting therapeutic measures and improving clinical outcomes. A meta-analysis evaluating the diagnostic accuracy of TE for PH reported a high accuracy for diagnosing PH and esophageal varices with an AUROC of 0.93 and 0.84, respectively[36]. High LSM, as evaluated by TE, has also been shown to correlate with the development of hepatocellular carcinoma, the most dreaded complication and the commonest cause of death among CLD patients[37,38].

Response to treatment: It is still unknown how, in the future, individual patient profiles of cirrhotic patients by LSM and SS measurement (SSM) may contribute to optimizing therapeutic management [for example, by transjugular intrahepatic portosystemic shunt (TIPS) or portal pressure lowering medications]. Kim *et al*[39] explored SS for this purpose because LS cannot be utilized to monitor PH under a non-selective beta blocker (NSBB). Before and after titrating NSBB (carvedilol), they assessed SS in 106 individuals with cirrhosis and high-risk oesophageal varices. By evaluating the HVPG at the same time points, they could also assess the hemodynamic response to NSBB. The hemodynamic response could be accurately predicted using the computed prediction model (model = 0.0490-2.8345 SSM) and 0.530 as the cut-off value (AUROC = 0.803). The model retained a strong capacity for discrimination in the validation cohort (AUROC = 0.848)[39].

Studies on LSM after TIPS insertion revealed an overall decline, but no significant correlation was detected between the decline in LS and that in portal pressure[40]. More recently, it has been proposed that only some patients' LS would drop after TIPS; patients with an early LS decline would demonstrate a positive outcome after TIPS, whereas patients with an early LS increase after TIPS would have a negative prognosis[41]. LS increase after TIPS could be due to an inflammatory response, triggering acute on chronic liver failure and death in this population.

Post liver transplant

Prognostication: The standard of care for patients with end-stage liver disease and those with inoperable liver malignancies is LT. Hepatic fibrosis is an important predictor of clinical outcomes in LT recipients. Advanced hepatic fibrosis is a surrogate for graft cirrhosis and hepatic decompensation and has been linked to both liver-related and non-liver-related outcomes. LSM can perform a role in the context of liver graft transplantation. In their study, Nacif *et al*[42] employed the technique of time-to-event analysis to assess and evaluate the mortality risk among individuals with end-stage cirrhosis who were on the liver transplant waiting list with and without the presence of hepatocellular carcinoma. Like the well-known model for end-stage liver disease (MELD) score, increased LS was associated with more significant mortality. The mean MELD score was 14.7 ± 6.4, whereas the mean LS was 32.7 ± 22.5 kPa. The survived group had a mean LS of 31.6 ± 22.2 kPa, in contrast to a mean LS of 50.8 ± 9.9 kPa seen in the non-surviving group (P = 0.098). Additionally, the surviving group showed higher MELD scores than the non-surviving group (P = 0.035). Therefore, elastography has the potential to serve as a valuable non-invasive tool in the diagnosis of cirrhosis and hepatocellular carcinoma, as well as in predicting mortality. However, further prospective data is required to support these findings.

Acute transplant rejection: Acute allograft rejection is still a significant postoperative complication following LT, affecting approximately 30% of recipients. It is an inflammatory process involving endothelial and biliary epithelial cells, typically within the first week after transplantation. Late episodes, *i.e.*, those that occur after the first year, suggest insufficient immunosuppressive therapy. Acute rejection is generally diagnosed using clinical, laboratory, and histopathologic criteria. Additionally, the inflammatory process that characterizes allograft rejection may exacerbate LS. In the study conducted by Nacif *et al*[42], graft damage was determined when the LS exceeded 7.9 kPa, but graft damage was ruled out when LS was below 5.3 kPa (AUROC = 0.93; P = 0.001). A distinct study found that LS cut-off values of more than 8.5 kPa accurately predicted the occurrence of moderate to severe acute rejection with a specificity of 100% and an AUROC value of 0.924. Conversely, LS values below 4.2 kPa effectively ruled out the presence of any acute rejection[43]. Identical outcomes were also observed in the AMUSE trial[44].

LIMITATIONS

Like any other clinical test, FibroScan has its own set of limitations. Even though TE is reported to be an operator-independent procedure with low inter-observer variability[45], poor operator technique may increase variability in the results[46]. Hence, at least ten measurements are required to ensure the reliability of the results. Patient positioning is also crucial for capturing correct readings[47]. Ideally, it is performed using an intercostal approach with the patient lying supine with the right arm in maximum abduction[47].

Several physiological or patient factors may also affect the accuracy of TE. Fatty meals[48], water intake[49], excessive exercise, and morbid obesity (BMI > 30 kg/m^2) may all affect its accuracy, and hence, it is recommended that FibroScan be performed in a fasting patient[5,45,50]. Even alcohol consumption may also affect LSM measurement using FibroScan; therefore it is recommended to repeat TE after a week of abstinence[51]. Apart from liver fibrosis, LS may be altered in several other clinical conditions, including cholestasis, congestion, hepatitis, liver necrosis, malignancy, and liver storage disorders, which may lead to false positive results[46,50-52].

Different cut-offs for LSM are recommended for the diagnosis of different liver diseases. On the one hand, cut-offs of < 7 kPa and > 12 kPa are recommended to rule out and rule in hepatitis B and hepatitis C related cACLD, whereas cut-offs of < 7 kPa and > 12 kPa are recommended to rule out and rule in alcohol and non-alcoholic fatty liver disease related cACLD[7,53]. Additionally, these cut-offs are still evolving as more literature becomes available.

Most of the data regarding TE has originated from studies conducted in relatively stable patients with chronic liver disease, and there is a dearth of data regarding its efficacy among critically ill patients. Several factors may affect the accuracy of TE, especially in critically ill patients and it is estimated that LSM cannot be accurately measured in about 30% of ICU patients[12]. Moreover, its efficacy may be further affected during the ICU course because of volume overload and the need for mechanical ventilation. FibroScan testing may be compromised in critically ill patients because of ascites, difficult positioning, feeding, invasive mechanical ventilation, and hemodialysis[7,12,47,48,54]. Even phases of respiration in which readings have been obtained may affect the reliability of LSM[55].

For SS, in addition to the technical restriction indicated for LS assessment, the operator cannot locate the splenic parenchyma in some individuals due to the spleen surface being smaller than the liver. However, with operator expertise, it has decreased over time. Another technical consideration for SS measurement by TE is that SS is performed using a probe approved solely to measure LS. Indeed, the FibroScan acquisition parameters were tuned for stiffness assessment for liver tissues, particularly in low-frequency excitation. Thus, utilizing the FibroScan on the spleen may overestimate stiffness values[56].

CONCLUSION

Detection of liver fibrosis is an important component of liver function evaluation as it correlates with severity and prognosis across different aetiologies causing liver dysfunction. Even though liver biopsy remains the gold standard for assessing the extent and severity of liver fibrosis, it has several limitations, including its invasive nature, high cost, need for clinical expertise, and relatively high complication rates. These complications may be more severe in critically ill patients, necessitating the preferable use of non-invasive and easily repeatable tests like TE for evaluating liver fibrosis. These tests may help in staging and monitoring fibrosis and its related complications and provide a reasonable alternative to more invasive testing. Evolving literature suggests several clinical applications; however, its application has limitations, which must be considered while performing TE, especially in ICU patients.

FOOTNOTES

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SYSTEMATIC REVIEWS

Comprehensive analysis of sodium polystyrene sulfonate-induced colitis: A systematic review

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Abstract

BACKGROUND

Sodium polystyrene sulfonate (SPS) is commonly prescribed for the management of hyperkalemia, a critical electrolyte imbalance contributing to over 800000 annual visits to emergency departments.

AIM

To conduct a systematic review of documented cases of SPS-induced colitis and assess its associated prognosis.

METHODS

Following the PRISMA-P guidelines, our study employed Medical Subject Headings and Health Sciences Descriptors, skillfully combined using Boolean operators, to conduct comprehensive searches across various electronic databases, including Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Embase, and Opengray.eu. Language criteria were confined to English, Spanish, and Portuguese, with no limitations on the publication date. Additionally, we manually scrutinized the reference lists of retrieved studies. To present our findings, we utilized simple descriptive analysis.

RESULTS

Our search strategy yielded a total of 442 references. After rigorous evaluation, we included 51 references, encompassing 59 documented cases of colitis. Predominant clinical presentations included abdominal pain, observed in 35 (60.3%) cases, and bloating, reported in 18 (31%) cases. The most frequently affected sites of inflammation were the cecum, rectum, and small intestine, accounting for 31%, 25.8%, and 22.4% of cases, respectively. Colonoscopy findings were described in 28 (48.2%) cases, and 29 (50%) of patients required surgical intervention. Among the subset of patients for whom outcome data was available, 39 (67.2%) experienced favorable outcomes, while 12 (20.6%) unfortunately succumbed to the condition. The mean time required for resolution was 36.7 d, with a range spanning from 1 to 120 d.

CONCLUSION

SPS demonstrates the capacity to effectively lower serum potassium levels within 24 h. However, this benefit is not without the risk of bowel injury. Our study highlights the absence of high-quality data pertaining to the incidence of adverse events associated with SPS usage, making it challenging to determine whether the potential risks outweigh the benefits. However, a significant mortality rate related to SPS-induced colitis was noted. Future investigations should prioritize randomized controlled trials with a sufficiently large patient cohort to ascertain the true utility and safety profile of this medication.

Key Words: Sodium polystyrene sulfonate; Hyperkalemia; Colitis; Bowel necrosis; Kayexalate

Core Tip: Our systematic review on sodium polystyrene sulfonate (SPS)-induced colitis underscores the critical need for a comprehensive understanding of the associated risks. While SPS effectively addresses hyperkalemia, our findings reveal a notable incidence of bowel injury. With limited high-quality data available, the balance between benefits and risks remains unclear. Future research, particularly randomized controlled trials, is essential to determine the true utility and safety profile of SPS in clinical practice.

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INTRODUCTION

Adverse drug events span a broad spectrum of clinical presentations, affecting various organ systems. Recognizing and understanding these medication-related effects is essential for mitigating associated morbidity and mortality[1]. Sodium Polystyrene Sulfonate (SPS) has found a specific niche in the management of hyperkalemia, a life-threatening electrolyte disturbance that leads to over 800000 emergency department visits annually[2]. This therapeutic agent gained approval from the United States Food and Drug Administration (FDA) in 1958, four years prior to the implementation of the Kefauver–Harris Drug Amendments, legislation designed to ensure drug efficacy and safety[3].

The effective management of hyperkalemia is of paramount importance for preserving life, as it serves as a protective barrier against potentially fatal arrhythmias by either facilitating potassium translocation from the serum into cells or enhancing renal potassium excretion[4]. SPS, a cation exchange resin, can be administered orally or rectally, primarily exerting its effects within the colon by facilitating the exchange of sodium ions for potassium ions[1,4,5]. Nevertheless, it is crucial to note that this drug is not without its share of side effects[6]. Historically, it has been co-administered with sorbitol, an osmotic laxative, to mitigate the risk of severe constipation or fecal impaction, which can occur when SPS is administered in isolation[1]. The FDA, in 2009, issued a black box warning to underscore the heightened risk of intestinal necrosis associated with this combination therapy[3].

Typically, gastrointestinal adverse effects manifest as mild symptoms, such as nausea and constipation[7]. However, more severe and potentially fatal complications, including colonic ulceration, severe colitis, and necrosis, have been linked to SPS therapy[7,8]. Notably, the severity of these complications tends to correlate with the overall clinical condition of patients, particularly those with a history of organ transplantation, chronic kidney failure, or individuals in the postoperative period[4].

One of the most widely accepted theories regarding the mechanism of injury revolves around the presence of renin in high concentrations among patients with renal failure. The activation of renin and subsequent splanchnic vasoconstriction may lead to non-occlusive mesenteric ischemia, predisposing the colonic mucosa to injuries and electrolyte disturbances. However, it remains unclear why patients with renal failure are more susceptible to this catastrophic complication. It is possible that they are more prone to hyperkalemia, necessitating higher doses of SPS treatment than

other patient groups[4].

Typically, the colon represents the gastrointestinal tract most frequently affected by SPS-induced complications. These lesions necessitate endoscopic or colonoscopic analysis with biopsy to rule out differential pathologies such as cancer. While gastric involvement is less common, it was identified in only two cases in our comprehensive review. Biopsy results typically reveal intestinal necrosis, ulcers, or perforations, with more than 90% of tissue samples exhibiting an accumulation of SPS crystals. The presence of kayexalate crystals in pathology specimens distinguishes kayexalate-induced necrosis from ischemic necrosis. Histological evidence of angulated crystals of sodium polystyrene sulfate in areas of mucosal erosions, ulcerations, or frank necrosis strongly suggests the diagnosis. Additional related findings include inflammatory exudates, pseudomembrane formation, and acute/chronic serositis. These crystals are typically identified adhered to the mucosa or embedded within the inflammatory milieu and ulcerations. Thus, in reaching a diagnosis, it is imperative to rule out conditions that can mimic SPS-induced effects, such as neoplasms, inflammatory diseases, and infectious diseases[4].

The objective is to conduct a systematic review of documented cases of SPS-induced colitis and to assess the overall prognosis associated with this condition.

MATERIALS AND METHODS

Methods

This study was carried out under the recommendations contained in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[9]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), maintained by York University (CRD42022265756).

Data sources

Studies were retrieved using the terms described in Supplementary material. Searches were run in January 2021 on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Embase and Opengray.eu. There was no date of publication restrictions. The reference lists of the retrieved studies were submitted to manual search. Authors were contacted when full text was not found.

Inclusion criteria and outcomes

Case report or case series studies were eligible for selection. If there was more than one study published using the same case, the most recent study was selected for analysis. Studies published only as abstracts were included, as long as the data available made data collection possible. Studies written in languages other than English, Spanish, French or Portuguese were excluded.

Study selection and data extraction

An initial screening of titles and abstracts was the first stage to select potentially relevant papers. The second step was the analysis of the full-length papers. Two independent reviewers (GPA and GFR) extracted data using a standardized form after assessing and reaching consensus on eligible studies. The same reviewers separately assessed each study and extracted data about the characteristics of the subjects and the outcomes measured. A third reviewer (LGB) was responsible for clearing divergences in study selection and data extraction.

Quality assessment

Methodological quality assessment of case reports and case series was performed by two independent authors (GPA and GFR) using the tool presented by Murad *et al*[10]. Divergences were discussed with a third reviewer (LGB) until consensus was reached. Since questions 5 and 6 of the original tool are mostly relevant to cases of adverse drug events, we modified them to better suit the cases of polystyrene-induced colitis. Therefore, we considered question 5 as 'was there gastrointestinal damage in the case of reexposure?' and question 6 as 'was there a temporal relationship between exposure and outcome?'.

Statistical analysis

Simple descriptive statistics, such as the mean and standard deviation (SD), frequency, and median were used to characterize the data. Data were summarized using RStudio (version 4.0.2).

RESULTS

Search and selection process

A systematic search yielded a total of 442 references, from which 203 duplicates were excluded. Subsequently, a meticulous evaluation of titles and abstracts led to the exclusion of 169 references. A total of 69 full-text papers underwent thorough analysis. In the final phase, 51 references, encompassing a total of 59 cases, were included in the study. The search process is visually depicted in Figure 1. The inclusion criteria for studies were either case reports or case series.

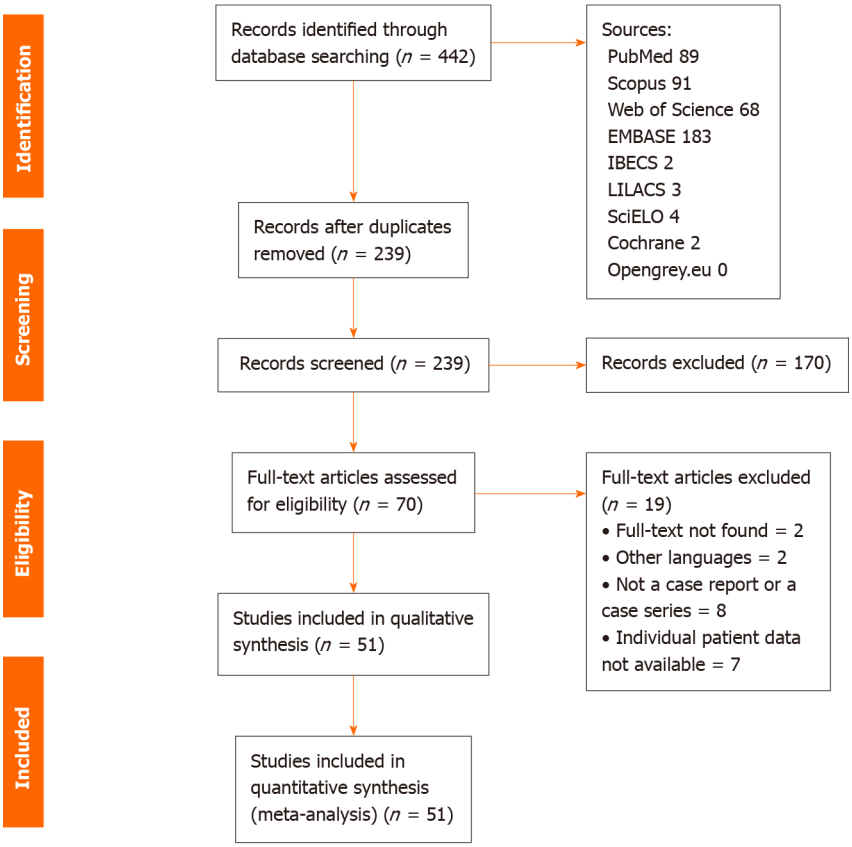

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Figure 1 PRISMA flow diagram.

Geographical distribution and baseline characteristics

The distribution of cases across different regions revealed that the United States of America (USA), India, Canada, and Thailand accounted for the majority, with proportions of 48.2%, 10.3%, 6.9%, and 5.1%, respectively. Table 1 presents the baseline characteristics of the included cases. Among the 59 patients, 34 (58.6%) were male. The age spectrum encompassed individuals from less than 1 year old to 89 years old, with a mean age of 60.6 years. All patients received a diagnosis of SPS-induced colitis. The predominant type of polystyrene was sodium (Kayexalte) in 47 (81%) patients, while calcium (Kalimate) polystyrene was administered to 11 patients, with a mean dose of 83.6 g administered orally in the 38 cases where the dose was reported. It is noteworthy that all cases included in the analysis were derived from publications in medical journals.

Clinical presentation

Abdominal pain and bloating were the most prevalent clinical presentations, observed in 35 (60.3%) and 18 (31%) cases, respectively. Hematochezia, constipation, and diarrhea followed, with frequencies of 29.3%, 12%, and 12%, respectively. A smaller proportion, 6 (10.3%) patients, presented with hypotension. Less frequent manifestations included melena, fatigue, fever, and vomiting, each reported in fewer than 5 cases. The mean time from polystyrene administration to the onset of symptoms was 5.5 d.

Comorbidities and laboratory values

Chronic kidney disease was reported in 37 (63.7%) patients, followed by hypertension (34.4%) and type 2 diabetes mellitus (20.6%). Strikingly, 75.8% of patients had some form of kidney disease, such as acute kidney injury, chronic kidney disease, end-stage renal disease, or had undergone kidney transplantation. The mean potassium levels prior to treatment initiation were 6.5 mmol/L.

Sites of inflammation and diagnostic procedures

The most commonly affected sites of inflammation were the cecum, rectum, and small intestine, accounting for 31%, 25.8%, and 22.4% of cases, respectively. Colonoscopy was mentioned in 28 (48.2%) of the reports, with biopsy being performed in 51 (87.9%) patients. Detailed findings from these diagnostic procedures are summarized in Table 2.

Treatment and outcomes

Out of the 59 patients, 29 (50%) required surgical intervention, with one patient necessitating reoperation. Among patients with available data, 39 (67.2%) experienced a favorable outcome, while 12 (20.6%) succumbed to the condition.

Table 1 Baseline features in 59 patients with colitis induced by polystyrene

Variable	Patients, *n* = 59 (100%)
Mean age (yr) (SD)	60.6 ± 16.6
Sex (male)	35 (60.3)
Signals and symptoms	
Abdominal pain	35 (60.3)
Bloating	18 (31)
Hematochezia	18 (31)
Constipation	7 (12)
Diarrhea	7 (12)
Hypotension	6 (10.3)
Melena	4 (6.9)
Fatigue	4 (6.9)
Fever	4 (6.9)
Vomiting	4 (6.9)
Pneumoperitoneum	3 (5.1)
Gastrointestinal involvement	
Cecum	18 (31)
Rectum	15 (25.8)
Small intestine	13 (22.4)
Transverse colon	10 (17.2)
Ascendent colon	9 (15.5)
Sigmoid	9 (15.5)
Descendent colon	8 (13.7)
Pancolitis	3 (5.1)
Stomach	2 (3.4)
Mean potassium levels (mmol/L) (SD)	6.5 ± 0.98
Comorbidities	
Chronic kidney disease	37 (63.7)
Hypertension	20 (34.4)
Type 2 diabetes	12 (20.6)
Peripheral arterial disease	7 (12)
Coronary artery disease	6 (10.3)
Polystyrene type	
Calcium (Kalimate)	11 (18.9)
Sodium (Kayexalte)	47 (81)
Mean polystyrene dose (g) (SD)	83.6 ± 70
Administration route	
Per os	38 (65.5)
Retal	5 (8.6)
Per os and retal	3 (5.1)
Mean time of onset symptoms (d) (SD)	5.5 ± 6.9
Biopsy	51 (87.9)

Treatment	
Surgery	29 (50)
Outcomes	
Recovery	39 (67.2)
Death	12 (20.6)
Mean time to outcome (d) (SD)	36.7 ± 35.5

The mean time to symptom resolution was 36.7 d, ranging from 1 to 120 d.

Quality assessment

In the quality assessment of the included cases, 2 (3.3%) were classified as having low quality, while the remaining 57 (96.7%) were considered to have moderate quality. None of the cases were categorized as high quality.

DISCUSSION

This systematic review delves into the analysis of documented cases of SPS-induced colitis, shedding light on the importance of collecting data on medication-related adverse events to enhance healthcare safety. Hyperkalemia, if left untreated, poses significant threats such as severe arrhythmias, cardiac arrest, and fatality[11]. The use of SPS for managing hyperkalemia has a historical legacy dating back to the 1960s[12], even though robust evidence substantiating its safety and efficacy remains scant[2].

Notably, mild adverse effects associated with SPS include symptoms like diarrhea, constipation, abdominal pain, bloating, nausea, and vomiting[13]. In the systematic review, bloating was reported in 31% of cases as a minor adverse effect, while vomiting occurred in 7% of patients. However, it is crucial to distinguish these relatively well-tolerated mild effects from severe adverse outcomes potentially linked to SPS use, which can significantly increase morbidity and mortality[14]. Such severe outcomes encompass colitis, ischemic colonic necrosis, seizures, confusion, irregular heartbeat, and pneumoperitoneum[13]. This systematic review reveals that all the cases included presented with colitis, and some cases developed more severe consequences.

Interestingly, descriptions of intestinal lesions first emerged in 1987 when catastrophic colonic necrosis was documented in five cases[15,16]. Subsequently, in 2012, a cohort study involving 2194 inpatients identified colonic necrosis in 82 cases related to SPS use[17]. Studies have reported varying incidences of colon necrosis after drug administration, ranging from 0.14% to 1.8%, with a higher incidence observed in the postoperative period[5,18]. Additionally, other concerning findings associated with SPS use, such as the three cases of pneumoperitoneum requiring urgent laparotomy, have been reported[19,20]. The characteristics of the patients are detailed in Tables 1 and 2.

Although these cases, though less common, are often detected early due to patients' complaints of increased abdominal pain and distention[5]. Typically, the time to the initial manifestation is around two days. A retrospective cohort study involving 19530 adults found that new users and users receiving the recommended dose 'per label' had a higher risk of adverse effects compared to chronic users and those on lower doses[21,22]. After adjusting for 26 covariates, SPS use was associated with hospitalization or death due to intestinal ischemia/thrombosis or gastrointestinal ulcers and perforation (HR 1.25, 95%CI 1.05-1.49)[21,22]. Therefore, the threshold dose for deleterious effects has yet to be determined, and caution is advised when prescribing this medication, especially for more fragile patients[4].

In a prior systematic review, 91% of included cases had a history of renal disease, a proportion slightly higher than the 75.8% observed in this study[4]. This aligns with expectations, as SPS is commonly used in patients with renal conditions. Other common comorbidities identified in our work included hypertension and diabetes mellitus, both of which are associated with chronic kidney disease[8,23,24]. In the literature, potential risk factors associated with deleterious adverse effects include uremia, hypovolemia, peripheral vascular disease, and immunosuppressive therapy, all of which were also evident in the cases reviewed[18,25-28].

Typically, the colon is the gastrointestinal segment most frequently affected by SPS-induced complications. These lesions necessitate endoscopic/colonoscopy analysis with biopsy to rule out differential diagnoses, such as cancer[16]. Gastric involvement is less common and was identified in only two cases in our review[29,30]. Biopsy results typically reveal intestinal necrosis, ulcers, or perforations, with an accumulation of SPS crystals in more than 90% of tissue samples [5]. The presence of kayexalate crystals in pathology specimens differentiates kayexalate-induced necrosis from ischemic necrosis[5]. Histologic evidence of angulated crystals of sodium polystyrene sulfate in areas of mucosal erosions, ulcerations, or frank necrosis strongly suggests the diagnosis[31]. Other associated findings include inflammatory exudates, pseudomembrane formation, and acute/chronic serositis[32]. These crystals are typically identified adhered to the mucosa or embedded within the inflammatory milieu and ulcerations[5]. Thus, to arrive at a definitive diagnosis, it is imperative to rule out conditions that can mimic SPS-induced effects, such as neoplasms, inflammatory diseases, and infectious diseases[16]. These histological characteristics are summarized in Table 2.

However, the pathophysiological mechanism underlying these lesions remains incompletely understood[4]. One of the most widely accepted theories suggests that the presence of renin in high concentrations among patients with renal failure plays a pivotal role. Activation of renin and subsequent splanchnic vasoconstriction can lead to non-occlusive

Table 2 Summary of systematically reviewed clinical cases

Ref.	Country	Age (yr)	Sex	Polystyrene type	Total dose (g)	First symptom (d)	Symptoms	Gastrointestinal compromise	Colonoscopy	Histology	Outcomes
Patel *et al* [52], 2017	United States	45	M	Kayexalate	30	-	None	Small intestine, cecum, ascending colon, transverse colon	Large ulcers at terminal ileum hepatic flexure and rectum	Small bowel: Acute enteritis and basophilic crystals with "fish-scales"	Recovery
Mizukami *et al*[53], 2016	Japan	64	M	Kayexalate	NR	30	Hematochezia	Rectum	Multiple ulcers were found in the upper to mid-rectum	Rectum: SPS crystals	Recovery
Rogers *et al* [33], 2001	United States	55	M	Kayexalate	NR	5	Diarrhea, Melena, Abdominal Pain	Sigmoid colon, descending colon	Large rectal ulcer and surrounding edematous and boggy mucosa	Rectum: Acute transmural necrosis with inflammatory and necrotic debris on the surface. Crystalloid foreign materials that were adherent to the ulcer bed	Recovery
Cervoni *et al* [54], 2015	United States	58	M	Kayexalate	NR	21	None	Descending colon	Severely friable mucosa with ischemic-appearing ulceration and apparent site of perforation in the proximal descending colon	Descending colon: Basophilic crystals with a mosaic pattern resembling fish scales	Recovery
Singla *et al* [55], 2016	United States	50	F	Kalimate	15	2	Constipation, Abdominal Pain, Bowel Sounds Were Absent	Cecum	NR	Cecum: Colonic necrosis and presence of SPS crystals in necrotic colonic mucosa	Recovery
Buraphat *et al* [34], 2019	Thailand	61	M	Kayexalate	210	NR	Constipation, Abdominal Pain	Small intestine	NR	Small intestine: Multiple erosions with ischemic changes and basophilic angulated crystals on the surface, Sigmoid Colon: numerous basophilic angulated crystals with a fish scale appearance were observed adhering to the surface of the mucosa	Death
Buraphat *et al* [34], 2019	Thailand	74	F	Kayexalate	150	NR	Abdominal Pain	Cecum	NR	NR	Death
Buraphat *et al* [34], 2019	Thailand	89	F	Kayexalate	180	NR	Constipation, Abdominal Pain	Sigmoid colon	NR	NR	Recovery
Fiel *et al*[19], 2018	Brazil	56	M	Kayexalate	NR	7	Constipation, Abdominal Pain, Fatigue, Abdominal Distension, Pneumoperitoneum, Hypokalemia CPS Bezoar	Cecum	NR	Serositis and transmural ischemia	Death
Jacob *et al*[1], 2016	India	75	M	Kalimate	NR	7	Abdominal Pain	Sigmoid colon	Inflamed edematous and ulcerated cecum, small ulcer with slough 4–5 cm from anal verge rectum, Stricture in splenic flexure scope could not be passed beyond, nodularity with superficial ulceration in rectum, ulcers	All biopsies showed similar findings with ulceration and inflammatory granulation tissue in most. Crystals which were basophilic and irregular ranging from 1 to 200 in number, ranging in size from 50 to 150 μ were noted. They had a mosaic or	Recovery

									in rectum and sigmoid colon	ribbed pattern or both	
Jacob *et al*[1], 2016	India	72	M	Kayexalate	NR	7	Abdominal Pain	Rectum	NR	Equal above	Recovery
Jacob *et al*[1], 2016	India	72	M	Kayexalate	NR	7	Abdominal Pain	Rectum	NR	Equal above	Recovery
Jacob *et al*[1], 2016	India	64	F	Kayexalate	NR	7	NR	Descending colon	NR	Equal above	Recovery
Jacob *et al*[1], 2016	India	48	F	Kayexalate	NR	7	NR	Rectum	NR	Equal above	Death
Jacob *et al*[1], 2016	India	52	M	Kayexalate	NR	7	NR	Sigmoid, Rectum	NR	Equal above	Death
Joo *et al*[8], 2009	South Korea	34	F	Kayexalate	215	2	Hematochezia	Descending colon	Diffuse active ulceration with mucosal necrosis and hemorrhage from the rectum to beyond the reach of an endoscope	Colitis with mucosal necrosis or ulceration and irregular shaped and sized angulated crystals with a characteristic crystalline mosaic pattern on the mucosa and ulcer bed tissue and within the necroinflam-matory debris	Death
Akagun *et al* [56], 2011	Turkey	78	F	Kayexalate	60	2	Abdominal Pain, Pneumoperitoneum	Sigmoid colon	NR	Necroinflammatory debris and various sized fragments of basophilic crystalloid material with angulated margins on microscopic examination	Recovery
Cheng *et al* [20], 2021	Australia	53	F	Kayexalate	30	15	Diarrhea, Vomiting, Abdominal Pain, Abdominal Distension, Fever, Pneumoperitoneum	Transverse colon	NR	Multiple discrete areas of deep ulceration with intramural necrosis abscess formation and focal transmural penetration SPS crystals were present in the inflammatory debris	Death
Castillo-Cejas *et al*[57], 2014	Spain	73	M	Kayexalate	NR	NR	Hypotension	Cecum, ascending colon, transverse colon	Ischemic lesions in cecum, ascending colon and hepatic angle	Ascending colon: Mucosal necrosis and Kalimate crystals with their characteristic mosaic pattern within the granulation tissue from one of the colonic ulcers	Recovery
Thomas *et al* [23], 2009	United States	64	F	Kayexalate	90	27	Hematochezia, Abdominal Pain, Abdominal Distension, Hypotension	Sigmoid colon, Rectum	Friable area of 15 to 25 cm from the anal verge	Rectum: Ulcerated mucosa and prominent granulation tissue with small eosinophilic angulated crystals embedded in mucosal ulcers	Recovery
Bomback *et al* [31], 2009	United States	56	F	Kayexalate	15	NR	Abdominal Pain	Transverse colon	Large sessile mass in the midtransverse colon	Transverse colon: Crypt miniaturization with leakage of red blood cells and fibrin into the lamina propria associated with polygonal basophilic crystals	Recovery
Scott *et al* [37], 1993	United States	48	M	Kayexalate	50	0.5	Abdominal Pain, Abdominal Distension	Descending colon, Sigmoid colon, Rectum	The rectum, sigmoid, and left colonic mucosa were erythematous and friable. The mucosa became frankly necrotic at the splenic flexure	NR	Recovery

Chou *et al* [58], 2011	Taiwan	30	M	Kayexalate	90	3	Hematochezia	Transverse colon	Colon ulcers included scattered erosion longitudinal ulcerations and sharply defined segment of involvement	Transverse colon and splenic flexure: Necrotic debris adjacent to eroded colonic mucosa. A few basophilic and rhomboid crystals with fish-scale-like mosaic pattern were identified	Recovery
Ribeiro *et al* [59], 2017	Portugal	72	M	Kalimate	NR	1	Abdominal Pain	Cecum, ascending colon	Congestive and ulcerated mucosa in the right colon and a deep necrotic ulcer in the cecum, with a diameter of 40 mm	Cecum: Necroinflammatory and granulation tissue containing basophilic-stained polystyrene sulfonate crystals	Recovery
Wootton *et al* [60], 1989	United States	48	M	Keyexalate	200	0.5	Abdominal Pain, Abdominal Distension, Fever	Transverse colon	NR	Transverse colon: Patchy transmural infarction of the colon. Near the necrotic mucosa were large quantities of amorphous Kayexalate material	Recovery
Chelcun *et al* [61], 2012	United States	51	M	Keyexalate	30	NR	Melena	Small intestine	Large ulcer surrounded by erythema was found at the ileocecal valve	Ileocecal valve: Reactive colonic mucosa with ulceration and prominent acute inflammatory exudate containing basophilic crystals consistent with SPS use	Recovery
Tapia *et al* [62], 2009	Switzerland	71	F	Kayexalate	80	10	Diarrhea, Abdominal Pain, Vomiting	Cecum, ascending colon	Segmental, circumscribed colitis in the cecum and at the left flexure	Cecum and left flexure: Segmental ulcers lightly distorted crypts with mucus depletion and fibrosis in the lamina propria accompanied by a mixed inflammatory infiltrate with lymphocytes and some neutrophils. Colon fragments with the angular crystals/foreign bodies	Recovery
Trottier *et al* [63], 2009	Canada	24	M	Kayexalate	110	1	Constipation, Abdominal Pain, Abdominal Distension, Fever, Hypotension	Small intestine	NR	Ileum-multifocal, acute ulceration. Patchy transmural necrosis and SPS crystal deposition within the intestinal mucosa	Recovery
Kao *et al*[64], 2015	Taiwan	59	M	Kalimate	120	2	Abdominal Pain, Abdominal Distension, Hypotension	Small intestine, Sigmoid colon	NR	Ileum-transmural necrosis and perforation with basophilic angulated crystals extending from the ulcerated luminal surface into the transmural	Death
Singhania *et al*[25], 2020	United States	30	M	Kayexalate	15	0.16	Hematochezia, Vomiting, Abdominal Pain, Abdominal Distension	All colon	NR	NR	NR
Goutorbe *et al* [65], 2011	United States	73	M	Kalimate	15	3	Abdominal Pain, Hypotension, Tachycardia	Small intestine, cecum	NR	Transmural abscess massive inflammatory infiltrate, ulceration and inflammation of the ceca mucosa with a fibrinous and purulent coating. Small fray-purple or blue angulated crystals	Death
Gerstman *et al*[18], 1992	United States	43	NR	Kayexalate	50	2	Abdominal Pain, Abdominal Distension, Confusion, Blood in the Gastric Aspirate	Cecum	NR	NR	Recovery
Gerstman *et*	United	42	NR	Kayexalate	135	NR	Hematochezia, Abdominal	Cecum	NR	NR	Recovery

al[18], 1992	States						Pain				
Aguilera *et al* [66], 2000	Spain	83	M	Kayexalate	NR	1	Abdominal Pain, Hypotension	Small intestine	NR	Transmural necrosis and in its course and in the peritoneal surface there are numerous basophilic crystals with hematoxylin	Death
Gardiner *et al* [30], 1997	Canada	66	M	Kayexalate	240	NR	NR	Stomach, small intestine	NR	Coagulative necrosis of the mucosa with overlying purple rhomboid kayexalate crystals, submucosal edema and acute transmural inflammation	Death
Gardiner *et al* [30], 1997	Canada	71	F	Kayexalate	105	NR	Hematochezia	Small intestine, ascending colon	NR	Hemorrhagic mucosal necrosis associated	Death
Pusztaszeri *et al*[67], 2007	France	87	M	Kalimate	NR	NR	Abdominal Distension	Small intestine	NR	Kayexalate crystals, submucosal edema and acute transmural inflammation	NR
Islam *et al* [26], 2015	United States	71	F	Kayexalate	15	0.5	Vomiting, Abdominal Pain, Nausea	Cecum	NR	Diffuse mucosal necrosis with dark purple crystals	Recovery
Kardashian *et al*[68], 2016	United States	65	F	Kayexalate	NR	2	Hematochezia, Constipation, Abdominal Pain, Fatigue, Abdominal Distension	NR	NR	Dark purple SPS crystals	Recovery
Shahid *et al* [69], 2019	United States	78	F	Kayexalate	43	1	Abdominal Pain	Cecum, ascending colon	NR	Findings of ischemic colitis with detached purple refractile material	Recovery
Strader *et al* [70], 2017	United States	60	M	Kayexalate	NR	NR	Nr	Cecum	4cm circumferential, ulcerating mass in the cecum partially obstructing the lumen as well	Biopsies in both areas reveal material morphologically consistent with kayexalate with associated colitis, ulceration and necroinflammatory debris, with no evidence of malignancy	Recovery
Albeldawi *et al*[71], 2014	United States	61	M	Kayexalate	NR	NR	Hematochezia, Fatigue, Dizziness	Cecum	Evidence of colitis and localized ulcerations in the cecum	Revealed basophilic, non-polarizable, rhomboid-like crystals without evidence of necrosis	NR
Ofori *et al* [72], 2017	United States	80	F	Kayexalate	NR	7	Hematochezia, Abdominal Pain, Abdominal Distension	Transverse colon	Revealed lumen obstructing clot in the mid transverse colon with adjacent unhealthy mucosa which was bleeding upon contact. Scope could not be advanced safely past the large clot	NR	Recovery
Abramowitz *et al*[27], 2014	United States	70	F	Kayexalate	NR	NR	Hematochezia	Rectum	Scattered diverticula throughout the colon and a 2 cm × 3 cm semi-circum-ferential friable rectal ulceration just proximal to the anorectal junction with active oozing of blood	Fragments of granulation tissue and crystalline fragments consistent with Kayexalate that were seen on the surface	NR
Rugolotto *et al*[73], 2007	Italy	0,01	NR	Kayexalate	6.8	4	Abdominal Distension	Small intestine	NR	Ileum specimen showed multiple areas of trans-mural necrosis, whereas the lumen	Recovery

										showed basophilic and Zihel–Neelsen stain positive angulated crystals surrounded by fibrinoid and giant cells exudates	
Edhi *et al*[74], 2018	United States	73	M	Kayexalate	30	1	Abdominal Distension	Cecum, ascending colon, transverse colon, descending colon	Highly consistent with ischemic colitis in the descending colon	Inflamed and ulcerated colonic mucosa and basophilic, non-polarizable, angulated, intramucosal crystals, highly consistent with SPS induced ischemic colitis	Recovery
Chatelain *et al* [75], 2007	France	46	M	Kayexalate	150	NR	Diarrhra, Hematochezia	Descending colon, Sigmoid colon, Rectum	Segmental ulcerations of the sigmoid colon	Ischemic colitis with ulcerations and transmural inflammation. Kayexalate crystals were present in the colonic lumen, adherent to ulcers. Thickened and fibrous submucosa containing numerous basophilic and purple polygonal crystals surrounded by macrophages and giant cells	Recovery
Oliveira *et al* [7], 2018	Portugal	83	F	Kayexalate	NR	2	Diarrhea, Abdominal Pain	Rectum	Visualization of the rectum, a depressed area in the lower rectum, partially ulcerated, without apparent necrosis was found and biopsied	Presence of basophilic structures with mosaic pattern, 1ilar to fish scales, surrounded by an intense active chronic inflammatory infiltrate, aspects compatible with lesion caused by ion exchange resin deposition (Kayexalate Crystals)	Recovery
Florian *et al* [76], 2019	United States	69	M	Kayexalate	NR	NR	Hematochezia	Cecum, Ascending colon	Extensive circumferential ulceration and pseudomembrane in the cecum and proximal ascending colon. Persistent ulcerations with erythematous friability in the same area	Revealed acute reactive epithelial atypia with embedded polystyrene sulfonate crystals	NR
Lee *et al*[77], 2017	United States	66	F	Kayexalate	NR	5	Hematochezia	Rectum	Two relatively isolated ulcers located in the transverse colon and in the rectum	The rectal ulcer demonstrated findings of crystal-like structures suggestive of kayexalate crystals	Recovery
Chang *et al* [78], 2020	United States	66	M	Kayexalate	30	NR	NR	Small intestine	NR	Acute ischemic enteritis featuring mucosal ulceration associated with crystals morphologically compatible with SPS, submucosal arterial and venous thrombosis and acute organizing serositis	Recovery
Moole *et al* [79], 2014	United States	80	F	Kayexalate	30	1	Diarrhea, Hematochezia, Abdominal Pain, Abdominal Distension	Sigmoid colon, Rectum	Severe well demarcated colitis in the rectosigmoid junction with a large amount of blood clots at the demarcation	Showed distal rectosigmoid ischemic colitis, with mucosal and focal submucosal necrosis and crystals consistent with Kayexalate	Recovery
Edhi *et al*[24], 2017	United States	78	M	Kayexalate	NR	NR	NR	Transverse colon, Descending colon	Diffuse moderate inflammation in the descending colon, with severe inflammation in the transverse colon	Ulceration of the colonic mucosa with basophilic crystal consistent with SPS induced injury and no features of ischemia, infectious changes or granulomas	NR
Huang *et al* [80], 2011	United States	57	M	Kayexalate	160	5	Constipation, Abdominal Pain, Abdominal Distension	NR	NR	Demonstrated crystals characteristic of SPS toxicity and concluded that the patient's	Recovery

										bowel perforation was likely caused by SPS	
Gürtler *et al* [81], 2018	Switzerland	56	M	Kayexalate	NR	1	Melena, Abdominal Pain	Small intestine	Gastroscopy demonstrated severe ulcerative duodenitis with no evidence of active bleeding	Revealed a severe erosive duodenitis. Abundant SPS crystals were detectable within the fibrinoleukocytic exudates of the duodenal ulcers and on the surface of the inconspicuous gastric mucosa	Recovery
Hajjar *et al* [29], 2018	Canada	48	M	Kayexalate	NR	NR	Abdominal Pain, Abdominal Distension	Stomach	NR	Revealed the presence of fibrinoleukocytic debris with rhomboid, birefringent crystals, suggestive of Kayexalate in the gastric wall	Recovery
Almulhim *et al*[28], 2018	Saudi Arabia	64	M	Kayexalate	30	9	Hematochezia, Melena, Abdominal Pain, Fatigue, Fever, Anemia	Descending colon, transverse colon	Findings were suggestive of right colon colitis with possible etiology of ischemia and necrotic appearing mucosa	Specimen was found to be granulated and contain SPS crystals	Recovery
Dunlap *et al* [5], 2016	United States	55	F	Kayexalate	30	2	Diarrhea, Hematochezia, Abdominal Pain, Abdominal Distension, Peritonite	All colon	Flexible sigmoidoscopy, which identified several ulcerations that were biopsied, later revealing ischemic necrosis of the bowel	Diffusely hemorrhagic with extensive multifocal ulcerations. Crystalloid particles consistent with kayexalate were identified throughout the bowel wall	Recovery
dos Santos *et al*[12], 2021	Brazil	77	F	Kayexalate	120	4	Diarrhea	Sigmoid colon	Revealed edema, enanthema, and erosion into the sigmoid colon	Typical fish scale-like SPS crystal	Recovery

NR: not reported; SPS: Sodium polystyrene sulfonate.

mesenteric ischemia, predisposing the colonic mucosa to injuries and electrolyte disturbances[32,33]. Nevertheless, it remains unclear why patients with renal failure are more susceptible to this catastrophic complication. It may simply be attributed to their higher likelihood of being hyperkalemic, necessitating treatment with higher doses of SPS than other patients[33].

Alternative theories propose that polystyrene's high water affinity leads to bulk formation with shear-thickening flow behavior, resulting in clumping and resin clogging, particularly in patients with compromised gastrointestinal motility [34]. This leads to resin impaction, subsequent gut obstruction, ischemic necrosis, and perforation, analogous to findings in stercoral colonic perforation[35]. Details about the drug are available in Table 3.

Despite the relatively common use of SPS, there is limited evidence regarding its effectiveness and safety in the literature. Therefore, vigilance is warranted regarding the drug's adverse effects[36]. A previous systematic review published in 2013 reported serious adverse reactions associated with colonic necrosis, which occupied a prominent position and resulted in a mortality rate of 33% among affected patients, higher than the 21% mortality rate observed in our study[4]. Conversely, in a double-blind, randomized, placebo-controlled trial, colonic necrosis was not reported[3]. However, the trial involved only 31 participants who were followed for a short period (7 d) and were less ill than the general patients who typically receive the medication[32]. Therefore, prescribing SPS should be a carefully considered decision, taking into account each patient's specific circumstances, especially in cases of sicker patients, such as older individuals and those with gastrointestinal hypomotility. Higher mortality rates have been observed in colitis induced by SPS. Therefore, it is essential to consider alternative approaches for controlling hyperkalemia. If alternative options are not available, it is strongly advised to implement routine monitoring to enable early detection of potential complications

Table 3 Sodium polystyrene sulfonate characteristics – adapted from Rahman *et al*[13]

Indications	Mechanism of action	Administration	Dose (g)	Adverse effects (mild)	Adverse effects (serious)	Contraindications
Hyperkalemia	Resin exchanges sodium with potassium ions from the intestinal cells	Orally or rectally	Usually, 15 to 60 daily	Diarrhea, nausea, vomiting, loss of appetite, bloating	Ischemic colonic necrosis, constipation, seizures, confusion, abdominal pain, irregular heart beat	Hypokalemia, previous hypersensitivity to SPS, bowel obstruction, neonates with reduced gut motility

SPS: Sodium polystyrene sulfonate.

[19,36].

In the adapted quality assessment tool, the majority of cases were classified as having moderate quality (96.6%)[10]. None of the cases were categorized as high quality. This was primarily due to causality questions, which, for example, implicate the danger of reexposing the patient to SPS. Additionally, none of the cases met the criteria to score in question one, as the authors did not specify whether the cases were unique in their centers. Nonetheless, only two cases were classified as low quality[34,37]. Further details can be found in Supplementary material.

The primary limitations of our study were the limited number of available cases (n = 59) and the scarcity of data in many of the reviewed cases. Despite our efforts, some full articles could not be located, even after contacting the authors, which could be attributed to the publication year. The inclusion of articles was restricted to those published in English, Spanish, French, or Portuguese, potentially resulting in the omission of articles in other languages. Despite these limitations, most of the variables presented in Tables 1 and 2 provide valuable insights into the characteristics of the patients.

Considering that observational trials suggest that SPS may lower serum potassium levels, but not without the risk of bowel injury[2] and death resulting from hyperkalemia is an unacceptable outcome[38], alternative options for addressing elevated potassium levels should be explored, and SPS should be considered a drug of last resort[39]. Some authors argue that despite many decades of experience with SPS and its low cost, it would be premature to abandon it in favor of more expensive alternatives with similar side effects or undefined long-term toxicity[17]. When evaluating patients exposed to SPS with diarrhea, it is essential to always consider a broad range of potential differential diagnoses for colitis and diarrhea in this group of patients, such as inflammatory bowel disease[40-42], infectious enteritis and colitis [43-45], angiotensin II receptor blocker induced sprue-like enteropathy[46], celiac disease[47,48], foreign body ingestion or food poisoning[49], neoplasm[50] or pellagra[51].

CONCLUSION

In conclusion, alternative methods such as hemodialysis or glucose, insulin, or bicarbonate injections may be more effective in controlling hyperkalemia[18]. There is currently insufficient high-quality data to estimate the number of adverse events associated with SPS use, making it challenging to determine whether the benefits outweigh the risks[2, 38]. Moreover, it is crucial to acknowledge that the mortality rate was notably significant, standing at 20.6% in this review. Therefore, future studies should ideally involve randomized controlled trials with an adequate number of patients to investigate the real risks and benefits of this drug.

ARTICLE HIGHLIGHTS

Research background

The study details the significance of Sodium Polystyrene Sulfonate (SPS) in managing hyperkalemia, a life-threatening condition. SPS, used to remove excess potassium, has side effects, including severe gastrointestinal complications. The exact mechanism of SPS-induced colitis is unclear, but it primarily affects the colon, requiring biopsy for diagnosis.

Research motivation

Comprehensive understanding of the SPS therapy and colitis relationship is crucial for patient safety. This research addresses knowledge gaps, aiming to contribute to future studies in drug safety and gastroenterology.

Research objectives

This study's main goal is to systematically review cases of SPS-induced colitis to understand its prognosis and influencing factors. Achieving these objectives enhances awareness of risks tied to SPS therapy, aiding clinical decisions for hyperkalemia management and guiding future research on risk mitigation.

Research methods

This systematic review followed the PRISMA guidelines for transparency and methodological rigor. A comprehensive search strategy covered multiple databases and utilized manual searches. Inclusion criteria prioritized case reports or case series studies, with language inclusion restricted to English, Spanish, French, or Portuguese. A two-step screening process and data extraction by independent reviewers ensured rigorous analysis. Methodological quality assessment employed a modified tool, addressing specific aspects related to polystyrene-induced colitis. Data were analyzed using descriptive statistics, providing a comprehensive dataset characterization.

Research results

The review examined 442 references, including 51 which comprised 59 cases meeting the criteria. The majority of cases were from the United States (48.2%). The patients age varied from less than 1 year to 89 years and were predominantly diagnosed with SPS-induced colitis. Common symptoms included abdominal pain, bloating, and gastrointestinal issues, with chronic kidney disease being prevalent. Diagnostic procedures such as colonoscopy and biopsies were frequently conducted. Surgical intervention was necessary for 50% of patients, and most had favorable outcomes, with a mean time to symptom resolution of 36.7 days.

Research conclusions

This systematic review underscores the importance of monitoring adverse events related to SPS in hyperkalemia treatment. It differentiates mild from severe side effects, advocating for alternative hyperkalemia management, especially for older or fragile patients due to higher associated mortality. The exact mechanisms remain unclear, but factors such as renin concentration and water affinity are implicated.

Research perspectives

Future research should prioritize randomized controlled trials to assess SPS use, considering its effectiveness and risks. Alternative hyperkalemia management methods and cautious SPS prescription are crucial, with a focus on addressing knowledge gaps for informed clinical decisions.

FOOTNOTES

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SYSTEMATIC REVIEWS

Burnout syndrome and anxiety among healthcare workers during global pandemics: An umbrella review

Clayton Yang Teng Bey, Jin-Uu Koh, Christopher Wai Keung Lai

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Abstract

BACKGROUND

Burnout syndrome and anxiety are two mental health symptoms experienced by healthcare workers (HCWs) that can be exacerbated during pandemics due to increased job demands and the global health workforce crisis.

AIM

To provide a comprehensive review and summary of evidence on burnout and anxiety in HCWs during previous global pandemics.

METHODS

A systematic search on electronic databases such as PubMed Central and MEDLINE was conducted to identify high-quality systematic review studies that reported on the prevalence of burnout and/or anxiety in HCWs during any previous global pandemic.

RESULTS

Twenty-four high quality systematic review articles were found to be suitable for inclusion. Twenty articles focused merely on Coronavirus disease 2019, while four articles examined multiple pandemics. Burnout was examined in nine articles, while anxiety was examined in the remaining 21 articles. Female HCWs and nurses were identified to be at a higher risk of developing burnout and anxiety during pandemic. We also observed a variation in the prevalence of burnouts and anxiety across different studies due to different mental health instruments were used in different studies.

CONCLUSION

Nurses and females HCWs had a high prevalence of burnout syndrome and anxiety during pandemic. More emphasis and attention should be paid to safeguarding the psychological well-being of these at-risk populations in the future pandemics.

Key Words: Burnout; Anxiety; Pandemics; COVID-19

Core Tip: During the pandemic, burnout syndrome and anxiety were highly prevalent among nurses and other female healthcare professionals. More emphasis and attention should be directed to protecting the psychological well-being of these at-risk populations in the event of future pandemics. This study has implications for healthcare stakeholders, advising them to prioritize safeguarding the psychological health of those who are vulnerable to pandemics in the future.

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INTRODUCTION

Burnout is defined as a "syndrome conceptualised as resulting from chronic workplace stress that has not been successfully managed"[1]. From this definition, it is obvious how pandemics, which can last from months to years, can result in an increased prevalence of burnout among healthcare workers (HCWs)[2]. Furthermore, it is also hard to predict the exact duration of pandemics, such as in the ongoing coronavirus disease 2019 (COVID-19) pandemic that has been ongoing since December 2019. Some other examples of pandemics that occurred in the 21st century include the Middle East respiratory syndrome (MERS) pandemic caused by the MERS-coronavirus (CoV), the H1N1 influenza pandemic caused by the H1N1 influenza virus, and the severe acute respiratory syndrome (SARS) pandemic, caused by the SARS-CoV[3].

Anxiety is characterised by "excessive fear and worry and related behavioural disturbances", producing significant distress or significant functional impairment[4]. If left unmanaged, anxiety can lead to burnout in high-risk individuals [5]. In a longitudinal study conducted in a large public hospital in Singapore to prospectively assess job-related burnout and psychological outcomes such as burnout and anxiety of HCWs during early COVID-19, 23% and 13% of 1410 participants experienced burnout and anxiety respectively[6].

Even during periods of non-pandemics, burnout and anxiety are prevalent in HCWs due to demanding job responsibilities. In addition, there is a serious shortage of HCWs across the globe, described by the World Health Organization as a global health workforce crisis, where they estimate an insufficiency of 10 million HCWs by 2030[7]. During pandemics, HCWs play a crucial role in their management, which can further exacerbate these issues as job demands intensify. By being on the front lines, HCWs receive increased exposure to stressors such as limited resources, increased occupational hazards, longer shifts, and disrupted work-life balance, which can lead to the development of burnout and anxiety, among other mental health symptoms[8].

A plethora of interventions exist to help curb mental health issues in HCWs, be it individual-focused or organizational interventions[9]. The former include cognitive-behavioural therapy, physical relaxations such as messages, or mental relaxations such as meditation; for the latter, working conditions and schedules are altered, communication skills are improved, as well as implementation of support programmes[10].

The systematic review and meta-analysis study by West *et al*[9] concluded that both approaches result in reduced incidence of burnout, but more research is necessary to establish the most effective interventions for a specific population. On the other hand, in a Cochrane review by Ruotsalainen *et al*[10], the authors concluded that only low-quality evidence is available that shows improvements in mental health outcomes with individual-focused interventions; for organisational changes such as improving work conditions and organising support or special care models, significant reductions in stress levels were not achieved. With the little information exist, therefore, this umbrella review hypothesis that prevalence of burnout and anxiety in certain group of HCW will be high during pandemics. This umbrella review also serves to provide a broader summation of relevant data on anxiety and burnout respectively, and to explore possible risk factors and interventions for HCWs.

MATERIALS AND METHODS

Study design

This umbrella review was conducted according to the recommendations of PRISMA, using the PRISMA 2020 checklist. There is no similar protocol exists in the International Prospective Register of Systematic Reviews (PROSPERO). Furthermore, this review was conducted in conformance to the Joanna Briggs Institute (JBI) umbrella review protocol.

Table 1 The search strategy of the present umbrella review study

Search terms	Results	Database(s)
Anxiety in healthcare professionals pandemic	82	Google Scholar
Burnout in healthcare professionals pandemic	50	Google Scholar
[(healthcare) OR (physician) OR (health personnel)] AND [(burnout) OR (anxiety)] AND (pandemic) NOT (intervention)	44	PubMed Central; MEDLINE
[(healthcare) OR (physician) OR (health personnel)] AND [(burnout) (health personnel)] AND [(burnout) OR (anxiety)] AND (COVID-19)	46	PubMed Central; MEDLINE
NOT (intervention) (burnout syndrome OR anxiety) AND (healthcare workers OR medical professionals) AND (global pandemics OR COVID-19 OR SARS OR MERS)	145	PubMed Central; MEDLINE

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome.

Search strategy

A PICO question was first developed with the population including HCWs, the interest including burnout and anxiety, the context including pandemics and the outcome including the comparison of prevalence of both burnout and anxiety and also the exploration of interventions for both mental health problems. Starting from August 31, 2022, initial keywords were identified such as "anxiety", "burnout", "healthcare", "healthcare workers OR medical professionals", "pandemic" and "COVID-19". Preliminary search on PROSPERO yielded no results however there were two similar ongoing systematic reviews (CRD42022259101) and (CRD42021260307). Next, the databases searched were PubMed Central, MEDLINE, and Google Scholar. Gray literature, which included internet sites and news articles, was also searched. Lastly, references from literature reviews that were done during screening were also included. Table 1 shows a summary of the search strategies used in the present study.

Eligibility criteria

Systematic review studies were only to be included if they fulfilled the eligibility criteria as follows: (1) Studies that conducted a systematic review with or without a meta-analysis; (2) Studies conducted with regard to pandemics (*e.g.*, SARS, MERS, COVID, *etc*); (3) Studies with at least 1 mental health outcome stated in the objective (*i.e.*, burnout and/or anxiety); and (4) Studies that investigated patient-facing healthcare personnel as the population of interest (regardless of age, gender, or ethnicity).

On the other hand, studies were to be excluded if they were: (1) Non-English; and (2) Systematic reviews and review articles that did not use a systematic approach (*i.e.*, rapid and scoping reviews).

Critical appraisal

Critical appraisal was also done independently by both researcher (Koh JU and Bey CYT). The JBI 2017 critical appraisal checklist for Systematic Reviews and Research Syntheses was used. An item would be scored "0" if it was answered "NO" or "UNCLEAR"; if it was answered "YES," then the item score was "1." The study quality was assessed as follows: low quality = 0–3, moderate quality = 4–7, and high quality = 8–11. Only high-quality studies were included in this umbrella review (*i.e.* scoring 9 out of 11). Of the 55 articles assessed, 16 articles were excluded for having a less than 80% for the critical appraisal (*i.e.* scoring 8 and below).

Study selection and data extraction

Two reviewers (Bey CYT and Koh JU) independently screened the titles and abstracts of the remaining studies according to the aforementioned inclusion and exclusion criteria. Should there be insufficient information provided in the titles and/or abstracts, the full text was obtained for evaluation. Any disputes were resolved by means of a discussion to obtain consensus and if the reviewers were unable to arrive at an agreement, the principal investigator (Lai CWK) was consulted.

Information extracted include: (1) Authors; (2) Database(s) searched; (3) Study design(s); (4) Risk of bias assessment; (5) Number of studies included; (6) Study location(s); (7) Study population(s); (8) Period of study; (9) Pandemic(s) studies; and (10) Mental health outcome(s).

Data collection

Data were retrieved from all included studies by one reviewer using a self-generated data extraction form and then double-checked by the second reviewer to minimize mistakes. The data included the author, publication year, database searched, study design, studies included, study population, study period, pandemic studied, mental health outcomes, risk of bias, burnout prevalence and anxiety prevalence. Synthesis of results was achieved by combining results of all included studies.

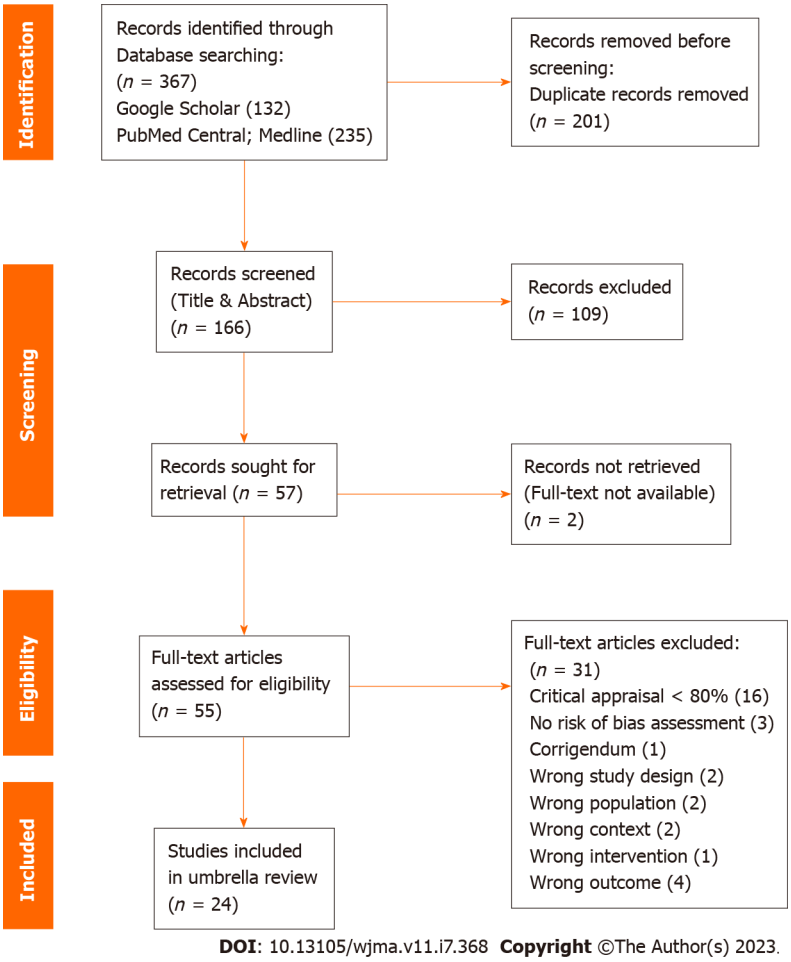

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Figure 1 PRISMA flow diagram.

RESULTS

Study selection process

The initial database search returned 367 results, of which 201 were removed during deduplication. The titles and abstracts of the 166 remaining records were then screened, which resulted in 109 records being excluded. When retrieving the full text of the 57 included records, two were found to be unavailable, resulting in 55 articles assessed for eligibility. During the screening of the full-text articles, 31 articles were rejected due to reasons such as having a critical appraisal score of < 80%, no risk of bias assessment, being a corrigendum, as well as having the wrong study design, population, context, intervention, and outcome. Figure 1 shows the PRISMA flow diagram depicting the details of the different phases of the systematic search.

Study characteristics

Table 2 shows the characteristics of the studies included in the umbrella systematic review. The majority of the included studies were systematic reviews with meta-analysis, with 16 (67%) articles, while the other 8 (33%) were solely systematic reviews. In addition, nurses were the population studied for 4 (17%) articles, while the rest studied HCWs as a whole. Twenty (83%) articles reviewed only COVID-19 while only 4 (17%) reviewed multiple pandemics including SARS, MERS, Ebola, H1N1, H7N9, and COVID-19.

Different mental health instruments used

Anxiety was examined in the majority of the shortlisted studies, with 21 articles reporting on its prevalence. In these studies, the tools used to measure anxiety include the Beck Anxiety Inventory (BAI), Depression Anxiety Stress Scale-21 (DASS-21), Generalised Anxiety Disorder-2 (GAD-2), Generalised Anxiety Disorder-7 (GAD-7), Hamilton Anxiety Scale, Hospital Anxiety and Depression Scale, Coronavirus Anxiety Scale, Patient Health Questionnaire, State-Trait Anxiety Inventory (STAI-S), and Zung Self-Rating Anxiety Scale (SAS).

Only Four articles examined burnout in HCWs during pandemics. Mini-Z Burnout Survey (Mini-Z), Copenhagen Burnout Inventory (CBI), Maslach Burnout Inventory (MBI), Oldenburg Burnout Inventory, Stanford Professional Fulfilment Index, and Professional Fulfilment Index.

Table 2 Summary of articles (*n* = 24) that included in this umbrella review

Ref.	Database(s) searched	Study design	Studies included	Study population	Study period	Pandemic studied	Mental health outcome(s) measured	Risk of bias (quality) assessment	Burn out prevalence	Anxiety prevalence
Abdulla *et al* [39], 2021	MEDLINE (PubMed); Cochrane Library; Scopus; Web of Science; Google; Google Scholar; ResearchGate	Systematic review and meta-analysis	23	Multi-professional healthcare workers	Until Feb 2021	COVID-19	Anxiety	Downs and Black checklist	NIL	42.87%
Adibi *et al* [26], 2021	ISC; Magiran; PubMed; Scopus; Web of Science; Cochrane; ProQuest; Science Direct; Embase; Google Scholar	Systematic Review and Meta-analysis	15	Multi-professional healthcare workers	Jan 2020 to Jun 2020	COVID-19	Anxiety	STROBE checklist	NIL	30.5%
Aymerich *et al*[12], 2022	Web of Science Core Collection; BIOSIS Citation Index; KCI-Korean Journal Database; MEDLINE; Russian Science Citation Index; SciELO Citation Index; Cochrane Central Register of Reviews; Ovid/PsycINFO	Systematic Review and Meta-analysis	239	Multi-professional healthcare workers	Until Mar 2021	COVID-19	Anxiety; Burnout	NOS	37.0%	42.0%
Busch *et al* [16], 2021)	PubMed; Web of Science Core Collection; MEDLINE; PsycINFO	Systematic Review and Meta-analysis	86	Multi-professional healthcare workers	Until Oct 2020	SARS, H1N1, Ebola, MERS, COVID-19	Anxiety; Burnout	JBI critical appraisal tool	31.81%	25.36%
Chen *et al* [30], 2022	CNKI; VIP; WanFang Data; PubMed	Systematic Review and Meta-analysis	30	Multi-professional healthcare workers	Dec 2019 to Apr 2022	COVID-19	Anxiety	Agency for Healthcare Research and Quality 11-item checklist	NIL	43.0%
Chigwedere *et al*[40], 2021	PubMed; PsycInfo; PsycArticles	Systematic Review	76	Multi-professional healthcare workers	Until June 2020	SARS, MERS, Ebola, H1N1, H7N9, COVID-19	Anxiety; Burnout	JBI checklist for cross-sectional studies and cohort studies	NIL	NIL
Ching *et al* [13], 2021	Medline; Cinahl; PubMed; Scopus databases	Systematic Review and Meta-analysis	148	Multi-professional healthcare workers	Until Mar 2021	COVID-19	Anxiety; Burnout	STROBE checklist	68.3%	39.7%
Dong *et al* [24], 2021	PubMed; Embase; PsycINFO; Wanfang Data; Chongqing VIP; Sinomed; Chinese National Knowledge Infrastructure databases	Systematic Review and Meta-analysis	22	Multi-professional healthcare workers	Jan 2020 to Oct 2020	COVID-19	Anxiety	Agency for Healthcare Research and Quality 11-item checklist	NIL	34.4%
Dutta *et al* [27], 2021	PubMed/MEDLINE; Cochrane Library; Scopus; PsycINFO	Systematic Review and Meta-analysis	33	Multi-professional healthcare workers	Dec 2019 to Aug 2020	COVID-19	Anxiety	NOS	NIL	32.5%
Galanis *et al*	PubMed; Scopus; ProQuest; Cochrane COVID-19	Systematic	6	Nurses	Jan 2020	COVID-19	Burnout	JBI critical appraisal	Emotional exhaustion:	NIL

[14], 2021	registry; CINAHL; pre-print services (medRχiv and PsyArXiv)	Review and Meta-analysis			to Nov 2020			tool	34.1%; Depersonalisation: 12.6%; Lack of personal accomplishment: 15.2%	
Ghahramani *et al*[15], 2021	PubMed; Scopus; EMBASE; ScienceDirect Web of Science; Cochrane Library; ProQuest	Systematic Review and Meta-analysis	27	Multi-profes-sional healthcare workers	Until Jan 2021	COVID-19	Burnout	STROBE checklist	52.0%	NIL
Gualano *et al* [11], 2021	PubMed; Embase; SCOPUS; PsycINFO	Systematic Review	11	Multi-profes-sional healthcare workers	Jan 2020 to Nov 2020	COVID-19	Burnout	AXIS tool	49.3% to 58.0%	NIL
Hao *et al*[29], 2021	PubMed; EMBASE; Scopus; PsycINFO; Chinese Biomedical Literature Database; China National Knowledge Infrastructure; China Science and Technology Journal Database; Wanfang database	Systematic Review and Meta-analysis	20	Multi-profes-sional healthcare workers	Jan 2020 to Apr 2020	COVID-19	Anxiety	Agency for Healthcare Research and Quality 11-item checklist	NIL	28.6%
Hill *et al*[28], 2022	MEDLINE; Embase; The Cochrane Library (Cochrane Database of Systematic Reviews); PsycINFO	Systematic Review and Meta-analysis	43	Multi-profes-sional healthcare workers	Until Mar 2020	SARS, MERS, COVID-19	Anxiety	Hoy quality assessment checklist	NIL	COVID: 16.1%; SARS: 14.8%; MERS: 5.8%
Koontalay *et al*[41], 2021	MEDLINE *via* PubMed; CINAHL Complete; Embase through Ovid; Scopus; Web of Science	Systematic Review	10	Multi-profes-sional healthcare workers	Nov 2020 to Feb 2021	COVID-19	Anxiety; Burnout	CASP Qualitative Research Checklist	NIL	NIL
Marvaldi *et al* [19], 2021	PubMed; PsycINFO	Systematic Review and Meta-analysis	70	Multi-profes-sional healthcare workers	Until Oct 2020	COVID-19	Anxiety	NIH's quality assessment tool and Crombie's items	NIL	30.0%
Pappa *et al* [18], 2020	MEDLINE; PubMed; Google Scholar databases; Medrxiv; SSRN server	Systematic Review and Meta-analysis	13	Multi-profes-sional healthcare workers	Until Apr 2020	COVID-19	Anxiety	NOS	NIL	23.2%
Salari *et al* [42], 2020	SID; MagIran; IranMedex; IranDoc; Science-Direct; Embase; Scopus; PubMed; Web of Science (ISI); Google Scholar	Systematic Review and Meta-analysis	29	Multi-profes-sional healthcare workers	Dec 2019 to Jun 2020	COVID-19	Anxiety	STROBE checklist	NIL	25.8%
Salazar de Pablo *et al* [17], 2020	Web of Science; grey literature	Systematic Review and Meta-analysis	115	Multi-profes-sional healthcare workers	Jan 2020 to Apr 2020	SARS,MERS,COVID-19	Anxiety; Burnout	Mixed Methods Appraisal Tool(MMAT)	COVID: 25.0%; SARS: 38.2%; Any coronavirus:34.4%	COVID: 22.2%; SARS: 45.7%; Any coronavirus: 29.0%
Saragih *et al* [20], 2021	PubMed; Academic Search Complete; CINAHL; Web of Science; MEDLINE Complete; SocINDEX	Systematic Review and Meta-analysis	38	Multi-profes-sional healthcare workers	Dec 2019 to Nov 2020	COVID-19	Anxiety	JBI tool for cross-sectional studies and the 10-questions of JBI tool for	NIL	40.0%

								case–control studies		
Ślusarska *et al*, 2022[25]	PubMed; Web of Science; SCOPUS	Systematic Review and Meta-analysis	23	Nurses	Mar 2020 to Feb 2021	COVID-19	Anxiety	Agency for Healthcare Research and Quality 11-item checklist	NIL	29.0%
Sun *et al*[22], 2021	PUBMED; EMBASE; WEBOF SCIENCE	Systematic Review and Meta-analysis	47	Multi-profes-sional healthcare workers	Nov 2019 to Sep 2020	COVID-19	Anxiety	Modified NOS	NIL	38.0%
Xiong *et al*[21], 2022	Medline; PsycINFO; EMBASE; the Cochrane Library (including Cochrane Database of Systematic Reviews); Sinomed; CNKI, WanFang data; Medrxiv; SSRN servers; Google Scholar; daily updated WHO COVID-19database	Systematic Review and Meta-analysis	44	Multi-profes-sional healthcare workers	Until Jun 2020	COVID-19	Anxiety	Modified NOS	NIL	17.0%
Zhang *et al*[23], 2021	PubMed; Embase; the Cochrane Library; E. B. Stephens Company data- base; Web of Science; ALOIS; PsycINFO; Cumulative Index to Nursing and Allied Health Literature database (CINAHL); ClinicalTrials.gov; Chinese National Knowledge Infrastructure (CNKI); Sinomed; Wanfang Data; Chongqing VIP database	Systematic Review and Meta-analysis	26	Multi-profes-sional healthcare workers	Jan 2020 to May 2020	COVID-19	Anxiety	Quality	NIL	27.0%

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; NOS: Newcastle-Ottawa Scale.

Mental health findings

Prevalence of burnout during COVID-19: Five articles reported on the pooled prevalence of burnout in HCWs during COVID-19, which ranged from 25.0% to 68.3%.

The systematic review by Gualano *et al* examined burnout in HCWs working in Intensive Care Units and Emergency Departments during the COVID-19 pandemic and found that the prevalence of overall burnout ranged from 49.3% to 58.0%[11]. Another systematic review and meta-analysis by Aymerich *et al*[12] reported a pooled prevalence of 37.0% for burnout symptoms. However, when looking at the individual instruments, the prevalence varied from 22.0% when using Mini-Z to 53.0% when using CBI. In the systematic review and meta-analysis by Ching *et al*[13], the pooled prevalence of moderate to severe burnout among HCWs was 68.3%, with Korea having the highest prevalence at 90.4%, and China having the lowest at 58.0%.

Two studies reported the prevalence of the three individual dimensions of burnout: emotional exhaustion, depersonalisation, and lack of personal accomplishment. In the systematic review and meta-analysis by Galanis *et al*[14], they were 34.1%, 12.6%, and 15.2,% respectively. Ghahramani *et al*[15] on the other hand, reported these to be 51.0%, 52.0%, and 28.0%, respectively.

Prevalence of burnout across multiple pandemics: Two articles reported on the pooled prevalence of burnout across multiple pandemics, which ranged from 31.81% to 34.4%.

The systematic review and meta-analysis by Busch *et al*[16] reported the prevalence of burnout in HCWs to be 31.81%. Salazar de Pablo *et al*'s[17] systematic review and meta-analysis reported pooled prevalence of SARS, COVID-19, and any

pandemic to be 38.2%, 25.0%, and 34.4% respectively. For SARS, 2 studies were analysed with a total of 1305 participants. For COVID-19, only one study with 32 participants was analysed. For any pandemic, three studies were analysed with a total of 1,337 participants.

Prevalence of anxiety during COVID-19: Sixteen articles reported on the pooled prevalence of anxiety in HCWs during COVID-19, which ranged from 16.1% to 43.0%.

The systematic review and meta-analysis by Pappa *et al*[18] examined anxiety in 12 studies and reported a pooled prevalence of 23.21%. However, when considering only studies that had a low risk of bias, the prevalence was 24.06%. Marvaldi *et al*[19] and Saragih *et al*[20] studies reported anxiety prevalence of 30% and 40%, respectively, but both studies noted the presence of substantial heterogenicity. Ching *et al*[13] found that the pooled prevalence of mild to severe anxiety in Asia was 39.7%.

Xiong *et al*'s[21] review of 18 studies with 34793 participants estimated a 17.0% prevalence of moderate to severe anxiety. Another study that specified the level of anxiety was a systematic review and meta-analysis by Sun *et al*[22], which reported the prevalence of moderate to severe anxiety to be 21.0%, while the prevalence of mild anxiety was 26.0%.

Two studies compared the prevalence of anxiety in HCWs during COVID-19 over time. The systematic review and meta-analysis by Zhang *et al*[23] investigated a total sample size of 21447 HCWs from 23 studies reporting a decrease in anxiety rates over time, from 37.7% to 56.3% in the first week of February to 27.0% to 30.8% in the final week of February. Similarly, Dong *et al*[24] divided the survey time of 22 studies into three stages and found that the pooled prevalence of anxiety was the highest in the earliest stage, and decreased in later stages.

Several reviews that included studies which emphasize different mental health instruments found that prevalence can vary depending on the tool used. Ślusarska *et al*[25] reported that in the 12 studies that used the GAD-7 scale, the prevalence was 22%, but in the four studies that used the SAS scale, the prevalence was 7.0%; for studies that used other scales, the prevalence was 57.0%. Adibi *et al*[26] performed a meta-analysis on 19 studies which used either GAD-2 or GAD-7 to measure anxiety, reporting a prevalence of 22.62% when using the former, and 32.04% for the latter. A systematic review and meta-analysis by Aymerich *et al*[12] reported anxiety prevalence in 179 studies, with a total sample size of 206513. Overall prevalence was 42.0% but was noted to vary substantially depending on the scales used. For instance, for studies using the BAI, the prevalence was 34.0%, but studies using STAI-S reported a prevalence of 68.0%. Lastly, Dutta *et al*'s[27] systematic review and meta-analysis consisted of 31 articles that used different tools for the measurement of anxiety – GAD-7 was used in nine studies and pooled prevalence was 45.1%; DASS-21was used in eight studies and pooled prevalence was 39.0%; SAS was used in six studies and pooled prevalence was 14.0%.

Prevalence of anxiety across multiple pandemics: Three articles examined the pooled prevalence of anxiety across different pandemics, which ranged from 25.4% to 29.0%.

Salazar de Pablo *et al*[17] reviewed two studies on SARS which consisted of a total of 1475 participants, four studies on COVID-19 which consisted of 7716 participants, and any pandemic, which consisted of 9191 participants. Prevalence was 45.7%, 22.2%, and 29.0%, respectively.

Hill *et al*[28] reported the prevalence of anxiety in HCWs during SARS, COVID-19, and MERS to be 14.8%, 18%, and 5.8%, respectively. The authors also noted that the overall prevalence of anxiety symptoms was higher than that of anxiety disorders, at 45.9% compared to 16.1%. A systematic review and meta-analysis by Busch *et al*[16] reported the overall prevalence of anxiety to be 25.36%.

The at-risk group 1 (Nurses): Multiple studies also reported that nurses were found to have a higher prevalence of mental health symptoms compared to other HCWs. In a review of HCWs in intensive care units and emergency departments, Gualano *et al*[11] reported that nurses had the highest prevalence of burnout at 64%, compared to advanced practice providers (56%), respiratory therapists (55%), physicians (49%), and physicians-in-training (48%). Emotional exhaustion and depersonalisation were also higher in nurses in critical care units, at 24.7%. Ghahramani *et al*'s[15] subgroup analysis reported overall burnout among the group which consisted of physicians and/or nurses to be the highest at 66%, compared to that of a group that mixed HCWs which were 40%. However, the mixed HCWs group had a higher prevalence for the individual components. Ching *et al*'s[13] data on burnout showed that the nurse population had an 80.2% prevalence of experiencing burnout, followed by doctors at 74.9% and lastly by allied healthcare personnel at 64.9%. Hao *et al*[29] reported that in seven out of 16 studies in their subgroup analysis that the prevalence of anxiety in nurses was 36.8% as compared to when mixed staff groups were analysed, where the prevalence was 26.8%. Similarly, Dong *et al*'s[24] meta-analysis also reported higher anxiety prevalence among nurses, 44.0% compared to 29.0% among overall HCWs. Ching *et al*[13] also found anxiety to be most prevalent in nurses at 43.1%, which surpasses that of doctors, dentists, allied healthcare professionals, and pharmacists, which had an anxiety prevalence of 38.6% to 39.6%. When compared to medical doctors, Chen *et al*[30] also reported a higher prevalence of anxiety in nurses, 45.0% compared to 25.0%.

The at-risk group 2 (Females HCWs): Other than nurses, HCWs of the female gender were also found to be more susceptible to anxiety. In 11 studies that reported on anxiety prevalence by gender, the pooled prevalence was 50.0% in females compared to 36.0% in males[22]. The prevalence of anxiety in females reported by Ching *et al*[13] was 50.6% compared to 40.4% in males. Chen *et al*[30] reported the prevalence of anxiety in females to be 38.0% compared to 26% in males. Salazar de Pablo *et al*[17] review found that studies which included nurses were associated with higher psychological distress compared to studies which included multiple professions or were physician-only.

DISCUSSION

This umbrella review provides a comprehensive summary of the prevalence of burnout and anxiety in HCWs during periods of pandemics, and showcases the high prevalence of burnout and anxiety during the period of pandemics. The findings of this review also highlight the utmost importance for interventions to support the mental health of HCWs during pandemics.

From this umbrella review, female HCWs, nurses and frontline HCWs are the main highlight of burnout and anxiety during pandemics. This was the result of increased workload, longer working hours, physical exhaustion and increases the need to make ethical decisions for treatment priority during pandemic[31]. The main concern for HCWs is the risk of infections to colleagues and family members and patient violence attributed to long waiting times and feeling of impatience and frustration. Poor mental health may affect their work performance, leading to lower quality care, higher medical errors and increased mortality[26].

In the systematic reviews articles that reported on the burnout syndrome prevalence in HCWs, a variety of burnout measurement tools were used. While the 22-item MBI can be considered the "gold standard" for measuring occupational burnout due to its alignment with the WHO's definition of burnout, all of the other tools are still validated instruments to assess the work-related well-being of respondents[32]. The issue that arises when multiple tools are used to assess a complex and multifaceted syndrome such as burnout is the heterogenicity of results[33]. In the review by Aymerich *et al* [12], burnout prevalence was 22.0% for studies using Mini-Z, but 53.0% for studies using CBI. This is likely due to the differences in focus and question content between the two instruments. Mini-Z measures emotional exhaustion, depersonalisation, and reduced personal accomplishment using 3 items for each dimension, for a total of 9 items. However, the CBI assesses personal burnout, work-related burnout, and client-related burnout using 5, 7, and 7 items for each type for a total of 19 items.

The high prevalence of burnout syndrome in HCWs has been highlighted in this umbrella systematic review, ranging from 31.81% to 34.4%, depending on the instruments used. During the COVID-19 pandemic, the prevalence of burnout was reported as high as 68.3% in the systematic review by Ching *et al*[13], whose focus was on HCWs in Asia. This information may be useful in Singapore's context as it demonstrates how the demographic may be more susceptible to mental health symptoms during periods of a pandemic.

Organisations may also consider putting more emphasis on the psychological well-being of HCWs. Policies were introduced to elevate HCWs' situations such as elderly care, addition of staff and makeshift hospitals. In China, specialized psychiatrists, social media and telephone services were added for support[34]. In France, some hospitals developed specific programmes with its purpose to distress and provide support amongst one another[35]. However, some obstacles faced are refusal and denial to psychological help[21]. Mental health problems are at its highest in the acute stages of the pandemic, suggesting interventions to be provided as soon as feasible. Thus, interventions should also target throughout the entire width of the pandemic and further[23].

Further research can also be conducted in the hospital setting to determine factors which may be diminishing the interventions' effectiveness when compared to the rest of the world. The results of these studies can then be used to aid modifications in either the nature or implementation of mental health interventions. Furthermore, it is essential to distinguish between anxiety, depression, and burnout, particularly for those working in the healthcare system, as anxiety can be a significant risk factor for burnout depending on the situation[36]. Additionally, many other fundamental resilience factors, such as self-compassion and sense of coherence, are believed to impact burnout in HCWs, particularly during pandemics[37].

The review by Salazar de Pablo *et al*[17] also provided insight into the prevalence of burnout and anxiety over multiple pandemics, namely the 2003 SARS pandemic and the ongoing COVID-19 pandemic, where the incidence of burnout decreased from 38.2% to 25% while incidence of anxiety decreased from 45.7% to 22.2%. This reduction in the incidence of burnout and anxiety may be due to the HCWs being better prepared for pandemics after having experienced SARS. Additionally, considering the two pandemics were more than 15 years apart, it is also likely that psychological interventions that were devised and implemented post-SARS were effective in the management of the HCWs' mental well-being, such that newer HCWs who did not experience the 2003 SARS pandemic did not bring up the overall prevalence.

In the present review, HCWs who were in the nursing profession were found to be at higher risk of developing burnout syndrome. Studies by Gualano *et al*[11], Ghahramani *et al*[15], and Ching *et al*[13] found that nurses were more likely to develop burnout during pandemics as compared to other healthcare professions such as advanced practice providers, respiratory therapists, physicians, and allied health professionals. This is likely due to the nature of the nurses' job scope, where they have to provide direct care and treatment to patients daily. During COVID-19, this frequent contact with patients puts the nurses at an increased risk of infection. Coupled with the longer than usual working hours due to a lack of manpower, this can result in the development of burnout[29]. Other than the increase in burnout prevalence, the risk of turnover intention among nurses also rose. However, this can be alleviated with better organisational support, thus emphasising its importance to avoid the vicious cycle of burnout and turnover[31]. With this information, more research can be conducted with nurses as the target population to fine-tune interventions to better suit their needs. Organisations may also look to explore areas of nurses' responsibilities during pandemics that can be delegated to volunteers or even robots with the help of artificial intelligence. Not only can this reduce the nurses' workload, but more time can also be spent on tasks that require specific nursing expertise, tackling the burnout dimension of reduced personal accomplishment.

Limitations of the present study

There are several limitations in this umbrella review. First, multiple mental health instruments being used in different studies. While this is unavoidable as certain tools may work better for different professions, future reviews can be done such that the population of interests have a common instrument used. Inclusion and exclusion criteria in the future study can also be altered to only include only studies which use specific instruments, in order to reduce heterogenicity. Second, for studies that reviewed multiple pandemics, it is unlikely that the population surveyed were similar in demographic, which results in a suboptimal comparison of prevalence. For better quality comparisons, longitudinal studies can be conducted in the future. At last, the incidence of mental health outcomes may not be solely attributed to pandemics, likewise, reviews should include longitudinal studies to allow the analysis of the prevalence of mental health symptoms pre- and post-pandemic[38].

CONCLUSION

In conclusion, this umbrella review has collected relevant data from high-quality systematic reviews on the prevalence of burnout syndrome and anxiety during the past pandemics, including COVID-19 pandemic, demonstrating its high prevalence among HCWs. Nursing profession and females HCWs were identified to be more likely to develop these symptoms. Thus, more emphasis and attention should be put on their psychological well-being.

ARTICLE HIGHLIGHTS

Research background

Burnout and anxiety are common among Healthcare workers (HCWs) during pandemics.

Research motivation

Relevant data on anxiety and burnout during pandemic is limited.

Research objectives

The objectives of this umbrella review are (1) to provide a more comprehensive summary of pertinent evidence on anxiety and burnout; and (2) to investigate potential risk factors and solutions for HCWs.

Research methods

Using the PRISMA 2020 checklist, this umbrella review was carried out in accordance with the criteria of PRISMA.

Research results

Female HCWs and nurses were shown to be more prone to experiencing these symptoms. As a result, their psychological well-being should receive more importance and care.

Research conclusions

This umbrella review gathered relevant data from high-quality systematic reviews on the prevalence of burnout syndrome and anxiety during previous pandemics, including the Coronavirus disease 2019 pandemic, demonstrating its high prevalence among HCWs.

Research perspectives

The occurrence of mental health outcomes should not be attributed only to pandemics; similarly, evaluations should include longitudinal research to allow for the investigation of the prevalence of mental health symptoms before and after the pandemic.

FOOTNOTES

Co-first authors: Clayton Yang Teng Bey and Jin-Uu Koh.

Author contributions: Lai CWK, Bey CYT and Koh JU conceived, designed and refined the study protocol; Bey CYT and Koh JU were involved in the data collection; Lai CWK, Bey CYT and Koh JU analysed the data; Lai CWK, Bey CYT and Koh JU drafted the manuscript; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Bey CYT and Koh JU contributed equally to this work as co-first authors. The reason for designating Bey CYT and Koh JU as co-first authors is because Bey CYT and Koh JU contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Bey CYT and Koh JU as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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