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OPINION REVIEW

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

Serafino Fazio, Flora Affuso

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Abstract

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

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

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

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INTRODUCTION

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

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

AT-HOME EARLY TREATMENT WITH NSAIDS

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

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

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

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

NSAID: Non-steroidal anti-inflammatory drug.

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

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

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

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

CONCLUSION

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

FOOTNOTES

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

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REVIEW

Liver dysfunction-related COVID-19: A narrative review

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

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Abstract

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

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

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

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INTRODUCTION

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

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

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

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

EPIDEMIOLOGY

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

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

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

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

CHARACTERISTICS OF SARS-COV-2

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

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

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

PATHOPHYSIOLOGY

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

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

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

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

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

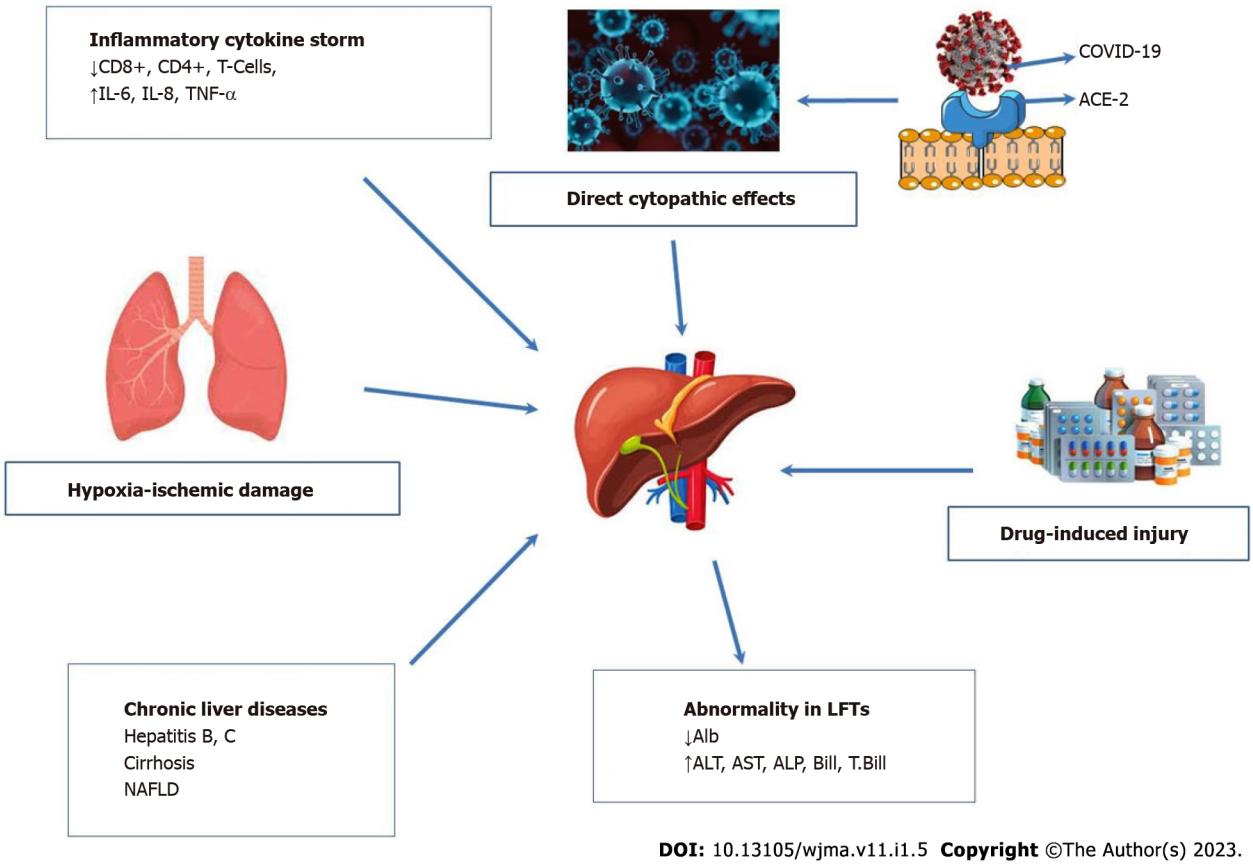

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Figure 1 The proposed mechanisms of liver injury with coronavirus disease 2019. ACE-2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine transaminase; AST: Aspartate transaminase;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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EFFECTS OF COVID-19 THERAPEUTIC AGENTS ON THE LIVER

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

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

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

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

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

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

COVID-19 VACCINES AND THE LIVER

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

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

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

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

PROGNOSIS

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

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

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

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

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

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

CONCLUSION

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

FOOTNOTES

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MINIREVIEWS

Cancer risk stratification system and classification of gastritis: Perspectives

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Abstract

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

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

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

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INTRODUCTION

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

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

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

NON-INVASIVE SEROLOGICAL SCREENING FOR MULTIFOCAL ATROPHIC GASTRITIS

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

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

USE OF COMPUTER DATA PROCESSING TO RISK STRATIFICATION OF GASTRIC CANCER

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

PERSPECTIVE FOR SEROLOGICAL SCREENING FOR ATROPHIC GASTRITIS

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

PATHOLOGICAL ASPECTS OF USE OF CLASSIFICATIONS OF GASTRITIS

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

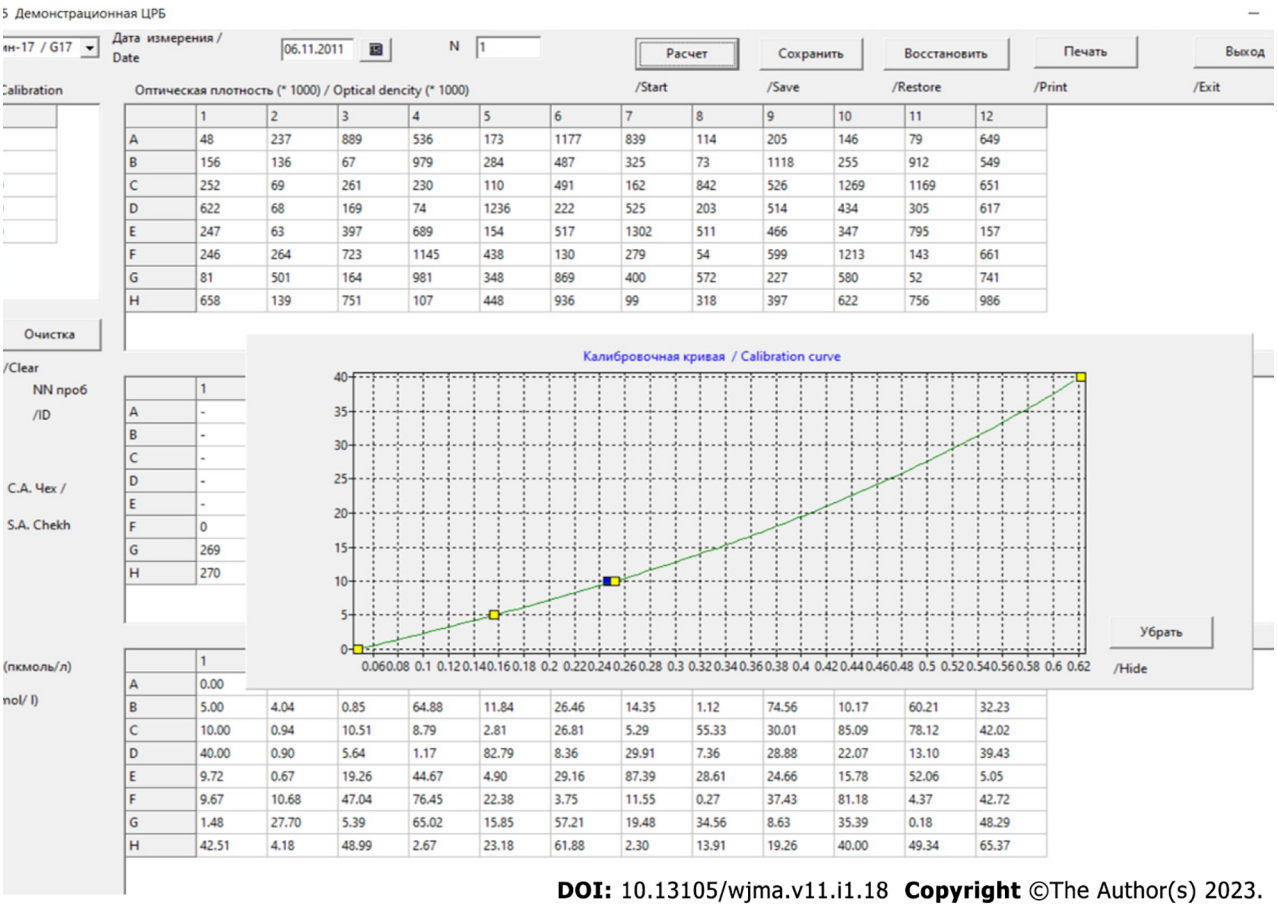

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Figure 1 Calculation of laboratory parameters by optical density.

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

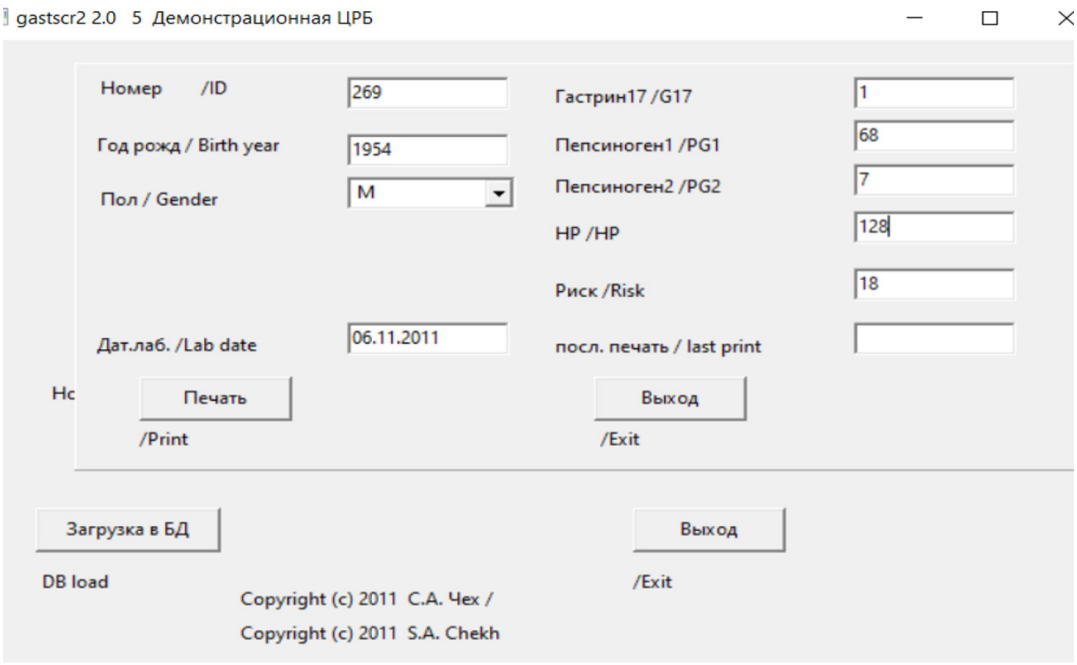

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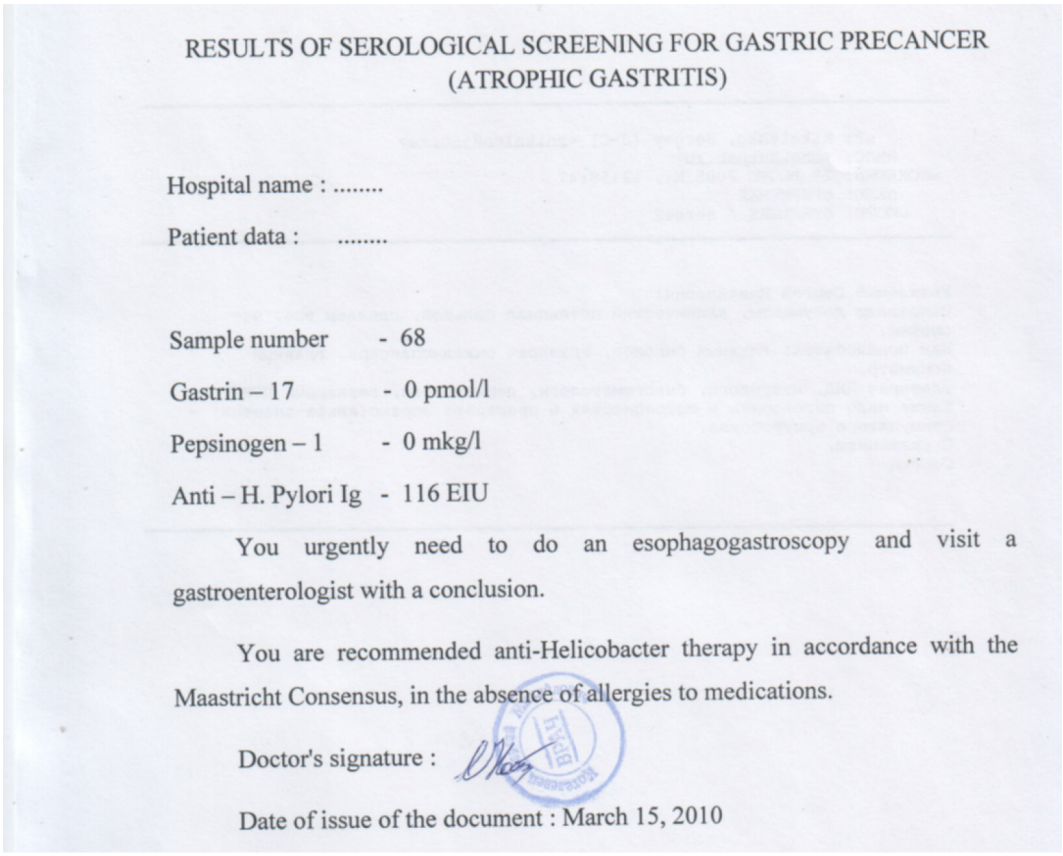
Figure 2 Linking serological screening results to a specific patient.

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



RESULTS OF SEROLOGICAL SCREENING FOR GASTRIC PRECANCER (ATROPHIC GASTRITIS)

Hospital name : .....

Patient data : .....

Sample number - 68

Gastrin – 17 - 0 pmol/l

Pepsinogen – 1 - 0 mkg/l

Anti – H. Pylori Ig - 116 EIU

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

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

Doctor's signature :

Date of issue of the document : March 15, 2010

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Figure 3 The conclusion of the patient after serological screening.

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

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

CONCLUSION

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

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

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

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

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

FOOTNOTES

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

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SYSTEMATIC REVIEWS

Post-COVID-19 cholangiopathy: A systematic review

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

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Abstract

BACKGROUND

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

AIM

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

METHODS

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

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

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

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

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

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

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INTRODUCTION

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

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

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

Mechanisms of cholangiocytic damage

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

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

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

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

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

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

MATERIALS AND METHODS

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

Statistical analysis

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

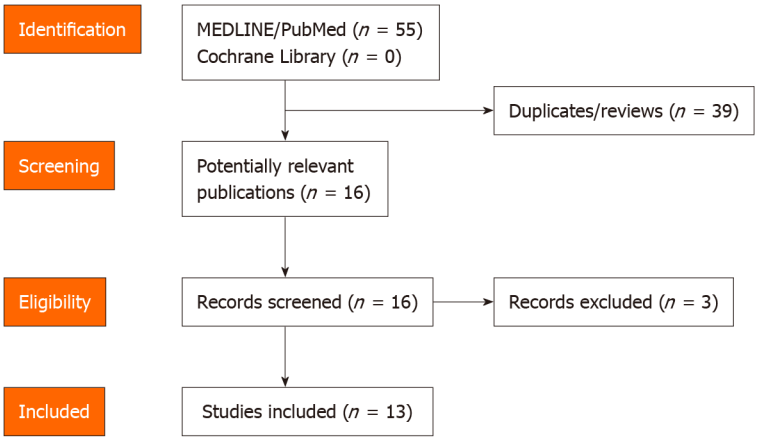

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Figure 1 Summary of study identification and selection.

RESULTS

Available studies

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

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

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FOOTNOTES

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META-ANALYSIS

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

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Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

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

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

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

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INTRODUCTION

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

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

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

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

MATERIALS AND METHODS

Data search and screening

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

Study selection

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

Data extraction

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

Quality assessment

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

Statistical analysis

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

RESULTS

Study selection and exclusion

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

Table 1 Characteristics of the included studies

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

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

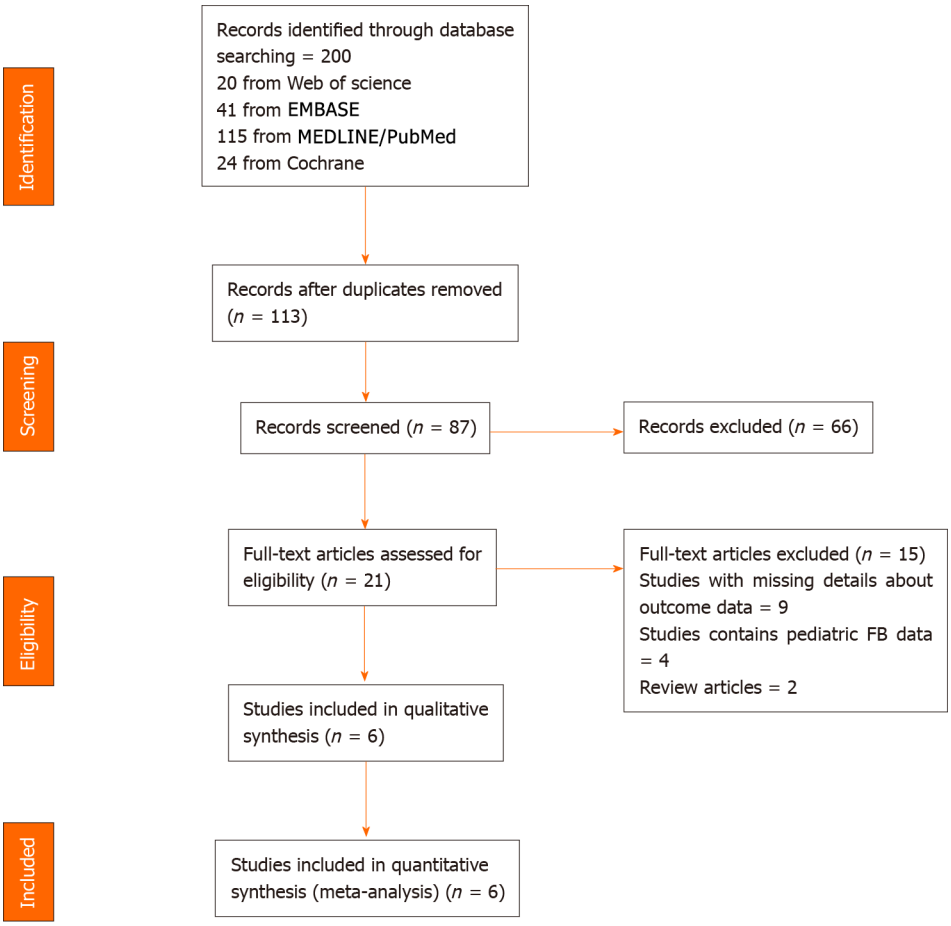

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Figure 1 Flowchart showing details on the article search and selection. FB: Foreign body.

Outcomes

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

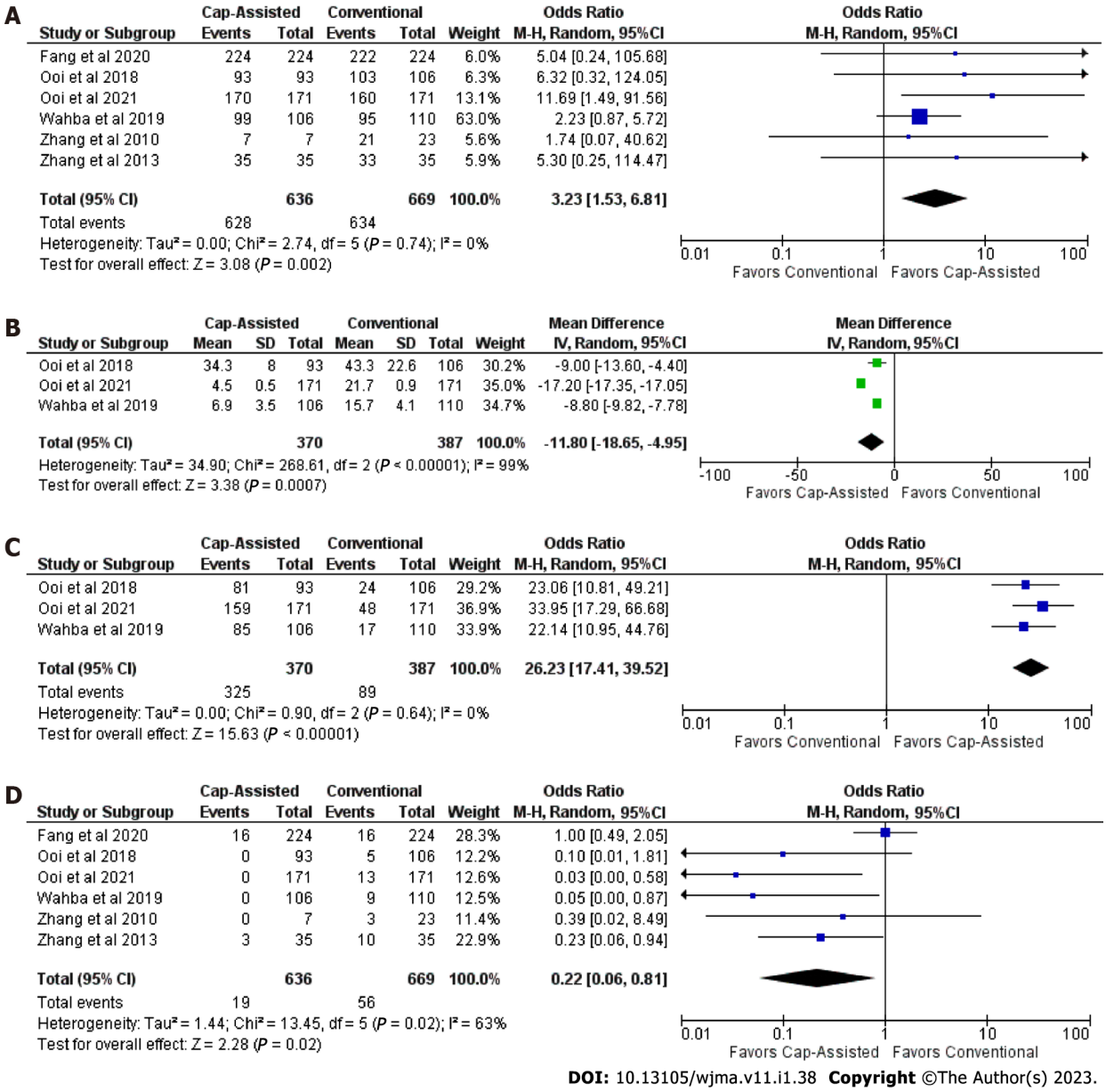

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Figure 2 Forest plot. A: Forest plot showing the technical success of cap-assisted endoscopy *vs* conventional endoscopy for esophageal foreign body removal; B: Forest plot showing the foreign body retrieval time of cap-assisted endoscopy *vs* conventional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

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

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

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

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

Publication bias

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

Quality assessment

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

DISCUSSION

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

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

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

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

CONCLUSION

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

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

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

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

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

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

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

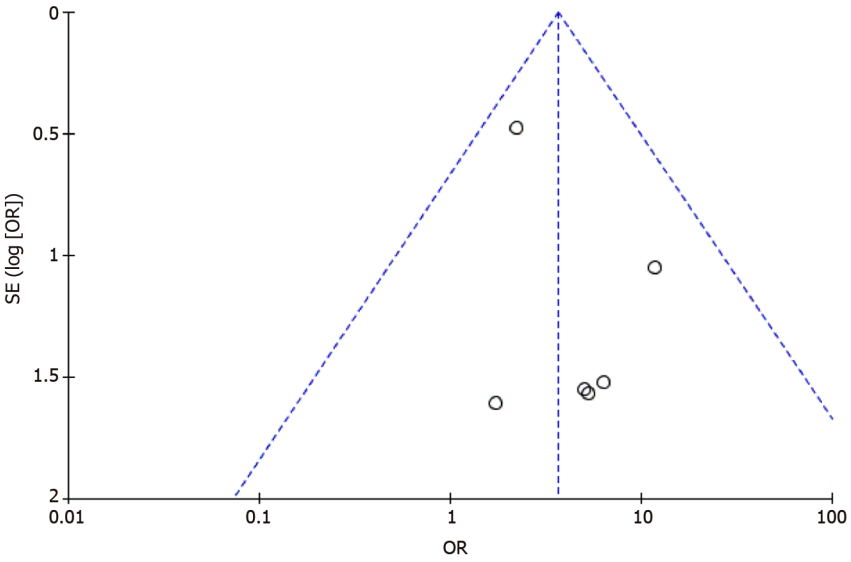

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Figure 3 Funnel plot showing no publication bias.

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

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

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Treatment of recurrent hepatocellular carcinoma following liver resection, ablation or liver transplantation

Shalom Z Frager, Weston Cooper, Yvonne Saenger, Jonathan M Schwartz

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and causes one third of cancer related deaths world-wide. Approximately one third of patients with HCC are eligible for curative treatments that include hepatic resection, liver transplantation or imaging guided tumor ablation. Recurrence rates after primary therapy depends on tumor biology and pre-treatment tumor burden with early recurrence rates ranging from 30%-80% following surgical resection and ablation. HCC recurs in over ten percent following liver transplantation for HCC. Treatment modalities for tumor recurrence following resection and ablation include repeat liver resection, salvage liver transplantation, locoregional therapies, and systemic chemotherapy/immunotherapy. Locoregional and immune mediated therapies are limited for patients with tumor recurrence following liver transplantation given potential immune related allograft rejection. Given the high HCC recurrence rates after primary tumor treatment, it is imperative for the clinician to review the appropriate treatment strategy for this disease entity. This article will review the current literature regarding HCC recurrence after primary curative therapies and will discuss the relevant future trends in the HCC field.

Key Words: Hepatocellular carcinoma; HCC recurrence; Hepatic resection; Locoregional therapy; Immunotherapy

Core Tip: Tumor recurrence is frequent following potentially curative modalities for hepatocellular carcinoma. Patients should undergo surveillance imaging following curative treatments and once diagnosed, are potentially eligible for repeat hepatic resection, ablation, trans-arterial embolic therapies, or systemic therapies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) incidence has been increasing over the last three decades[1] but fortunately may have potentially begun to plateau in the United States[2]. HCC is the most common form of primary liver cancer[3] and the sixth most common cancer overall and has a high case fatality rate[4]. Based on the Scientific Registry of Transplant Recipients (SRTR) 2020 data[5], HCC composes 10.9% of new liver transplant waiting list registrations, a rate that has doubled over the past decade.

The treatment algorithm and prognostic staging for primary HCC after initial diagnosis has been clearly defined by the Barcelona Clinic Liver Cancer (BCLC) staging system[6]. The BCLC system characterizes patients according to tumor size, tumor number, severity of liver disease using the Child Turcotte Pugh classification, and the Eastern Cooperative Oncology Group performance status[7]. Imaging guided tumor ablation, liver resection, or orthotopic liver transplantation (OLT) are considered curative options for very early and early-stage HCC with a post treatment median overall survival between 6-10 years[8]. The Milan Criteria has been used for over twenty-five years to risk stratify HCC patient eligibility for OLT in the setting of HCC. The Milan criteria is defined as a single lesion greater than or equal to 2 cm and less than or equal to 5 cm, or 2 to 3 Lesions, each greater than or equal to 1 cm and less than or equal to 3 cm in the absence of extrahepatic metastases or main portal vein invasion[9]. Patients with intermediate stage HCC are treated with trans-arterial modalities including chemoembolization and Yttrium-90 (^{90}Y) radio-embolization.

Efforts to expand criteria for primary resection and liver transplantation have evolved. For example, Yin *et al*[10] in 2014, data has shown that resection of HCC outside Milan criteria might lead to better outcomes compared to trans-arterial chemoembolization (TACE) in the appropriate clinical setting. In addition, successful reduction of tumor burden to within the Milan criteria has resulted in successful transplant outcomes[11].

Over the last decade, the systemic therapeutic options for HCC have advanced dramatically[3]. The improvement of imaging modalities and vascular techniques have also allowed for earlier diagnosis and more selective locoregional therapies for both ablation and chemo-embolic options.

Nevertheless, HCC recurs 50%-70% of patients after primary hepatic resection and in 8%-17% of patients after liver transplantation[12-15] with early recurrence (< 24 mo) portending worsening survival[16]. There is long-term data showing a 34.3% chance of recurrence after 10 year survival with 10% of the overall cohort surviving with locoregional therapy alone[17]. Given the high overall rate of HCC recurrence, this article will review the available options for patients specifically regarding HCC recurrence following curative modalities such as hepatectomy/resection, tumor ablation, and liver transplantation.

HCC RECURRENCE AFTER RESECTION

Hepatic resection is considered the primary treatment modality for patients with BCLC stage 0-A HCC without evidence of portal hypertension or hepatic decompensation (ascites, varices, hepatic encephalopathy). The Model for End Stage Liver Disease score (MELD) and CPT score[18,19] have been used for risk stratification. Data by Bismuth *et al*[20] showed 5%-15% of patients presenting with HCC will be eligible for hepatic resection. Post resection HCC recurrence rates are 19%, 54%, and 70% for 1, 3, and 5 years, respectively. As with pre-treatment HCC diagnosis, tumor recurrence is defined radiographically using the Liver Reporting and Data System (LI-RADS)[21] or modified Response Evaluation Criteria in Solid Tumors (mRECIST)[22]. When imaging is indeterminate, a liver biopsy can be performed for tissue sampling, however tumor biopsy is typically not performed to establish a diagnosis of HCC recurrence.

Repeat hepatectomy

In patients with early-stage HCC and compensated liver disease, all Eastern and Western societies[15,23,24] recommend hepatectomy as the first-line therapy with 5-year survival rates ranging from 60%-80%. However, recurrence can occur in up to 80% of patients despite resection[23]. Tumor recurrence can be characterized as early and late based on the time to recurrence from initial resection with a cut-off of 2 years[25]. Intrahepatic metastasis is associated with early recurrence of HCC. Late recurrence of HCC is often not related to the primary tumor and likely reflects the underlying malignant predisposition of the background liver parenchyma. There is no specific treatment guidance for repeat hepatectomy for HCC recurrence and practices are based on local expertise and expert opinion. In general, patients with a single localized recurrent tumor without portal hypertension and normal liver synthetic function are good candidates for repeat hepatectomy.

There is heterogeneity in the surgical trials advocating for repeat hepatectomy stemming from diverse inclusion criteria. The data has been collected in the Eastern Hemisphere with only one large Western study presented by Roayaie *et al*[26] (2011). The 5-year survival rate was 67% in this study. In this cohort, a higher five-year overall survival (OS) (66.8% *vs* 55.5% respectively, $P = 0.006$) was seen in patients undergoing anatomic resection (AR) *vs* non-anatomic resection (NAR). However, there was no significant difference in peri-operative morbidity or mortality rates between anatomic *vs* AR or NAR. A large Eastern series by Zou *et al*[27] showed a 1, 3, and 5-year overall all survival rates of 96.9, 74.8, and 47.8%, respectively. Post-operative complication rates range from 0-6% (ascites, bile leak, liver failure)[28].

There is scant data comparing repeat laparoscopic resection *vs* open hepatectomy. In a study by Cai *et al*[29], 2019, there was a similar 90-d mortality between these groups although other metrics (blood loss, hospital length of stay) were better in the laparoscopic cohort. The selection of surgical techniques is based on both patient and tumor characteristics and is an evolving area of interest in surgical literature.

Locoregional therapy

Locoregional therapies are available for patients with unresectable recurrent HCC or for a patient with worsening portal hypertension/Liver function following primary hepatic resection. Radiofrequency or microwave ablation has been utilized for recurrent tumors < 3 cm in diameter although caution must be used to avoid collateral structural damage. A meta-analysis of 18 prior studies showed ablation for recurrent HCC has a post-ablation recurrence rate of 79% with a complication rate of near 2.9% although this may be an inaccurate value given much of the data was not reported[30]. There are very few good studies comparing the outcomes for post recurrence ablation *vs* hepatic resection alone[31].

Trans-arterial chemoembolization (TACE) is a non-curative modality that can be used for tumor control for patients who are not candidate for repeat hepatic resection. Three-year survival post-TACE is 29% for primary HCC[32]. In a review from Erridge *et al*[33], the 5-year survival was 15.5% in patients who underwent TACE for recurrent HCC. Other studies have shown that the outcome could be worse, and that palliation is the end goal for this therapy modality[34].

Salvage liver transplantation

In the United States, patients who are eligible for liver transplantation following HCC recurrence benefit from early evaluation and placement on the transplant waiting list without a 6-mo waiting period[15]. Studies by Hu *et al*[35], 2012, and Kostakis *et al*[36], 2019, and have evaluated salvage liver transplantation after hepatic resection within mixed populations which has been difficult to generalize. There is also the consideration of post OLT immunosuppression agents which are known to increase malignancy risk. In practice, patients with indications for liver transplantation should be listed for liver transplantation as this approach will allow for removal of micro hepatic metastasis and will eliminate the sequalae of portal hypertension and chronic liver disease.

Adjuvant systemic immunotherapy

A burgeoning area of interest and study is adjuvant immunotherapy post following hepatic resection [37]. The NIVOLVE trial tested adjuvant nivolumab with median recurrence free survival of 26.3 mo [38]. This compares quite favorably with the median recurrence free survival of 8.5 mo observed with sorafenib in the STORM trial[39]. Based on data in the metastatic setting, the addition of a vascular endothelial growth factor/vascular endothelial growth factor receptor inhibitor (such as bevacizumab) to an immune checkpoint inhibitor backbone could further improve outcomes. Multiple trials of adjuvant immunotherapy are ongoing including IMBRAVE 050 (atezolizumab+ bevacizumab), KEYNOTE 937 (pembrolizumab), and Checkmate 9DX (nivolumab) for which results are anticipated.

Systemic immunotherapy for metastatic hepatocellular cancer

When recurrence is not amenable to surgical resection or local regional therapy, systemic therapy is often the only option. The current standard of care is to use the combination of the immune checkpoint inhibitor atezolizumab with bevacizumab, a regimen that showed significant survival benefit relative to sorafenib, the prior standard therapy[40]. For patients with prior episodes of bleeding or mucosal inflammation precluding use of bevacizumab, single agent anti-PD1 therapy may offer benefit. The

combination of ipilimumab (anti-CTLA-4) and nivolumab is now FDA approved based on trial data showed a 30% response rate in all treatment arms[41]. Multiple novel immunotherapy combinations are being studied including combinations with anti-Lag3 antibodies, a therapeutic that has yielded survival benefit in melanoma[42].

HCC RECURRENCE AFTER ABLATION

Based on the BCLC staging system, HCC ablation is offered for patients who are not candidates for surgical resection or are ineligible for liver transplantation based on medical or psychosocial barriers. HCC recurrence after RFA occurs can occur in up to 15% of patients undergoing this treatment modality [43]. While not fully understood, the reason is thought to be due to micro-tumor spread *via* arterial-portal shunts related to thermal and mechanical damage caused during the RFA procedure. Patients with recurrence can be treated by repeating RFA alone or combining RFA and TACE or initiation of systemic therapy based on the extent of tumor recurrence.

Locoregional therapy combined with immunotherapy

There is strong rationale for combining local therapy with immunotherapy in the setting of recurrent HCC, both because the probability of long-term cure with repeat local treatment is lower than with initial therapy, and because local treatment can release tumor antigens and favorably alter the tumor immune micro-environment. Multiple studies are ongoing examining these combinations including trials combining ablation, RFA, brachytherapy and/or TACE with pembrolizumab, tislezumab, atezoliczumab and bevacizumab, and others[44]. One recent retrospective study examined 31 patients who underwent concurrent TACE and nivolumab and found that they achieved a significantly longer median survival (8.8 mo) than patients treated with TACE alone (3.7 mo) with some patients achieving prolonged survival greater than 20 mo[45].

HCC RECURRENCE AFTER LIVER TRANSPLANTION

Liver transplantation for HCC

Liver transplantation can be curative among select patients with hepatocellular carcinoma who are ineligible for hepatic resection. Initial studies by Mazzaferro *et al*[9] showed excellent long term recurrent free survival. These criteria are known as the Milan criteria.

HCC recurs at a rate of 10%-15% following liver transplantation among patients who meet the Milan criteria prior to liver transplantation with higher recurrence rates in patients who exceed the Milan criteria[12]. HCC typically recurs in the lungs, bones, and in the liver. Other sites of recurrence include the adrenal glands and the central nervous system.

Data regarding pre transplant risk factors for HCC recurrence including pre-transplant Alpha fetoprotein (AFP) and a short duration between listing for transplantation and the transplant surgery has influenced the United States transplant regulatory agency, United Network of Organ Sharing to incorporate AFP criteria and as well as a six-month waiting period prior to transplant eligibility.

There are several prognostic systems that help to predict HCC recurrence following liver transplantation (LT). Markers of tumor biology such as pre transplant AFP, explant tumor differentiation and the presence of microvascular tumor invasion are incorporated into most of these models. One such model, metroticket 2.0 includes AFP and tumor morphology can be used to predict post-transplant outcomes[46]. Another readily applied model is the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) predictive model that included AFP, tumor size and microvascular invasion[47].

HCC typically recurs in the first 3 years following LT and the tumor biology of recurrent HCC is influence by the immunosuppressed state[48]. It is unresolved whether reduced calcineurin inhibitor and addition or substitution of calcineurin inhibitors with m-TOR inhibitors leads to reduced HCC recurrence[49].

Patients typically undergo surveillance imaging for up to five years following LT with contrast enhanced computed tomography (CT) or magnetic resonance imaging every six to 12 months as well as non-contrast chest CT and AFP testing to identify HCC recurrence as early as possible. Evidence to support this practice is lacking, and it may be appropriate to target patients at highest risk with more frequent surveillance.

There is also no data to support chemoprevention with systemic chemotherapy in this context. In addition, it is unclear whether pre transplant immunotherapy reduces rates of HCC recurrence.

Treatment of HCC recurrence following liver transplantation

Patients with HCC recurrence have significantly lower survival than patients who do not recur. Most recurrences occur in extrahepatic locations, and patients who are eligible for surgical intervention are

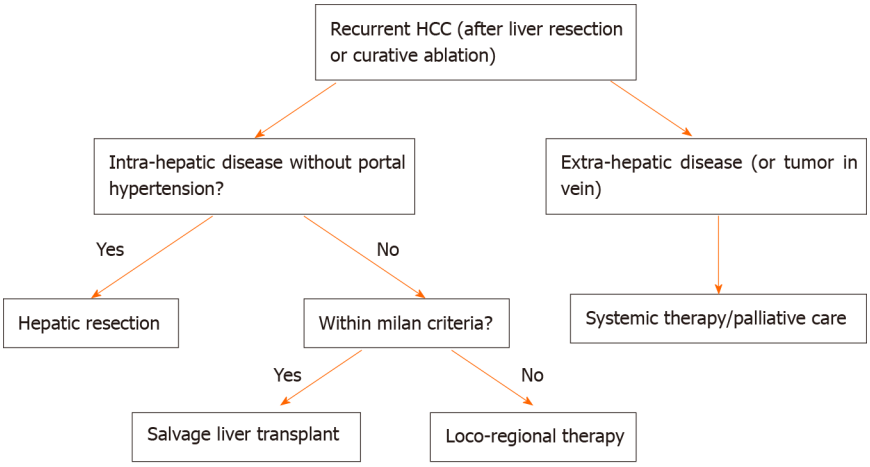

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Figure 1 Proposed algorithm for treatment options after hepatocellular carcinoma recurrence (after initial therapy). HCC: Hepatocellular carcinoma.

more likely to have improved outcomes[50].

Patients with widely metastatic recurrent HCC following LT are eligible for systemic therapy as described above including the use of sorafenib, regorafenib, lenvantinib and cabozantinib. These agents are often difficult to tolerate given significant drug interactions with immunosuppressive agents.

Immunotherapy following LT

Treatment with immunotherapeutic agents that target programmed cell death protein 1 (PD1)/programmed cell death ligand 1 (PD-L1) mechanistically enhance immune response against malignant cells. These agents can activate the immune cascade with resultant graft loss due to rejection.

While there are multiple reports of safe use of immunotherapy prior to transplant, use of immunotherapy after transplant is much riskier. A literature review identified 28 patients who had immunotherapy after transplantation[51]. Early mortality occurred in 6 patients and 9 patients experienced allograft rejection that was frequently severe. Rejection was more likely to occur earlier after transplantation. Median overall survival was 7.3 mo. If used at all, these agents should be used with extreme caution, perhaps with higher levels of immunosuppression or in the context of a clinical trial at a specialized high volume transplant center.

CONCLUSION

HCC recurrence is common after initial therapy and early *vs* late recurrence may impact overall survival. The increase is treatment options for primary HCC over the last decade has allowed the field to evolve and extrapolate these modalities for use in HCC recurrence. In general, the overall therapeutic approach to HCC recurrence is similar to primary HCC despite specific anatomical and immune related constraints which may occur after liver transplantation or hepatic resection. Advancement in systemic chemo/immune therapies both in the adjuvant and neoadjuvant phase has allowed for additional survival in cases of unresectable HCC recurrence. New frontiers in locoregional therapies have also allowed for better HCC tumor recurrence control. The authors recommend using the treatment algorithm based on Figure 1. These treatment approach incorporates all of the aforementioned treatment modalities and gives the clinician a data driven and simplified approach to HCC recurrence.

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REVIEW

Infertility, pregnancy and breastfeeding in kidney transplantation recipients: Key issues

Mohamad Habli, Dawlat Belal, Ajay Sharma, Ahmed Halawa

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Abstract

Chronic kidney disease (CKD), especially in advanced stages, is an important cause of infertility. In CKD patients, infertility has been linked to multiple factors. The pathophysiology of infertility related to CKD is complex and forked. Correction of modifiable factors can improve fertility in both genders. In males as well as females, successful kidney transplantation offers good chances of restoration of reproductive function. In female renal allograft recipients, recovery of reproductive functions in the post-transplant period will manifest as restoration of normal menses and ovulation. Owing to this improvement, there is a significant risk of unplanned pregnancy, hence the need to discuss methods of contraception before transplantation. In kidney transplant recipients, different contraceptive options for pregnancy planning, have been used. The selection of one contraception over another is based on preference and tolerability. Pregnancy, in renal transplanted females, is associated with physiologic changes that occur in pregnant women with native kidneys. Immunosuppressive medications during pregnancy, in a recipient with a single functioning kidney, expose the mother and fetus to unwanted complications. Some immunosuppressive drugs are contraindicated during pregnancy. Immunosuppressive medications should be discussed with renal transplant recipients who are planning to breastfeed their babies. In addition to antirejection drugs, other medications should be managed accordingly, whenever pregnancy is planned.

Key Words: Infertility; Chronic kidney disease; Pregnancy; Kidney transplantation;

Immunosuppression; Breastfeeding

Core Tip: Chronic kidney disease (CKD) is a major cause of infertility in both sexes. Multiple factors amplify infertility in CKD patients. Kidney transplantation can restore fertility in men and women. Menses will return in the majority of females after kidney transplantation. This improvement increases the risk of accidental pregnancy, so contraception should be discussed in advance. Kidney transplant recipients utilize several contraceptives to plan pregnancy. Preference and tolerability determine contraception choice. If pregnancy occurs, transplanted women experience the same physiologic changes as pregnant women with native kidneys. During pregnancy, immunosuppressive drugs can cause consequences. Breastfeeding kidney transplant recipients should discuss immunosuppressive and other medicines.

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INTRODUCTION

Chronic kidney disease, especially in advanced stages causes fertility and sexual dysfunction in males as well as in females[1] (Figure 1). The male sexual health malfunction manifests as erectile dysfunction in up to 80% of end-stage renal disease (ESRD) patients on hemodialysis[2]. The pathophysiology is due to a combination of vascular calcification, accelerated atherosclerosis, uremic neuropathy, impairment of the hypothalamic-pituitary-testicular axis and secondary hyperparathyroidism[3]. ESRD is also with alteration in the levels of sex hormones which include reduction in testosterone level and elevation in luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[4]. The prevalence of infertility in females, of childbearing age, with ESRD, has been reported as high as 92%[5].

Factors that are implicated in the pathogenesis of infertility in women with ESRD include impairment at the level of the hypothalamus-pituitary-ovarian axis manifesting as high FSH and LH and low estrogen levels[6], menstrual disorders in up to 75% of patients manifesting as amenorrhea, oligomenorrhea or functional menopause[7], and abnormal endometrial atrophy due to reduced estrogen level [8]. Other contributions to infertility include reduced libido and orgasmic impairment, in addition to vaginal dryness or failure of vaginal lubrication[9], as shown in Figure 2[10].

Improvement of fertility in patients with kidney disease is achieved by correction of modifiable factors like anemia, hyperparathyroidism, dialysis adequacy[11], avoidance of toxic medications[12], and hormonal replacement therapies[13], However, kidney transplantation remains the best option for the management of infertility due to ESRD for both genders[14].

Following successful kidney transplantation, the function of the hypothalamic-pituitary-gonadal axis is gradually restored leading to normalization of sex hormone levels in men and women in the majority but not in all patients[15,16]. In males, this recovery manifests as improvement in erectile dysfunction, libido, and spermatogenesis, whereas in women as restoration of menses and ovulation[16].

Owing to the improvement in reproductive functions and sexual health within 3-6 mo, these patients should be counselled about the significant potential of conceiving shortly after successful kidney transplantation. Hence it is imperative to explain contraception during the pre-transplantation assessment so that pregnancy can be planned at a time when the risk to mother and fetus is minimal *i.e.*, after one year of uneventful kidney transplantation.

IMPACT OF PREGNANCY ON GRAFT SURVIVAL

Intra-renal hemodynamics is reported to be altered, starting from the 1st week of pregnancy, due to a reduction in vascular resistance[17], increase in cardiac output[18], and increase in plasma volume[19], which finally lead to an increase in renal blood flow[20] and subsequently increase in GFR. In normal pregnancy with native kidneys, GFR increases along with an increase in renal size[19,21]. Despite volume expansion and increase in cardiac output, mean arterial blood pressure is reduced by about 10-15 mmHg in the 1st trimester and then returned to normal by the 2nd trimester[22].

It is well established that acute kidney injury can occur during pregnancy in non-transplant females due to pregnancy itself. Pregnancy-related acute kidney injury can also happen in the transplanted

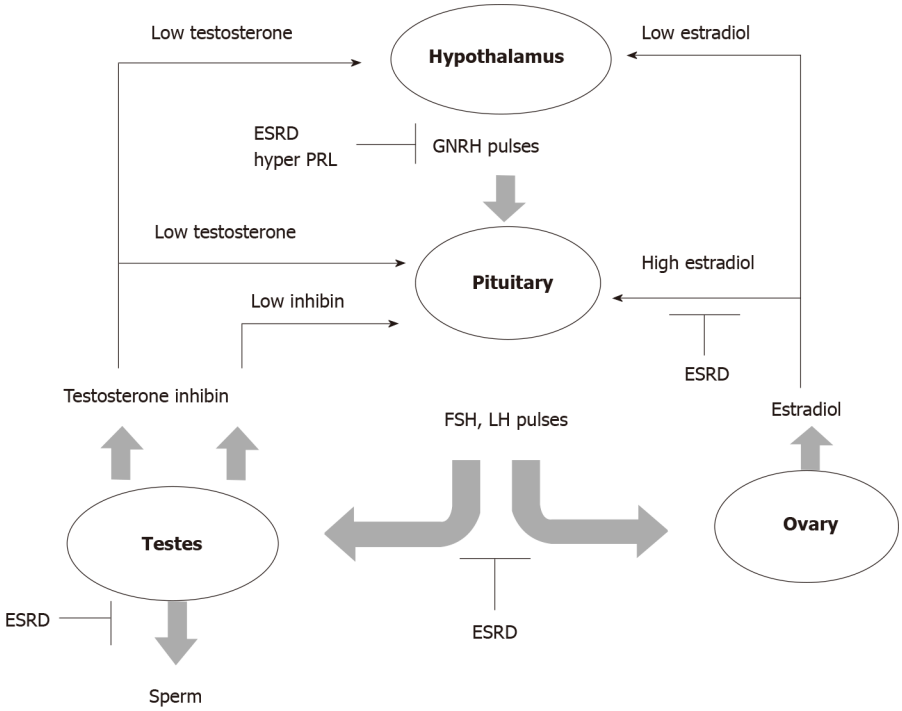

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Figure 1 The hypothalamic-pituitary-gonadotropin axis in men and women with end-stage renal disease. ESRD: End-stage renal disease; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

allograft, however, when it occurs it affects not only the pregnant patient but also the fetus. Refer to Figure 3[23].

Several studies evaluated the impact of pregnancy on graft survival. Levidiotis *et al*[24], using ANZDT Registry data of pregnancy in transplant recipients, demonstrated that the delivery of first live birth was comparable between the study group and control group, and was not associated with worse twenty-year graft survival.

Rahamimov *et al*[25] evaluated the long-term impact of pregnancy on allograft and patient survival and reported that graft and recipient survival did not differ from the control group in the follow-up.

Shah *et al*[26] conducted a systemic review and meta-analysis about pregnancy outcomes in kidney transplant recipients. They reported that the rejection rate during pregnancy was 9.4% which is comparable to the United States mean of 9.1%.

To evaluate possible bias in patients' selection that may affect outcomes and interpretation of results, M. Pappias and colleagues evaluated pregnancy outcomes after living kidney donation in a systematic review. In this study, 2 authors used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) method to evaluate participant selection, exposure, and results. Robvis online software plotted risk-of-bias evaluations. Grading of recommendations, assessment, development, and evaluations method graded study certainty. As a result, authors concluded that after donation, the absolute chance of pregnancy related and associated complications remain minimal, which is comparable to other studies[27].

In conclusion, pregnancy is not associated with worse graft outcomes in kidney transplanted recipients, however, female recipients should be carefully selected before pregnancy planning and should be counseled about possible complications. Stability of kidney function at time of pregnancy detection, should be monitored attentively throughout the course of pregnancy.

IMPACT OF TRANSPLANTATION ON THE OUTCOME OF PREGNANCY

Although the majority of female recipients restore their ability to conceive, pregnancy rates are much lower when compared to the general population[24,28,29]. Gill *et al*[28] demonstrated that the rate of pregnancy in transplanted females was less than 1/3 of the general population in the first 3 years following transplantation surgery.

Shah *et al*[26], based on a meta-analysis of the outcomes of pregnancy in transplanted patients, reported an increased risk of gestational diabetes and gestational hypertension. Preeclampsia was reported to be sixfold higher in transplant women. Shah *et al*[26] reported higher rates of preterm delivery, stillbirths, and neonatal death. Other pregnancy-associated complications such as induced

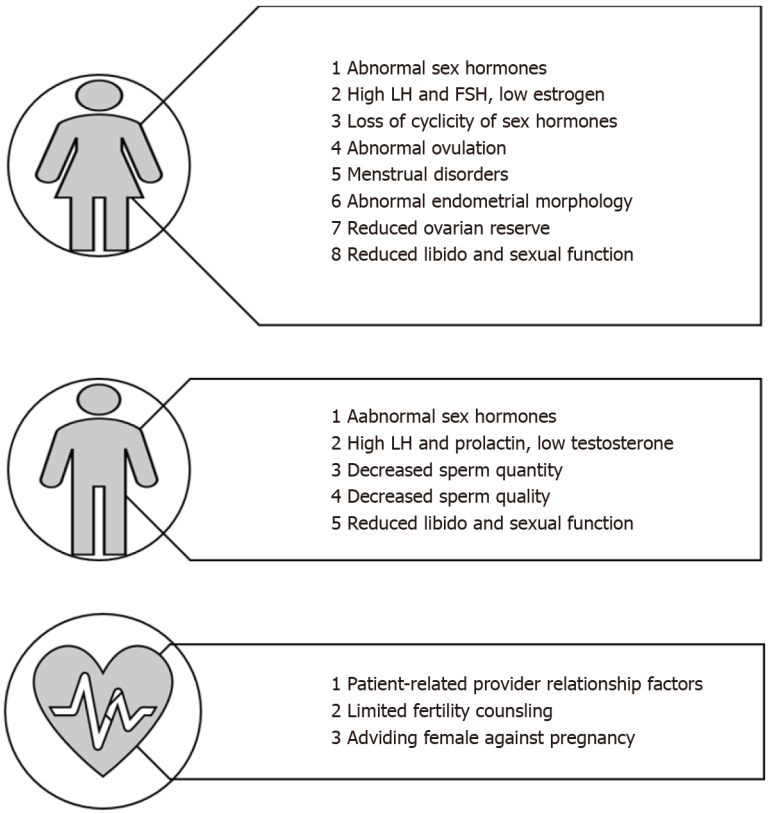

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Figure 2 Male and Female factors implicated in the development of infertility in chronic kidney disease patients. FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

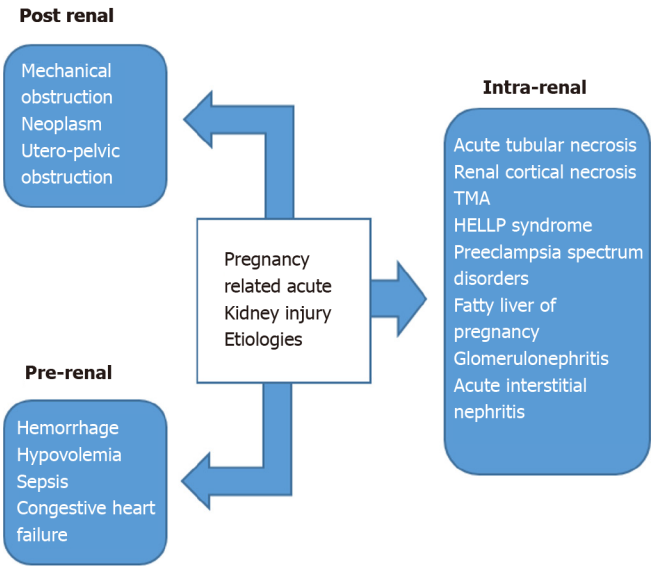

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Figure 3 Pregnancy related acute kidney injury etiologies. TMA: Thrombotic microangiopathy; HELLP: Hemolysis, elevated liver enzymes and low platelet.

abortions, miscarriages and ectopic pregnancies were reported to be more common in kidney transplant recipients.

Deshpande *et al*[29] reported a live birth rate among pregnant renal transplant recipients comparable to that of the general population. Other retrospective studies have reported live birth rates of up to 79% [30,31]. Preterm delivery was reported to occur in 46% of recipients[30].

Cesarean delivery was significantly more frequent in the transplant population reaching 43%-72%, although no clear evidence to support this practice[29-31]. The United Kingdom Transplant Pregnancy Registry, showed a higher rate of low birth weight in 20% to 50% of cases[30,31].

MANAGEMENT OF IMMUNOSUPPRESSION

T-lymphocyte-depleting agents and IL-2 inhibitors (basilixumab) are commonly used as induction therapy for transplant patients. Maintenance therapy is commenced in the hospital and continued to prevent acute rejection. Before conception, modification of immunosuppression is frequently needed, as some drugs have shown to be associated with adverse outcomes in the pregnancy and fetus[32].

In addition to female recipient preparation for pregnancy, male recipients who desires paternity should be also properly counseled about the impact of immunosuppression on fertility. Few studies have reported the negative effect of immunosuppressive drugs, particularly sirolimus, on male fertility. Sirolimus was shown to be linked to reduced fertility following kidney transplantation, due to its toxic effect on the sperm[33,34]. That's why, unrecovered fertility in male recipients maintained on mammalian target of rapamycin inhibitors (mTORi) following renal transplant surgery, should raise the suspicion of possible drug toxicity.

In the other hand, maintenance immunosuppression in females is modified to avoid teratogenic effect on the fetus. Generally, Mycophenolate Mofetil (MMF)/Mycophenolic Sodium (MPS) is considered unsafe during pregnancy. Kidney transplant recipients who are on MMF during pregnancy are at higher risk of pregnancy loss in the first-trimester first trimester along with severe congenital fetal structural malformations[35-37]. Following exposure to MMF, congenital malformations such as ear, eye, and lip/palate malformations have been reported in 23%-27% of live births[38]. Therefore, MMF should switch over to azathioprine that is, not associated with maternal or fetal risks[39].

Calcineurin inhibitors are the cornerstone of maintenance immunosuppressive therapy in any kidney transplant recipient. Calcineurin inhibitors (CNIs) have been evaluated during pregnancy in renal transplant females. The use of tacrolimus in kidney transplanted pregnant is considered safe. Physiologic changes during pregnancy can alter some pharmacokinetic properties of tacrolimus, that's why frequent monitoring of tacrolimus levels is recommended[40]. Furthermore, several studies have examined the effect of cyclosporine on the fetus and demonstrated that it is not teratogenic[41,42]. However, the Food and Drug Administration (FDA) categorizes Cyclosporin as category C, which indicates that human risk cannot be excluded. CNIs, in particular tacrolimus, are associated with increased risk of Post-transplant Diabetes Mellitus. It is well established that tacrolimus is more diabetogenic than cyclosporine[43,44]. Increased tacrolimus levels have been strongly linked to altered glucose tolerance, toxic effect on islet cells with subsequent development of diabetes mellitus. In pregnant recipients treated with tacrolimus with new onset hyperglycemia, shifting to safer drug such as cyclosporine could be an option. However, a recent systematic review and meta-analysis compared the impact of cyclosporine and tacrolimus on pregnancy outcomes in liver/kidney transplant recipients, found no significant differences in the incidence of gestational diabetes between them[45].

The use of mammalian target of rapamycin (mTOR) inhibitors is considered a contraindication during pregnancy. Sirolimus should be discontinued at least 12 wk before pregnancy, while everolimus should be discontinued at least 8 wk before conception. Boulay *et al*[46], and Framarino *et al*[47]. Reported limited data on the use of mTOR inhibitors in pregnant patients.

With the increased use of co-stimulation blocker, Belatacept, in non-pregnant recipients, there is still no clear evidence on the safety of its use in pregnant recipients[48].

In conclusion, the combination of calcineurin inhibitors, azathioprine and steroids is the mainstay maintenance therapy in pregnant recipients, as no major fetal or maternal effects have been reported.

APPROACH TO THE USE OF COMMON NON-IMMUNOSUPPRESSION DRUGS

Hypertension is reported to be more common in pregnant transplant recipients accounting for 20%-70% compared to 1%-5% in pregnant women in the general population[26,30,49]. Hypertension in pregnant transplant recipients, is associated with a higher risk of preeclampsia and eclampsia.

In hypertensive pregnant females, medications such as labetalol[50], calcium channel blockers of dihydropyridine group[51], methyldopa[52], and hydralazine[53] can effectively manage hypertension with a safe profile regarding the pregnant transplant recipient and fetus.

Non-dihydropyridine calcium channel blockers (such as diltiazem and verapamil), should not be administered with calcineurin inhibitors, because of their effect on enzyme CYP3A4 metabolism[54].

Angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, and direct renin inhibitors are not acceptable during pregnancy because they are associated with significant fetal risk[55]. Therefore, it is recommended to plan conception at least 6 wk after discontinuation of these drugs.

There is very limited data on the safety of angiotensin-converting enzyme inhibitors in normal lactation. The minimal concentration of angiotensin converting enzyme inhibitors, in breast milk, can cause hemodynamic instability in premature infants and neonates in therapeutic doses. Captopril and Enalapril are excreted in very low doses in breast milk and considered safe with breastfeeding, nonetheless, babies should be monitored for adverse events[56].

Thiazide and loop diuretics use during pregnancy, have not been linked to increased risk of fetal unfavorable outcomes, when prescribed for volume overload and elevated blood pressure. Diuretic usage should be limited, because of major concern about affecting physiologic volume expansion during pregnancy[57].

In the other hand, antibiotics during pregnancy are used more frequently, as the incidence of infections is higher in transplanted patients, owing to the use of potent immunosuppression. Urinary tract infections are prevalent in female transplant patients, and the risk rises by up to 40% during pregnancy, presumably due to physiologic anatomic changes occurring in the urinary tract[58]. The prescription of antibiotics in kidney transplant recipients should always be considered for a potential interaction and possible adverse effects. Antibiotics such as Nitrofurantoin, Amoxicillin, Cephalexin, Cefpodoxime and Fosfomycin are considered safe in pregnancy in kidney transplant recipients with no drug-drug interaction[59]. Ciprofloxacin and Trimethoprim/Sulfamethoxazole are generally not recommended in pregnancy with and without transplantation. Antibiotics that are generally used for the management of upper and lower tract infections include macrolides, quinolones, penicillins and cephalosporins. Clarithromycin, but not azithromycin should be avoided in kidney transplant recipients irrespective of pregnancy, because of its effect on the hepatic/intestinal enzyme CYP3A4 metabolism and subsequent increase in tacrolimus level and possible toxicity. Azithromycin is safe to use during pregnancy in renal transplant recipients, but attention should be paid to the risk of arrythmia as both drugs increase QTc interval. The use of quinolones in pregnancy is still controversial in literature because of concerns on their adverse effects on the fetus formation. However, animal studies did not show an increase in major birth defects, abortion or maternal complications[60]. Hence, quinolones can be prescribed in complicated and life threating infections.

Penicillins and cephalosporins are generally acceptable in kidney transplant recipients in the context of pregnancy.

IMPACT OF KIDNEY TRANSPLANTATION AND PREGNANCY ON THE INCIDENCE OF INFECTION AND OUTCOMES

After kidney transplantation, infection is the second major cause of mortality among transplant patients, behind cardiovascular disease. Up to seventy percent of kidney transplant recipients will encounter an infection episode during the first three years following transplantation, according to estimates[61]. As mentioned earlier, bacterial urinary tract infections are more prevalent during pregnancy in a kidney transplant recipient because of potent immunosuppression used.

Other than urinary tract infection, pregnant transplant recipients are at risk of TORCH infections. TORCH infections are a category of infectious disorders that can be transmitted to a newborn during pregnancy, delivery, or shortly after birth. Toxoplasmosis, rubella, cytomegalovirus, herpes, and others are termed as TORCH. In transplant recipients, the risk of cytomegalovirus infection during pregnancy is minimal, as conception is often planned 1-2 years following transplantation. Congenital cytomegalovirus (CMV) is the leading nongenetic cause of congenital sensorineural hearing loss and neurological impairment[62,63]. Therefore, it is essential that CMV infections be monitored.

Another TORCH virus, Herpes simplex virus can occur during pregnancy in immunocompromised patients as primary infection or activation of latent infection. In case of herpetic infection valacyclovir or acyclovir can be used safely during pregnancy. Caesarean delivery in infected mothers reduces the incidence of newborn herpes 1 or 2. Therefore, caesarean section should be performed if cervical cultures show herpes. To prevent primary varicella-zoster virus (VZV) infection after transplantation, pretransplant screening for past VZV infection should be conducted, and naive patients should be immunized with live attenuated varicella vaccine if possible[58].

Toxoplasmosis in pregnant transplant recipients can be caused by either reactivation of a latent infection or primary infection. In a fitting clinical setting, toxoplasmosis should be evaluated in the differential diagnosis of pneumonia, culture-negative sepsis, and encephalitis. Toxoplasmosis should be screened quarterly in pregnant kidney transplant patients. Sulfadiazine, pyrimethamine and spiramycin should be given to immunosuppressed individuals with growing antibody titers to prevent congenital toxoplasmosis infection[64].

As a conclusion, many illnesses can be avoided or ameliorated by pre- and post-transplant care, pretransplant screening of infections and updated immunization remain the major standard of treatment. Protocol polymerase chain reaction screening of CMV, BK virus and others, in the post-operative period has been also shown to reduce the incidence of infectious complications. Finally, most opportunistic infections occurring in pregnant transplanted patients can be preventable, therefore, transplant nephrologists carry a major responsibility in the delivery of best available medical care for all

patients.

IMPACT OF PROTEINURIA AND KIDNEY DYSFUNCTION ON THE ALLOGRAFT SURVIVAL IN PREGNANT KIDNEY TRANSPLANT RECIPIENTS

Pregnancy in transplant patients with stable kidney function and no risk factors is associated with favorable graft outcomes. The graft failure rate in pregnant transplanted women was comparable to that in non-pregnant allograft recipients at a follow-up of ten years[65]. Renal transplant recipients with hypertension, pre-gestational elevated creatinine, and proteinuria are at higher risk to develop accelerated graft loss.

National Transplantation Pregnancy Registry revealed that recipients who faced graft loss in five years had lower eGFR at baseline before pregnancy, higher serum creatinine after pregnancy, and a higher rejection rate three months after pregnancy[66]. Recurrent acute rejections with renal impairment before and during pregnancy increase the risk of graft failure.

The likelihood of graft failure at five years was significantly higher when serum creatinine was > 1.3 mg/dL pre-pregnancy. Serum creatinine at > 1.6 mg/dL was associated even with a more than 7-fold higher risk of graft failure. Keitel *et al*[67] reported that pre-pregnancy creatinine was > 1.5 mg/dL in all recipients who experienced graft failure 2 years following childbirth.

Schwarz and colleagues also reported poor graft outcomes in patients with low eGFR before or during pregnancy[68].

Proteinuria before or during pregnancy, especially proteinuria of > 1 g/d, is associated with worse graft survival[69]. Higher the proteinuria, the higher the risk of premature birth, Intrauterine growth retardation, and miscarriages. Hence, it is strongly recommended to achieve low proteinuria levels below 500 mg before pregnancy to avoid adverse events[69].

CONTRACEPTION OPTIONS FOR KIDNEY TRANSPLANT RECIPIENTS

Despite the fact that end-stage renal disease negatively affects fertility, there is a recovery of reproductive function after a kidney transplant, and pregnancy is common. Fertility can be efficiently reverted in the few months after a kidney transplant. Hence, to guarantee that pregnancies do not occur prior to maternal optimization, it is crucial that women with a history of kidney transplants plan their pregnancies and have access to adequate contraception[70]. Female recipients should be educated about contraceptive methods which could be selected based on old experience, medical history, comorbidities, and preference[71].

Irreversible contraception is usually achieved by surgical procedures like vasectomy[72,73], or tubal ligation[74,75]. Reversible contraception is achieved using an intrauterine device (IUD), hormonal pills/injections or patches and other barrier methods.

Hormonal contraceptives are commonly used and highly effective with a minimal failure rate[76]. Estrogen-based contraceptives are associated with exacerbation of migraines, the risk of venous thromboembolism (VTE), and worsening hypertension control. Depo medroxyprogesterone (DMPA) is an effective and safe contraceptive method, with prolonged effect over 3 mo. The use of DMPA increases the risk of VTE[77]. Other hormonal contraceptives include etonogestrel implant[78], transdermal patch and others.

IUDs are highly effective, easy to insert and low failure rate with no increased risk of VTE. IUDs are not associated with an increased risk of infectious complications[79].

The vaginal ring is another effective method of contraception. It is associated with a lower incidence of adverse events[80].

Barrier methods include condoms, spermicides, diaphragm, cervical caps and sponges are associated with failure rates due to compliance issues. Education of couples on its correct use may reduce the failure rate[81]. In conclusion, there is no study comparing the efficacy of different types of contraception in transplanted females. Therefore, an individualized approach to contraception is recommended, based on comorbidities, associated risk, and preference. A comparison of the effectiveness of contraceptive methods is demonstrated in Figure 4[82].

POST-TRANSPLANT BREASTFEEDING

Pregnancy in a kidney transplant recipient remains to be complicated because of the detrimental effects of immunosuppressive therapy on the renal allograft, fetus and the transplant recipient. The safety of immunosuppression therapy on breastfed babies was addressed in a few studies[83-100]. There is reassuring data on the use of calcineurin inhibitors based regimen in addition to prednisone and azathioprine during lactation. Prednisolone is excreted at very low levels in breast milk. The studied

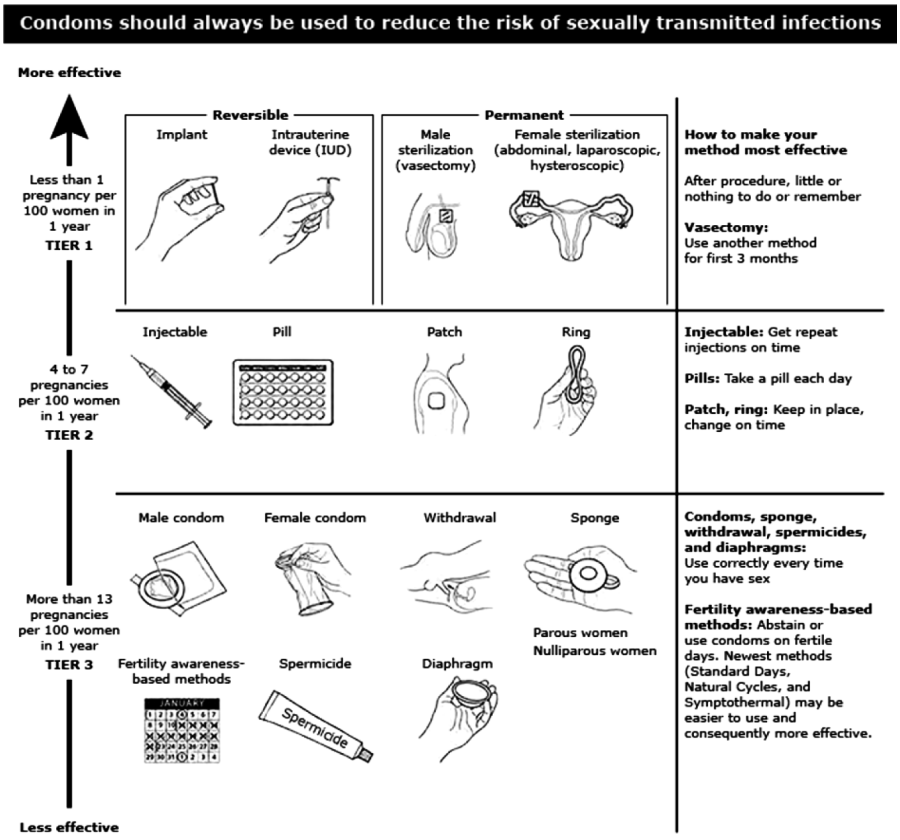

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Figure 4 Different contraceptive methods options for pregnancy planning in kidney transplant recipients.

dose of 50 mg/d was not shown to affect growth. The risk of infections or hematological complications in infants is not increased[31].

Regarding azathioprine, its metabolites were undetectable in the breast milk and there was no side effect noted in the infants. Infants of mothers receiving azathioprine did not show any significant increase in infection rate[84-88].

Cyclosporine was reported to have minimal excretion in breast milk. The study showed no nephrotoxic effect, growth retardation or immunosuppressive effects on the baby. Another study demonstrated undetectable Cyclosporine levels in breastfed babies from mothers on Cyclosporine[89-96]. Tacrolimus levels were undetectable in infants. Studies demonstrated that lactation in renal transplant recipients on tacrolimus was safe but needs close monitoring of the infant[97-100].

As mTORi are contraindicated during pregnancy, it is also advised not to initiate mTORi during lactation, as there are no studies that support this practice[101]. MMF usage in breastfeeding was not studied in humans, however, results extrapolated from animal studies demonstrated harm[35]. Belatacept was suggested by transplant experts not to be used while breastfeeding as no study evaluated its effect on infants[102].

CONCLUSION

As ESRD is associated with infertility, kidney transplantation offers the best option to restore sexual health and the ability to conceive. Proper contraception and pregnancy planning are mandatory, to avoid unwanted pregnancy and the toxic effects of immunosuppression on the fetus. Modifications in immunosuppression are essential before conception. Normal lactation is the best feeding for babies, but patients on immunosuppressive drugs should be counseled about their possible side effects. Normal delivery is considered the normal way of delivery, although practice patterns may differ.

Primary care physicians and nephrologists should make a greater effort to discuss menstrual and reproductive issues with women who have received a kidney transplant. The transplant team should provide complete information and counseling to women of childbearing age who are considering pregnancy.

Finally, pregnancy is generally considered safe in the setting of kidney transplant, however, a team approach to care that includes the primary care physician, a transplant nephrologist, and a qualified obstetrician in high-risk pregnancies, is crucial for a successful pregnancy and better outcomes.

FOOTNOTES

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MINIREVIEWS

Pancreatic fat in type 2 diabetes: Causal or coincidental?

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Abstract

Type 2 diabetes (T2D) is a multifactorial metabolic disorder affecting more than 450 million people across the globe. With the increasing prevalence of T2D and obesity, the role of fat accumulation at sites other than subcutaneous adipose tissue has received significant attention in the pathophysiology of T2D. Over the past decade and a half, a pressing concern has emerged on investigating the association of pancreatic fat accumulation or pancreatic steatosis with the development of disease. While a few reports have suggested a possible association between pancreatic fat and T2D and/or impaired glucose metabolism, a few reports suggest a lack of such association. Pancreatic fat has also been linked with genetic risk of developing T2D, prediabetes, reduced insulin secretion, and beta cell dysfunction albeit some confounding factors such as age and ethnicity may affect the outcome. With the technological advancements in clinical imaging and progress in assessment of pancreatic beta cell function, our understanding of the role of pancreatic fat in causing insulin resistance and development of various etiologies of T2D has significantly improved. This review summarizes various findings on the possible association of pancreatic fat accumulation with the pathophysiology of T2D.

Key Words: Type 2 diabetes; Pancreatic fat; Steatosis; Glucose metabolism; Beta cell function; Non-alcoholic fatty pancreas disease; Obesity; Insulin resistance

Core Tip: The concomitant rise in the incidences of obesity and type-2 diabetes (T2D) has increased interest in understanding the role of pancreatic fat accumulation or pancreatic steatosis in causing T2D. In the past few years, various researchers have attempted to decipher whether pancreatic fat has any causative role in the pathogenesis of T2D. While a few cross-sectional and retrospective studies have shown a positive association between pancreatic fat and T2D, there is a lack of well-controlled, prospective, and long-term follow-up studies that could clearly establish the role of pancreatic fat in causing T2D. Therefore, in light of the presently available evidence, the role of pancreatic fat as an independent predictor of T2D must be interpreted with caution.

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INTRODUCTION

The global increase in the incidence and prevalence of type 2 diabetes mellitus (T2D) has been linked to a parallel epidemic of obesity observed during the last few decades. This association of T2D and obesity has brought research interest in adipose tissue biology with gradual conceptual changes, and adipose tissue is no longer considered an inert lipid store but rather a metabolically active endocrine organ with an enormous capacity to secrete numerous metabolically active compounds and hormones[1-3].

In obese individuals, when storage capacity in adipose tissue is overwhelmed by the circulating lipids, progressive and abnormal accumulation in non-adipose tissue results in steatosis, which may involve the liver, skeletal tissue, heart, and pancreas[4,5]. Accumulating lipid droplets within cells may result in cellular dysfunction and cell death, also known as lipotoxicity[6]. Further, human studies suggest that lipid content in hepatocytes and skeletal tissue is a more important determinant for insulin resistance than circulating free fatty acids[7]. Although obesity-related ectopic fat deposition in the liver, primarily caused by non-alcoholic fatty liver disease (NAFLD), and its relationship with metabolic syndrome and T2D have been studied extensively, ectopic fat accumulation in other organs, especially the pancreas, and their clinical significance have received little attention from the researchers until recently.

Ogilvie first described the term "pancreatic lipomatosis" to denote excessive fat accumulation in pancreatic tissue. After that, various terminologies were used to describe the same, which include pancreatic steatosis, fatty infiltration or replacement, fatty pancreas, and non-alcoholic fatty pancreas disease (NAFPD)[8]. However, pancreatic fat accumulation or steatosis may also be seen in nonobese individuals due to various other etiologies, including chronic alcohol use, viral infections, chemotherapy, and cystic fibrosis[8,9]. Therefore, some authors suggested restricted use of the term NAFPD for those cases of pancreatic steatosis which are associated with metabolic syndrome and obesity, as this condition may be reversed by weight loss or the use of certain medications[9-11]. Whereas, in the other situations where irreversible fatty replacement occurs following acinar cell death, the preferred terminology used is 'fatty replacement'[9]. Table 1 depicts the nomenclature used to describe accumulation of fat in the pancreas[9,12]. The pancreas can be roughly sub-divided into endocrine pancreas containing islets and exocrine pancreas that is responsible for secretion of digestive enzymes, and is comprised of lobes, segregated by connective tissues. Pancreatic fat accumulation involves intralobular or interlobular adipocyte infiltration or presence of intracellular lipid droplets[13,14].

The association between T2D and NAFPD is controversial. Some studies reported more pancreatic fat accumulation in T2D subjects than in those without diabetes, while others reported no difference[15-17]. In this review, we will discuss the epidemiology of NAFPD, the pathophysiology of pancreatic fat accumulation in T2D, its relationship with T2D, and the effect of anti-diabetic medications on pancreatic steatosis.

EPIDEMIOLOGY

The studies documenting the true global prevalence of pancreatic steatosis are limited[18]. Besides, the available data is highly variable, affected largely by the ethnicity and age of the population being studied and the modality used for the detection of pancreatic fat[19]. Accordingly, the prevalence of pancreatic steatosis in the general population is estimated to be roughly between 16% to 35%[3-6,20-23]. In a recently conducted cross-sectional study in Japan, the prevalence of pancreatic fat accumulation, as determined using transabdominal ultrasonography, was 46.8%. Amongst the subjects with pancreatic steatosis, there was preponderance of males and subjects with higher prevalence of lifestyle-related

Table 1 Nomenclature of pancreatic fat accumulation

Name	Definition
Pancreatic steatosis or fatty pancreas or pancreatic lipomatosis	General terminology for accumulation of pancreatic fat
Lipomatous pseudohypertrophy	An extreme form of pancreatic fat accumulation with uniform or focal enlargement of the pancreas and replacement of exocrine system by adipose tissue which is unrelated to obesity
Fatty replacement	Replacement with adipocytes following death of pancreatic acinar cells
Fatty infiltration	Obesity-related infiltration of the pancreas with adipocytes
NAFPD	Pancreatic fat accumulation along with obesity and metabolic syndrome
Non-alcoholic fatty steatopancreatitis	Pancreatitis resulting from accumulation of pancreatic fat

NAFPD: Non-alcoholic fatty pancreas disease.

diseases, including fatty liver disease[7,24].

A systemic review and meta-analysis involving over 12000 individuals showed a prevalence rate of 33% [95% confidence interval (CI): 24%-41%]. The results of meta-regression showed that the prevalence of pancreatic steatosis was associated with hypertension, T2D, and metabolic syndrome. Of note, 9 of 11 studies included in this study were conducted in Asian populations, thereby raising questions regarding the generalizability of the data[8,25]. More studies in different ethnic populations, especially those with high rates of obesity and metabolic syndrome, would be valuable in delineating the true global prevalence of pancreatic steatosis.

DIAGNOSIS OF NAFPD

Pancreatic enzymes are rarely raised in NAFPD, therefore, serological investigations are not useful in diagnosing NAFPD. There are various imaging modalities available, however, there are certain challenges associated with the use of these technologies in diagnosing NAFPD, as listed below.

Transabdominal ultrasonography: It is a widely available and non-invasive method of pancreatic fat assessment. It detects pancreatic steatosis as an increase in echogenicity within the pancreatic parenchyma, as compared to renal and hepatic echogenicity. This is an operator dependent procedure and presence of overlying bowel gas shadow and obesity may interfere with the visualization and interpretation of pancreatic steatosis[26].

Endoscopic ultrasound (EUS): It is an invasive endoscopic procedure, which allows good visualization of the pancreas. Various studies have revealed the relationship between increased pancreatic echogenicity and the presence of obesity and fatty liver[22,27]. This modality is also limited by operator dependency. Further, apart from NAFPD, the presence of pancreatic fibrosis may also result in increased echogenicity of pancreatic parenchyma, thus resulting in false positive interpretation[28].

Computed tomography (CT): Fat infiltration in the pancreas is detected as hypodensity (in Hounsfield units) as compared to the adjacent spleen[29]. However, this method is also operator dependent. Saisho *et al*[16] demonstrated that CT evaluation using fat/parenchyma ratio is a useful method to detect NAFPD.

Magnetic resonance imaging (MRI): MRI is the most preferred method for detecting pancreatic steatosis at present. It is non-invasive, safe, and highly sensitive for detecting pancreatic fat. Its accuracy in identifying pancreatic steatosis is comparable with that of histopathological examination[30,31].

MRI proton density fat fraction: This modality allows quantification of pancreatic fat with high accuracy[32].

PATHOPHYSIOLOGY OF PANCREATIC FAT ACCUMULATION

Obesity has been implicated as the most important risk factor for NAFPD[33]. Increased BMI in human studies was found to be associated with pancreatic fat accumulation[21]. Moreover, animal studies in mice models revealed that obesogenic diets for mothers during pregnancy and lactation might result in NAFPD through alterations in circadian metabolic patterns and endoplasmic reticulum stress[34,35]. In obesity, both mechanisms of pancreatic steatosis, *i.e.*, fat replacement (adipocytes replacing dead acinar cells) and fat infiltration (*i.e.*, fat accumulation), go hand in hand[9].

Age and male sex are other risk factors for NAFPD[36]. Evidence from epidemiological studies indicates a positive association of NAFPD with age[36,37]. NAFLD is another important risk factor for

pancreatic steatosis. Lee *et al*[38] found a concurrence rate of 67.9% between NAFPD and NAFLD, with a high negative predictive value for NAFLD (96.4%) in patients with a normal pancreas. Uygun and colleagues reported a strong association between non-alcoholic steatohepatitis (NASH) and NAFPD. About half of these patients with NASH had concurrent NAFPD[39]. In contrast to the above finding, another study reported that NAFPD was significantly associated with advanced stage of hepatic fibrosis but lacked any correlation with NASH[40].

Besides, sedentary lifestyle, smoking, consumption of excessive meat, hypertension, hyperferritinemia, and low lipase activity in serum are other potential risk factors for pancreatic steatosis[20-22,41-43]. The various risk factors for NAFPD are summarised in Figure 1.

While the association between obesity and NAFPD has been conclusively demonstrated, the underlying mechanism remains unclear. Contemporary research on NAFPD mainly focuses on the prevalence and clinical implications, but the literature is scarce regarding genetics and underlying molecular mechanisms. However, some evidence points towards the role of adipocyte-derived cytokines and inflammatory factors in the pathogenesis of NAFPD, particularly those induced by free fatty acids (FFAs). Animal studies in rats revealed that FFA-induced hyperlipidemia was associated with increased expression of tumor necrosis factor (TNF-α), interleukin (IL-6), and monocyte chemoattractant protein-1 (MCP-1) with a significant simultaneous increase in body fat[44,45]. An *in vitro* study has shown that palmitic acid (a saturated FFA) could induce increased expression as well as secretion of IL-6 and IL-8, which was associated with a significant increase in intracellular fat content[46]. However, there is some contradictory evidence as well. In a recent *ex vivo* study on blood mononuclear cells, palmitic acid, γ-linolenic acid, and arachidonic acid were found to have minor effects on the gene expression of pro-inflammatory factors, including TNF-α, IL-6, and cyclooxygenase-2, whereas, oleic acid, α-linolenic acid, and docosahexaenoic acid reduced the expression of these genes[47]. Further research in this area is warranted to draw some meaningful conclusions.

Further, progressive accumulation of pancreatic fat may have a role in the pathogenesis of pancreatic cancer. This hypothesis was endorsed by a study which showed relation between high-fat diets and pancreatic cancer risk[48]. There is also evidence in the literature which revealed a direct association between pancreatic steatosis and the incidence of pancreatic cancer[49,50].

Influence of adipocyte-derived factors on beta cell function

Adipocytes and preadipocytes secrete adiponectin and leptin, respectively[51]. The direct effect of adiponectin and leptin on beta-cell survival and function has been studied widely using *in vitro* models and are detailed in several reviews[52-55]. Adiponectin secreted from the adjacent adipocytes acts on beta cells *via* the adiponectin receptor 1 and thereby promotes beta cell survival and insulin secretion. Leptin secreted from preadipocytes acts on the leptin receptor in a paracrine fashion, resulting in inhibition of insulin release.

Sympathetic stimulation and fasting state result in adrenaline and glucagon secretion, which in turn leads to activation of β-adrenergic receptors and glucagon receptor on adipocytes, respectively, with a consequent increase in lipolysis and release and local elevation of fatty acids[56]. In acute conditions, fatty acids act on fatty acid receptor 1 (FFAR1/GPR40) and stimulate insulin release from the beta cells [57]. However, when chronically elevated, fatty acids at high concentrations may lead to endoplasmic reticulum stress and beta cell apoptosis[58,59]. Fatty acids can also act on the Toll-like receptor 4 (TLR4) and mediate beta cell death and islet inflammation[55,60]. TLR4-dependent activation of IL-8 and MCP-1 results in monocyte chemotaxis. Besides, activation of TLR4 on tissue macrophages induces the cytotoxic cytokine IL-1β release resulting in beta cell death[60].

ASSOCIATION OF PANCREATIC FAT AND T2D

Studies showing association of pancreatic fat with T2D

With respect to pancreatic fat accumulation, several studies have reported its positive association with the development of T2D[39] (Table 2). In 2007, Tushuizen *et al*[15], reported the association between beta cell dysfunction and pancreatic fat content, leading to T2D development for the first time. The authors observed higher median pancreatic fat content in T2D subjects as compared to age and BMI matched controls (20.4% *vs* 9.7%, P = 0.032). However, they noted a significant association of pancreatic fat content with beta cell dysfunction in non-diabetic controls, rather than in patients with T2D. These findings suggest that pancreatic fat accumulation may contribute to beta cell dysfunction and T2D development in susceptible individuals and once overt diabetes sets in, additional factors may account for further decline in beta cell function. Nevertheless, all subjects demonstrated that pancreatic fat content had an inverse correlation with insulinogenic index and beta-cell glucose sensitivity. The findings suggest that pancreatic fat accumulation might contribute to the development of T2D, although the results need to be validated in larger cohorts[15]. A cross-sectional study in 2013 by Ou *et al*[37], found that NAFLD participants were more likely to acquire prediabetes [odds ratio (OR) = 1.798, 95%CI: 1.544-2.094] or diabetes (OR = 2.578, 95%CI: 2.024-3.284). Amongst all subjects, those with fatty pancreas were associated with diabetes (OR = 1.379; 95%CI: 1.047-1.816) as well as prediabetes (OR = 1.222;

Table 2 Studies showing association or lack of association between pancreatic fat and type 2 diabetes

S.No.	Title	Inference/key observation	Ref.
Studies showing association of pancreatic fat with T2D			
1	Pancreatic fat infiltration, β-cell function and insulin resistance: A study of the young patients with obesity	Elevated blood glucose levels and reduced beta cell function (HOMA-β and IGI) were reduced in subjects with HPF	Wen *et al*[65], 2022
2	Association of pancreatic fat content with type II diabetes mellitus	Elevated fat content in the pancreatic tail region may identify patients at risk for T2D	Nadarajah *et al* [64], 2020
3	Pancreatic steatosis associates with impaired insulin secretion in genetically predisposed individuals	Pancreatic fat leads to impairment of beta-cell function in subjects at genetic risk for diabetes	Wagner *et al* [66], 2020
4	Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: a 6-year computed tomography-based cohort study	Lean subjects with fatty pancreas can lead to development of T2D	Yamazaki *et al* [67], 2020
5	Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus	T2D is associated with higher pancreatic fat along with visceral and subcutaneous adiposity	Tirkes *et al* [62], 2019
6	Pancreatic fat content is associated with β-cell function and insulin resistance in Chinese type 2 diabetes subjects	Male subjects with T2D, demonstrated positive association between pancreatic fat content and insulin resistance	Lu *et al*[63], 2019
7	The effect of fatty pancreas on serum glucose parameters in patients with non-alcoholic steatohepatitis	NASH patients with high pancreatic fat had impairment in glucose metabolism	Uygun *et al* [39], 2015
8	Pancreatic fat and β-cell function in overweight/obese children with non-alcoholic fatty liver disease	Association of higher pancreatic fat content in subjects with prediabetes as compared to non-diabetic NAFLD obese children	Pacifico *et al* [61], 2015
9	The association between non-alcoholic fatty pancreas disease and diabetes	NAFLD and fatty pancreas were linked to diabetes, irrespective of age, gender, obesity, or other cardiometabolic risk factors	Ou *et al*[37], 2013
10	Pancreatic fat content and β-cell function in men with and without type 2 diabetes	Inverse correlation of pancreatic fat content with insulinogenic index and beta-cell glucose sensitivity in all the study subjects	Tushuizen *et al* [15], 2007
Studies showing lack of association of pancreatic fat with T2D			
1	Lack of independent association between fatty pancreas and incidence of type 2 diabetes: 5-year Japanese cohort study	No independent association between T2D and pancreatic fat was observed upon correction for possible confounders such as BMI and hepatic attenuation	Yamazaki *et al* [68], 2016
2	Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans	Pancreatic fat was related to age, but not to blood glucose levels. No association between pancreatic fat and insulin secretion or beta cell activity in T2D subjects was observed	Begovatz *et al* [71], 2015
3	Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers	No correlation between pancreatic fat and beta cell function was observed, during intravenous glucose tolerance tests in obese normoglycemic adolescents	Lê *et al*[69], 2011
4	Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β-cell function in individuals with impaired glucose metabolism	Pancreatic fat was increased in individuals with impaired glucose tolerance, without any direct relation with β-cell function	van der Zijl *et al*[70], 2011
5	Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome	Association between pancreatic fat and insulin resistance was mediated by visceral adiposity	Lee *et al*[38], 2009
6	Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes	Pancreatic fat levels increases with aging and obesity; however, it remained unchanged in subjects with T2D	Saisho *et al* [16], 2007

HPF: High pancreatic fat; HOMA-β: Homeostasis model assessment of β-cell function; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; T2D: Type 2 diabetes; IGI: insulinogenic index.

95%CI: 1.002-1.491), particularly in males. Similarly, an observational study in obese children with NAFLD by Pacifico *et al*[61] reported a significantly higher pancreatic fat content in subjects with prediabetes (3.60%) as compared to non-diabetic subjects (1.90%).

Over the last 5 years, the number of studies demonstrating the association between pancreatic fat content and T2D development has been on the rise. A retrospective study by Tirkes *et al*[62] in 2019, reported a direct association between pancreatic fat accumulation and fat within the visceral compartment. Subjects with T2D had higher pancreatic steatosis and elevated subcutaneous fat content. A retrospective study by Lu *et al*[63] in 2019, reported that T2D subjects (n = 78) had more pancreatic fat in comparison to non-diabetic subjects (n = 35) (pancreatic fat content 7.06% *vs* 5.36%). The pancreatic fat content had a positive association with insulin resistance and abnormal glucose metabolism as assessed by oral glucose tolerance test (OGTT) in male T2D subjects. The authors also reported that subjects with shorter diabetes duration were associated with insulin resistance and beta cell dysfunction. Another retrospective study by Nadarajah *et al*[64] in 2020, was performed to determine

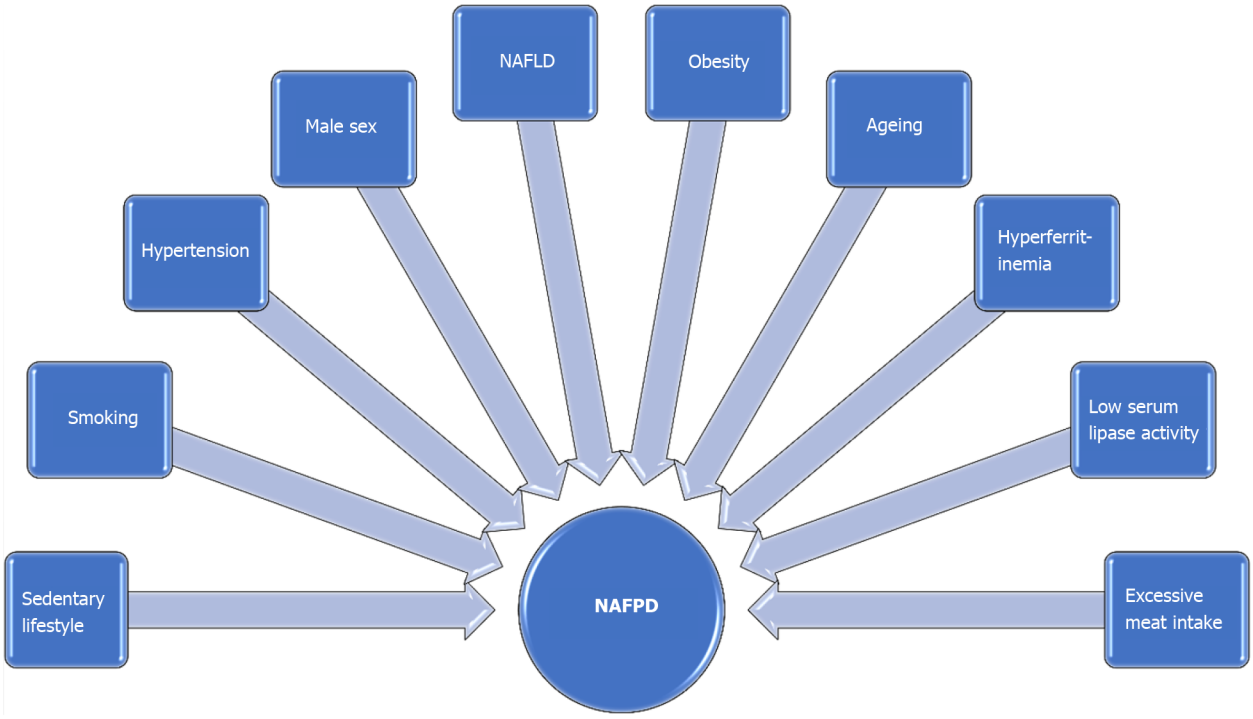

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Figure 1 Implicated risk factors for non-alcoholic fatty pancreas disease. NAFPD: Non-alcoholic fatty pancreas disease.

the association between regional pancreatic fat content and the risk of developing T2D. A significant difference was observed in the fat content in the pancreatic head, pancreatic body, and pancreatic tail in subjects with T2D and healthy controls, respectively. Upon regression analysis between the healthy control and prediabetes group, a significant difference was observed between fat content in the pancreatic tail region (OR = 1.1, 95%CI: 1.026–1.178; P = 0.007). ROC curve analysis showed an 81.3% specificity and 45.5% sensitivity in predicting the development of T2D within 4 years in subjects with fat content > 10% in the pancreatic tail region. Recently, a retrospective study in obese young subjects was performed, where pancreatic fat content was analysed by IDEAL-IQ MRI, on the basis of which the subjects were subgrouped as having high pancreatic fat (HPF) (> 6.2%) and normal pancreatic fat (NPF) (< 6.2%). The early and total insulin secretion during OGTT, *i.e.*, $AUCINS_{0\text{-}120}/AUCGLU_{0\text{-}120}$, was reported to be significantly reduced in the HPF group when compared with the NPF group (6.41 *vs* 16.01). Further, the subjects with HPF had significantly higher glucose levels during OGTT and the beta cell function in terms of homeostasis model assessment of β-cell function (HOMA-β) and insulinogenic index was also significantly reduced[65].

The genetic background has also been implicated in influencing pancreatic fat accumulation and insulin secretion. Subjects with a high genetic risk of T2D reported an increase in pancreatic fat content associated with lower insulin secretion by Wagner *et al*[66] in 2020. Upon multivariate regression analysis, insulin secretion was observed to be negatively correlated with pancreatic fat and genetic risk score for T2D. Therefore, based on the intensity of the genetic risk score of T2D, pancreatic fat may have a different association with insulin secretion. Recently, a retrospective cohort study by Yamazaki *et al* [67] in 2020, demonstrated a strong link between high levels of pancreatic fat and T2D in lean individuals. Subjects with low pancreas attenuation (< 46.9 HU) on CT were reported to have fatty pancreas and the incidence of T2D (4.13%) was higher at lower pancreas attenuation levels in lean individuals. Upon regression analysis, a strong association between pancreas attenuation and T2D incidence was observed (OR = 2.62, in subjects with fatty pancreas and OR = 1.20, in subjects with normal pancreas). A similar association was observed when P/S (ratio of pancreas attenuation to spleen attenuation) & P-S (difference between pancreas attenuation and spleen attenuation) were calculated.

Studies showing lack of association of pancreatic fat with T2D

While some of the cross-sectional observational studies have noted the association of NAFPD with T2D, controversies exist in this regard (Table 2). There is some evidence that also suggests that NAFPD may be a marker of beta cell dysfunction rather than a causative factor for the same.

Saisho *et al*[16] in 2007 reported that pancreatic fat, as measured by CT scans and at autopsy, increased with aging and obesity; however, it did not increase in T2D. Although most of the previously reported studies showing the association of pancreatic steatosis with T2D are cross-sectional in nature, the literature is sparse in regards to longitudinal studies. Yamazaki and colleagues, in a retrospective

cohort study, did not find an independent association between T2D and pancreatic steatosis as the association disappeared after the results were adjusted for potential confounders, including BMI and hepatic attenuation[68].

Many authors also did not find any independent association of pancreatic steatosis with marker of insulin resistance, the pathophysiologic hallmark of T2D. Lê *et al*[69] in 2011 did not observe any significant association between pancreatic fat fraction and markers of insulin sensitivity in obese individuals. They also noted that visceral adipose tissue and circulating free fatty acids were the most important determinant for pancreatic steatosis. In another study, pancreatic steatosis was found to be associated with visceral fat and HOMA-IR. However, after adjustment for the visceral fat area, the correlation with insulin resistance disappeared. It suggests that the association between pancreatic fat and insulin resistance was mediated by visceral adiposity. This observation revealed that a fatty pancreas might be a merely associated finding with generalized visceral adiposity[38].

Beta cell failure is required for transition from prediabetes to overt T2D stage. As far as beta cell function is concerned, most human and animal studies have shown an inverse relationship with pancreatic fat accumulation; however, contradictory evidence also exists.

van der Zijl *et al*[70] in 2011 demonstrated that the impairments in beta cell function as assessed by the hyperglycaemic clamp in patients with prediabetes were accompanied by pancreatic fat accumulation; however, they failed to show any relation between pancreatic steatosis and beta cell function. Lê *et al*[69] also did not find any correlations between pancreatic fat fraction and markers of beta cell function as assessed during intravenous glucose tolerance tests in obese normoglycemic adolescents. Further, no relations were observed between pancreatic fat infiltration and beta cell function across the spectrum of glucose tolerance in another study[71].

CONCLUSION

With the first report on pancreatic fat accumulation or pancreatic steatosis emerging as early as in 1933 [9], it took over 60 years to suggest a possible link between pancreatic steatosis and T2D, when van Geenen *et al*[72] in 1984 hypothesized that obesity and the associated insulin resistance are implicated in the infiltration of adipocytes in the pancreas. The studies conducted thereafter, established the fact that pancreatic fat accumulation is a major manifestation of metabolic syndrome, a common denominator in pathogenesis of T2D as well. The concept is still evolving and it is only after the studies in the past decade and a half that the picture is getting clearer. Several cross-sectional studies and a very few longitudinal studies have shown a positive association of pancreatic steatosis with T2D, however, BMI and NAFLD remain as potential confounders. Although the advancements in imaging technologies have now improved assessment of pancreatic fat content, there is a dearth of well-controlled prospective studies indicating functional consequences of pancreatic steatosis, especially in terms of insulin resistance and/or beta cell function.

Next, the age and population specific variations add to the complexities in correlating pancreatic fat with pathophysiology of T2D. Nevertheless, the emerging data suggests that pancreatic fat is an important contributing factor in the pathogenesis of T2D. Data from studies in lean subjects- and use of dynamic tests like OGTT and advanced methods of assessment of beta cell function indicate that pancreatic fat accumulation can predict development of T2D to some extent. Whether or not obesity, especially visceral obesity, is the initiating factor in causing pancreatic steatosis leading to T2D again remains to be seen. However, T2D being a multifactorial entity with varying genetic predispositions, the role of pancreatic fat must be interpreted with caution after taking into considerations various other factors associated with pathogenesis of T2D.

Finally, the concomitant increase in the incidence and prevalence of obesity and T2D worldwide necessitates the need for well controlled longitudinal cohort studies to stratify the role of pancreatic fat as an independent predictor of T2D.

FOOTNOTES

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REVIEW

Artificial intelligence ecosystem for computational psychiatry: Ideas to practice

Xin-Qiao Liu, Xin-Yu Ji, Xing Weng, Yi-Fan Zhang

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Abstract

Computational psychiatry is an emerging field that not only explores the biological basis of mental illness but also considers the diagnoses and identifies the underlying mechanisms. One of the key strengths of computational psychiatry is that it may identify patterns in large datasets that are not easily identifiable. This may help researchers develop more effective treatments and interventions for mental health problems. This paper is a narrative review that reviews the literature and produces an artificial intelligence ecosystem for computational psychiatry. The artificial intelligence ecosystem for computational psychiatry includes data acquisition, preparation, modeling, application, and evaluation. This approach allows researchers to integrate data from a variety of sources, such as brain imaging, genetics, and behavioral experiments, to obtain a more complete understanding of mental health conditions. Through the process of data preprocessing, training, and testing, the data that are required for model building can be prepared. By using machine learning, neural networks, artificial intelligence, and other methods, researchers have been able to develop diagnostic tools that can accurately identify mental health conditions based on a patient's symptoms and other factors. Despite the continuous development and breakthrough of computational psychiatry, it has not yet influenced routine clinical practice and still faces many challenges, such as data availability and quality, biological risks, equity, and data protection. As we move progress in this field, it is vital to ensure that computational psychiatry remains accessible and inclusive so that all researchers may contribute to this significant and exciting field.

Key Words: Computational psychiatry; Big data; Artificial intelligence; Medical ethics; Large-scale online data

Core Tip: This study reviews and integrates the methods and models in the clinical practice of computational psychiatry and constructs a complete and mature Artificial Intelligence ecosystem. The ecosystem for computational psychiatry includes data acquisition, preparation, modeling, application, and evaluation. This approach allows researchers to integrate data from a variety of sources to obtain a more complete understanding of mental health conditions. Despite the continuous development and breakthrough of computational psychiatry, it has not yet influenced routine clinical practice and still faces many challenges, such as data availability and quality, biological risks, equity, and data protection.

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INTRODUCTION

Mental illness is a significant threat to human health, which was especially evident during the coronavirus disease 2019 (COVID-19) pandemic[1,2]. In recent years, artificial intelligence has played an increasingly prominent role in the clinical practice of psychiatry. The birth of computational psychiatry represents not only the inevitable choice to conform to the trend of the fourth industrial revolution but also an important means to solve the real dilemma.

Psychiatry mainly studies the causes, symptoms, and clinical diagnosis of human mental diseases. Computational psychiatry[3] uses computational and mathematical techniques to better understand mental disorders and to develop new treatments. Computational psychiatry is an emerging psychiatry approach that integrates various multidisciplinary approaches, such as psychiatry, neuroscience, machine learning, psychology, statistics, and computer science, to develop quantitative models of mental illness and to assess the effectiveness of different treatments[4]. Specifically, computational psychiatry builds computational models of brain function based on the neurological and cognitive phenomena associated with mental illness, predicts the abnormal degree of mental function, and evaluates the efficacy of treatment by using detailed multidimensional computational models[5,6].

Computational psychiatry includes two approaches: Data-driven computational psychiatry and theory-driven computational psychiatry[6]. Data-driven approaches involve machine learning and big data analytics, and they can improve predictive accuracy in clinical diagnosis, prognosis, and treatment by learning clinical and biological data. The theory-driven approach derives from computational neuroscience and focuses more on constructing models to understand the mechanisms of psychosis[7]. Due to the fact that computational psychiatry is based on mathematics, computer science, biological science, and other deep theories, it has the advantage of multidisciplinary integration[3]. One of the key goals of computational psychiatry is to move beyond the traditional "black box" approach to understanding the brain[8], whereby researchers study the symptoms and behaviors of individuals without fully understanding the underlying mechanisms. By introducing computational and statistical approaches, computational psychiatry has opened the "black box" of pathological mechanisms[9]. Moreover, neural computing functions provide precise algorithmic details for the analysis and solution of specific problems.

Computational psychiatry can identify the pathogenesis of mental diseases from both theory-driven and data-driven aspects, which is the result of the fusion of computational neuroscience and psychiatry [10]; in addition, it has a significant contribution to the diagnosis, treatment, and prevention of mental diseases. Overall, computational psychiatry is a rapidly growing and exciting field that has the potential to revolutionize our understanding of mental illness and to allow for the development of new treatments. By using computational and mathematical techniques to build quantitative models of mental illness, researchers in the field are working to identify the underlying mechanisms of mental illness and to develop more effective treatments.

Although various experimental studies have provided valuable information for understanding and explaining the underlying mechanisms of mental illness[11-13], the development of computational psychiatry is challenged by multiple interactions[14]. For instance, one of the biggest challenges faced by computational psychiatry today is the availability and quality of data. Mental health disorders are complex and multifaceted, and it is difficult to collect data that accurately reflect experiences with the disorders. Another challenge is the interpretability of the results. Many techniques that are used in computational psychiatry are highly complex and even difficult for experts in the field to understand, which makes it difficult for researchers to communicate their findings with others and for clinicians to

apply these findings to actual treatment. Many other problems also need to be solved, such as the technical connection between model development and clinical practice and ethical acceptability. Despite these issues, we remain optimistic about the future of computational psychiatry.

Establishing a complete artificial intelligence ecosystem of computational psychiatry is an effective method to solve the challenges in the clinical practice of psychiatry. In this study, we focus on building an artificial intelligence ecosystem for computational psychiatry to better facilitate the elimination of barriers to clinical practice. This review aims to make a fundamental contribution to shaping the ecosystem and for allowing the modules to be smoothly applied. Moreover, it outlines the responsibilities of the different agents and the linkages between them and builds a loop from data collection to modeling, evaluation, and clinical practice. We plan to sort out and integrate the same and different methods and models in the field, overcome the existing limitations, provide full attention to the role of each subject, and eventually form a complete and mature ecosystem. It is believed that as the field continues to evolve, researchers will eventually find ways to overcome the challenges and make greater advances in our understanding and treatment of mental health conditions.

METHODS

In this review, we used "computational psychiatry", "machine learning", "artificial intelligence", "psychiatry", and "deep learning" as keywords and retrieved the English literature in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science. We also manually screened the retrieved literature according to the relevance of the literature content to the topic and narrowed it down to a more accurate scope.

ARTIFICIAL INTELLIGENCE ECOSYSTEM FOR COMPUTATIONAL PSYCHIATRY

Based on the literature concerning clinical thinking and life cycle management of artificial intelligence projects, we conducted an integrated design of the ecosystem of computational psychiatry. We divided the clinical practice process of computational psychiatry into the following four main stages: data acquisition, modeling preparation, model construction, and application evaluation (Figure 1).

Data collection

One of the strengths of computational psychiatry is its ability to integrate big datasets of various forms to help researchers gain a more complete understanding of a patient's mental health. Thus, the first and most critical step in the artificial intelligence ecosystem for computational psychiatry is data collection. During this process, researchers can select one or more input data that can be measured according to the relevance of the research problem[15]. Common forms include clinical scales, visual data, voice, physiological signals, and Internet of Things data, *etc.* Although there are a wide variety of input data, tool selection should be based on a clear understanding of treatment strategies and the realistic evaluation of clinical effectiveness. Moreover, it should consider the mutual limiting effect of different data acquisition methods and technology operations, as well as the quality of original data and the details of processing methods, which will directly affect the reliability of the tools, and thus affect the effectiveness of clinical application[16,17].

Preparation for modeling

Modeling relies on different theoretical traditions[18]. For example, algorithm engineers are required to follow industry practice rules and conference content, articles, or implicit guidelines related to machine learning, and psychiatrists are bound by rules in the legal and medical fields, such as the National Institute for Health and Clinical Excellence guidelines or the American Psychiatric Association Practice guidelines. In addition, judgments are often made differently depending on the unique personality of the model builder. For example, clinicians' decision-making styles and willingness to take risks have a direct impact on their treatment paths and diagnostic strategies, and conservative and adventurous engineers also exhibit differences in aesthetic awareness and modeling styles. Therefore, the theoretical basis is worth fully preparing before building the model. The second is data preprocessing and quality checking. Since the collected data are often incomplete, as well as the fact that data from heterogeneous data sources may need to be collected, the raw data need to be preprocessed and quality checked to ensure the quality of the data. Only after data cleaning, data integration, data reduction, data transformation, and other processing can standardize data for model construction. The establishment of the compilation environment is also one of the preparatory works of model construction. There are several open source platforms that can be used for training, testing, and benchmarking algorithms based on different design requirements, such as OpenAI Gym[19], which provides a range of tasks, including some classic arcade games including Doom, as well as models, tests, and diagnostic paradigms that can be used for mental illness.

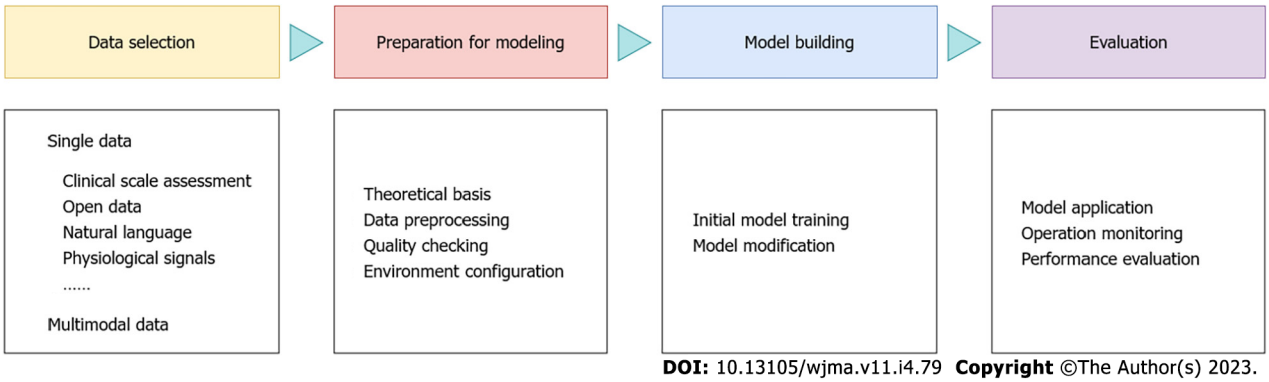

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Figure 1 Framework for modeling artificial intelligence ecosystems.

Model building

The first two steps in the computational psychiatry ecosystem both serve the third step; specifically, after collecting and processing the corresponding data in the theoretical context, the next step involves normative model building[20-22]. This step is divided into two parts: initial model training and model modification. Machine learning[23-27] is often used in model training to recognize emotional states[28], to detect mood swings[29], and to diagnose mental diseases[30]. There are two main types of machine learning: supervised learning and unsupervised learning. Supervised learning uses categorization and regression to learn from examples of existing labels. This method is often used to build classifiers to distinguish healthy people from sick people or to build predictive models. Washington *et al*[31] designed Guesswhat, which is a smartphone game for emotional data collection. They trained a pediatric emotion classification convolutional neural network classifier to recognize children's expressions, such as sadness, surprise, disgust, happiness, and neutral expressions. Their results demonstrated the value of mobile digital health. Although mood classifiers have made remarkable progress in automatic emotion recognition, the computational cost of existing models is too high. Banerjee *et al*[32] optimized the design of the machine learning model. The MobileNet-V2 network that they trained on ImageNet achieved a balanced accuracy rate of 65.11% and an F1 score of 64.19% on CAFE. Through optimization techniques, machine learning models can achieve greater accuracy and lighter weight. Unsupervised learning[33,34] is a classification method that does not require human data classification but automatically divides the structure based on the inherent distribution characteristics of datasets. In addition, clustering methods are often used in unsupervised learning. Regardless of which training method is used, professional school education and clinical training are needed. For example, clinicians require training in psychiatric education based on clinical case studies (fictional or nonfictional), and machine learning engineers require systematic schooling and professional experience. Finally, the initial model is reasonably built.

Computational psychiatry seeks to develop quantitative, mechanistic models of psychiatric disorders [35] that can help researchers better understand the biological and cognitive processes that lead to these disorders. A key benefit of computational models is that they can help researchers generate testable hypotheses about the underlying mechanisms of mental disorders. For example, reinforcement learning models of addiction[36,37] can be used to generate hypotheses about specific brain regions and pathways associated with addiction, as well as types of interventions that may be effective in treating addiction. The model, which is based on principles of neuroscience and psychology, suggests that addiction is caused by a disorder in the brain's reward system, which leads to obsessive behavior and a loss of control over behavior. Another benefit of computational models in psychiatry is that they can help researchers assess the effectiveness of different treatment options. For example, the cognitive-affective neural circuit model of depression[38] can be used to evaluate the efficacy of different antidepressants or psychotherapy based on predictions of their effects on basic brain circuits associated with depression. The model, which is based on evidence from neuroscience and psychology, proposes that depression is caused by the disequilibrium of the brain's emotional and cognitive processing systems, which leads to symptoms such as low mood, reduced negative thinking, and reduced motivation. However, regardless of how good the model is, there is room for improvement. As more theoretical background is accumulated in clinical practice, updated data will be incorporated into the model[39, 40]. Moreover, the model will expose more practical problems in clinical application; thus, it needs to be constantly adjusted and modified to adapt to new challenges.

Evaluation

Computational psychiatry is not currently used clinically, but it has the potential to inform new clinical interventions and treatments for mental illness to help guide the treatment of mental disorders. For example, clinicians can use computational models to assess an individual's brain activity and symptoms

to choose the most appropriate treatment for them. By using computational and mathematical models to better understand the underlying mechanisms of these diseases, researchers in the field can identify potential targets for intervention and assess the likely effects of different treatment options. However, more research is needed to fully understand the clinical potential of computational psychiatry and to develop the necessary tools and techniques to apply it in the clinical setting. Given the complexity of psychiatric disorders, future applications should be subject to enhanced regulatory oversight of clinical practice, as well as the evaluation and post hoc analysis of actual clinical benefits and model performance[41].

DATA SOURCES OF COMPUTING PSYCHIATRY

Based on the review of the existing studies, we conclude that data sources mainly include the following methods: scales, public data, language, physiological signals, blood, multimodal data, *etc.* (Table 1). This paper will discuss some of these categories.

Scales

Clinical scales[42-45] are one of the most widely used tools in clinical evaluation, and mature scales include the World Health Organization-Quality of Life-Brief (WHO-QoL-Bref), cognitive function test, Hamilton Depression Scale, Autism Diagnostic Observation Schedule, Hamilton Anxiety Scale, Fibromyalgia and Chronic Fatigue Rating Scale, *etc.* Large datasets accumulated through electronic medical records[46] facilitate the determination of goals by using computational methods. Self-reported digital scales[47,48] are used in the following manner. Researchers load the quantitative list of questions into the app, allow users to answer questions by using smart devices, and ultimately screen for symptoms based on the answers. This approach relies on mobile technology rather than traditional clinical scales.

Large-scale online data

Dubois *et al*[49] used a large online sample to demonstrate an association between human exploration strategies and impulse psychiatry, which not only demonstrated that impulsivity is associated with specific forms of exploration but also explored links between impulsivity and other psychiatric dimensions. Moreover, Nam *et al*[50] used machine learning and web analysis to identify factors associated with depression from national population surveys. Nielsen *et al*[51] discussed how large multisite public datasets contribute to the application of machine learning in psychiatry. Furthermore, Hu *et al*[52] collected users' text expressions on social platforms (such as Weibo) as data sources to predict their depression symptoms. Artificial intelligence (especially big data)[53] plays a vital role in health care, thus demonstrating its significant potential in applications[54].

Images and videos

Research indicates that psychiatric patients have different color vision and are less able to discriminate between colors than ordinary people. Therefore, the color recognition of images can be used to examine the difference between psychiatric patients and control groups or as a prognostic diagnosis. Shen *et al*[55] reviewed the paintings of 281 patients with chronic schizophrenia and 35 patients with healthy controls and used a series of computational analyses to scan and process the images. The results showed that color paint images have the potential to be used as a clinical diagnostic and prognostic tool for patients with chronic schizophrenia. The video data collected by the camera exhibit a large deviation, which is caused by noise in the natural environment. Moreover, existing studies provide optimized schemes through data collection pipelines, feature engineering, and data expansion strategies. The standard diagnosis for autism spectrum disorders takes several hours and assesses 20 to 100 behaviors (*e.g.*, eye contact, social smiling, *etc.*). Leblanc *et al*[56] introduced feature replacement methods to analyze family videos to establish the diagnosis of autism. They rated 140 videos of children on YouTube, filled in missing values by using feature replacement methods, and optimized the performance of the autism detection classifier. Dynamic feature replacement methods are superior to traditional methods in terms of performance and can reduce the impacts of missing values on video diagnosis[56]. Furthermore, Tariq *et al*[57] used mobile devices to classify videos by machine learning and labeled video features. This method ensures the accuracy of assessment and improves the speed of diagnosis.

Language

Automated speech analysis has been used in psychiatric diagnosis[58,59] and learns baseline interview data through machine learning algorithms to predict mental illness. Carrillo *et al*[60] conducted baseline autobiographical interviews with patients and transcribed them by using machine learning algorithms to predict the effectiveness of psilocybin for depression. The combination of machine learning with automated speech algorithms[61] contributes new ideas for the prediction and diagnosis of psychiatry. Moreover, the acquisition of language is relatively mild compared to acquiring intrusive data and

Table 1 Data sources for computational psychiatry

Module	Category
Single data	Clinical scales[42,45], electronic medical records[46], and digital scales[47,48]
	large online sample[49], national population surveys[50], and large multisite public datasets[51]
	Images[55] and videos[56,57]
	Language[62] and baseline interviews[60]
	Emotional faces[63,64], electrocardiogram[65], electroencephalogram[68-70], magnetoencephalogram[71], and magnetic resonance imaging[72,73,75]
	Human motion bone data[79]
	Blood[81,85]
Multimodal data	Multimodal data[45,86,89]

supports self-testing by users[62]. Computational linguistics combined with artificial intelligence provides a good aid to clinical diagnosis and risk monitoring.

Physiological signals

Physiological signals include emotional faces[63,64], electrocardiogram[65], electroencephalogram (EEG)[66-69], magnetoencephalogram[71], and functional magnetic resonance imaging (fMRI)[72-77]. There are two main methods to collect biological signals: invasive and noninvasive methods. Noninvasive data acquisition is commonly used, including electroencephalogram and functional magnetic resonance imaging. In recent years, physiological signals have been increasingly used to measure emotional responses. Compared with audiovisual data, physiological signals provide more detailed and real information. However, there are too many interference factors in the collection process of physiological signals, and the processing mechanism is more complex.

Human motion bone data

The clinical and scientific value of full body movement assessment has been increasingly recognized, and it is often used in the diagnosis of cerebral palsy. Previous studies were mostly based on computer vision[78]. However, during the process of sorting out the relevant studies, we noticed an interesting experimental study[79]. From the perspective of full body kinematics, the team built a machine-learning model to establish the purpose of automatic recognition and classification of depression. They used Kinect to capture human motion bone data, conducted experiments with four machine learning tools (including a support vector machine, logistic regression, random forest, and gradient lift), and finally utilized the evaluation and classification of patients with depression and without depression. This experimental study allows us to demonstrate the auxiliary role of kinematics in the identification of depression. However, when motion capture equipment is used to record the joint skeleton data of participants in motion, the captured data often contain noise due to the influence of the environment and sensor accuracy, which limits the accuracy of the data.

Blood

Biomarkers[80] are a group of proposed markers in recent years related to cell growth, proliferation, and disease occurrence, and they can be used to reflect drug reactions during pathological processes or after therapeutic interventions. Wagh *et al*[81] reviewed gene expression studies based on peripheral blood to identify gene expression biomarkers for schizophrenia. According to a genome-wide association study (GWAS), C-reactive protein (CRP) which is a biomarker of chronic inflammation, in the blood is likely associated with an increased risk of major depression; however, it is also correlated with a decreased risk of anorexia nervosa, obsessive-compulsive disorder, and schizophrenia[82]. By examining RNA, researchers can determine the patient's current state of anxiety, depression, and mania[83]. Moreover, despite the differences in population characteristics, analysis methods of gene expression, and nature of the research, the results still proved the validity of blood-based gene expression. Fernandes *et al*[84] used a machine learning algorithm composed of peripheral blood immunoinflammatory biomarkers and cognitive biomarkers in the diagnosis of bipolar disorder and schizophrenia with clinical effectiveness. The manner in which machine learning is combined with pharmacogenomic data provides a new way to predict patients with major depression. In a systematic review of recent advances in machine learning and pharmacogenomics studies, Bobo *et al*[85] demonstrated the effectiveness of pharmacogenomics in predicting short-term antidepressant responses and suggested that the prediction of treatment outcomes may depend on background factors that cannot be captured by machine learning algorithms.

Multimodal data

In addition to collection methods of single data, multimodal datasets are increasingly used in psychiatry, such as the use of clinical scale evaluation and resting-state functional magnetic resonance imaging (MRI) to establish a prediction model of mood disorders, anxiety, and anhedonia[45], as well as a machine learning framework based on multimodal neuropsychiatric data to predict the responses of patients with schizophrenia to treatment[86]. Chen *et al*[87] conducted a comprehensive review of the practice of machine learning combined with neuroimaging in psychiatry, which emphasized the importance of multimodal data and the extraction of multimedia information. Data were collected through a combination of electronic questionnaires, standard clinical care record reviews, and device output analysis[88]. Although this statistical method integrating multimodal data demonstrates advantages over the general methods of single data, it is usually prone to overfitting and poor generalization[89]. The method of how to avoid these problems should be further explored in the future.

CHALLENGES OF COMPUTATIONAL PSYCHIATRY

The building of an AI ecosystem for computational psychiatry currently faces multiple challenges, which can be broadly divided into three categories: technical factors, cost and context, and ethical challenges. In this section, each challenge is explained separately.

Technical factors

It is important to note that computational psychiatry is still in its early stages, and there are many challenges that must be overcome. The most fundamental challenge is technical difficulty. Examples include data availability and quality, data transparency[90], technology openness, and professional integration. The quality of the raw data and the details of the processing are directly related to the interpretation of the results. One primary way to address this challenge is to increase collaboration with experts in other fields, such as computer science and engineering. By combining their expertise, researchers can develop new algorithms and tools to better handle the complex datasets associated with mental health research. Automation, rigor, and standardization of treatment methods[16] is another manner to advance the field of computational psychiatry, which can help to ensure that the results of computational research are replicable and can be generalized to a wider population. Due to the fact that "data-driven" research is based on the analysis and application of data, the transparent presentation of data results without bias and selectivity is the norm that researchers must follow. In response, there is a need to develop an interpretable, transparent, and universally applicable scientific review framework [91] to ensure the feasibility of using AI in psychiatry. Although the rapid development of artificial intelligence approaches has made up for the shortcomings of traditional mental illness research methods, thus identifying increasingly more information related to brain function, it must be stated that mental illness researchers and clinicians know very little about computational technology methods[92, 93]. It is recommended that there should be improvements in the computational literacy of neuroscientists and mental health professionals[94] while also leveraging the talent development role of higher education to bring more people with cross-disciplinary professional backgrounds into the field. Another note about computational psychiatry is the importance of ensuring that the field remains accessible and inclusive. As computing becomes more widely used in mental health research, it is important that these technologies are not just reserved for the best-funded or best-known researchers. Instead, an open and inclusive approach should be taken to provide researchers from diverse backgrounds and institutions with the tools and resources that are needed to conduct computational psychiatry research. It is also important for researchers to engage with policy-makers and advocacy groups[95] to ensure that findings from computational psychiatry are translated into practical applications.

Costs and different theoretical backgrounds

The costs mentioned in this section include time costs[18] and labor costs, which are uncontrollable factors that should be considered in clinical modeling. Due to the wide range of projects contained in the ecosystem, the system operation needs to be repeatedly monitored, evaluated, adjusted, and optimized, thus requiring a large amount of time. Moreover, there are many participating roles in each link, and there are cost consumption problems in coordination and communication management. For example, a team of clinicians may accept social and institutional pressures, and there may be conflicts between experienced mature doctors and novice decision-makers. The intersection and unification of viewpoints under different theoretical backgrounds in interdisciplinary cooperation also require coordination and compromise. Second, the reasonable match between professional salary structure and working style will also affect the clinical practice effects. In addition to the abovementioned overt factors, some individuals have raised concerns about the use of computational techniques in studies of mental health conditions, wherein they have argued that these methods may oversimplify complex phenomena and ignore important environment-specific factors. We also need to consider whether the modeling state of computational psychiatry follows the natural trajectory of core neurobiology[3] and whether computational psychiatry is detached from the developmental background of the field of psychiatry. When we

discuss the development of psychiatry with sophisticated AI approaches, we must not lose sight of the core purpose of disease treatment.

Ethical challenge

In addition, there are ethical issues with the use of computing in mental health research[96,97]. The application of AI to psychiatry needs to consider AI ethical issues, including respecting patient autonomy by providing adequate consent[70,98], data ownership, the ignoring of conscious experience, privacy protection[99], and equity[100]. An ethically acceptable manner[101,102] is an obstacle to the transformation of computational psychiatry from theory to practice. Some researchers have argued that the use of these techniques can lead to biased or discriminatory results, especially if the algorithm is not properly trained or verified. In the practice of treating and predicting mental illness, we call upon researchers and health care professionals to approach patients with rigorous optimism concerning the principles of kindness[103], harmfulness, respect for autonomy and justice[42], and prevention of ethical issues from the aspects of communication, consent, and contrast[104]. According to four basic ethical principles (respect, no harm, benefit, and justice), researchers should fully respect the independent will of data providers when collecting and using data, as well as pay attention to the protection of their personal privacy and process data anonymously. In addition, the participants' rights and interests should be the first priority. Justice and fairness should be adhered to. Moreover, informed consent should be obtained, and the process should be open and fair. Although we are aware that computational AI approaches (such as machine learning) can have a profound impact in psychiatry, there are still no applications that constitute standard clinical practice. The early consideration of these ethical challenges and the establishment of standards and requirements to eventually allow for the early use of the benefits of AI for mental health care should be enacted. Despite these concerns, we remain convinced that the potential benefits of computational psychiatry far outweigh the risks[105]. By properly using AI to study mental health conditions, researchers can gain a more comprehensive and nuanced understanding of mental illness, which could ultimately lead to better treatments.

LIMITATIONS

There were several limitations to this study. First, all of the relevant literature that was analyzed in this paper is in English and does not cover studies in other languages (such as Chinese, Korean, Japanese, and German). Thus, the coverage of the research may still be insufficient. Second, this paper is only a summary of the research in related fields, which cannot be applied to clinical treatment. This review only collates extensive research on data sources, tools, and model frameworks in computational psychiatry and does not use explicit methods, such as systematic reviews, nor does it address substantive clinical outcomes.

CONCLUSION

This paper builds an artificial intelligence ecosystem for computational psychiatry by reviewing the literature, including the following four stages: data acquisition, preparation for modeling, model building, and application evaluation. In terms of data acquisition, we discussed different data acquisition methods and data forms and summarized single data source methods, such as scale, open data, language, and physiological signals, as well as multimodal data statistical methods combining different types of data. In terms of preparation for modeling, we explored constraints from both the clinician and algorithm engineer industry norms and emphasized the importance of data preprocessing and quality testing. For model building, we proposed two steps of normative modeling (initial model training and model modification) and discussed supervised learning and unsupervised virtual seats in machine learning. Finally, based on the relevant theory and experience, we prospectively assessed the aspect of application evaluation and clarified the complexity and necessity of model performance evaluation and post analysis.

In conclusion, computational psychiatry is a promising field that has the potential to revolutionize our understanding and treatment of mental health conditions. In recent years, research on computational psychiatry has produced many good results. For example, it has made profound theoretical breakthroughs in the integration of computer science, biology, psychiatry, statistics, and other disciplines. In addition, it has allowed for the performance of more in-depth research in the use of computing and mathematical techniques to explain mental diseases and has made many attempts and modifications in data collection, model construction, and other aspects. It is worth mentioning that this field has accumulated a rich amount of data, with data originating from traditional clinical scale evaluations to the application of big data, from language to EEG, and from a single dataset to multimodal data, which provides a solid foundation for future clinical practice.

However, it should not be ignored that computational psychiatry is still in its early stages and experiences of technical challenges, such as data quality and tool openness, cost issues (such as role conflict and development cycle), and ethical challenges (such as data privacy, respect, and equity). More work will need to be performed to realize its full potential to ensure that existing discoveries are eventually translated into clinical applications. Specifically, the need for an artificial intelligence ecosystem for computational psychiatry can help researchers clarify their work, build on it, further develop better algorithms and techniques to analyze complex datasets, establish more rigorous and standardized experimental methods, and collaborate with policy-makers and advocacy groups to ensure that the findings of computational psychiatry are translated into practical applications. When considering that the use of artificial intelligence needs to experience a series of ethical problems caused by computing technology, the establishment of relevant application standards and moral guidelines should be emphasized in the future. Moreover, future research should focus on the integration of computational psychiatry with other disciplines, such as psychology, neuroscience, and genetics. By combining multidisciplinary and multidisciplinary expertise, researchers can gain a more comprehensive understanding of the crux of mental illness and develop more effective treatments and interventions.

FOOTNOTES

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MINIREVIEWS

Lipocalin-2 as a biomarker for diabetic nephropathy

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Abstract

Diabetes is a major global public health issue. The prevalence of type 1 diabetes is comparatively static, as hereditary and genetic causes are involved, while type 2 diabetes (T2D) prevalence is increasing day by day. T2D is associated with chronic complications, including diabetic neuropathy (DN), nephropathy, retinopathy, and other complications like diabetic foot. DN is the main complication of both types of diabetes. DN can be diagnosed by routine laboratory tests, microalbuminuria > 300 mg/24 h, and a gradual decrease in glomerular filtration rate. As the appearance of microalbuminuria is a late manifestation, an early marker for renal damage is needed. Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin (NGAL), is a small protein purified from neutrophil granules and a good marker for kidney disease. NGAL is a transporter protein responsible for many physiological processes, such as inflammation, generation of the immune response, and metabolic homeostasis. NGAL has been reported to depict the early changes in renal damage when urine microalbumin is still undetecable. Therefore, elucidating the role of NGAL in detecting DN and understanding its mechanism can help establish it as a potential early marker for DN.

Key Words: Type 1 diabetes; Type 2 diabetes; Diabetic nephropathy; Lipocalin-2; Early biomarkers for kidney disease; Acute kidney injury

Core Tip: Diabetic nephropathy (DN) is a chronic complication of diabetes. The mainstay markers for kidney injury are a gradual decrease in glomerular filtration rate and microalbuminuria. Microalbuminuria appears late in DN; thus, new biomarkers are required. Different researchers highlighted the role of lipocalin-2 (NGAL) in the early detection of nephropathy before the appearance of microalbumin in urine. In this review, we briefly describe the role of NGAL in various diseases and cancers and detail its role as an early biomarker in DN.

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INTRODUCTION

Diabetic nephropathy (DN) is a chronic complication of diabetes, and it affects more than 40% of both type 1 diabetes (T1D) and type 2 diabetes (T2D) cases and may lead to end-stage renal disease as reported worldwide. DN can be diagnosed clinically based on a gradual decrease in glomerular filtration rate (GFR) and an increase in urine albumin > 300 mg/24 h, which is shown to be associated with cardiovascular complications. An early diagnostic and prognostic marker is still needed to detect DN early for better treatment outcomes and predictive value[1,2].

The current diagnostic markers for DN, *i.e.*, microalbuminuria and serum creatinine levels, have questionable reliability even when specific indicators like creatinine clearance or ratio of creatinine and albumin in 24-hour urine samples are used. Microalbuminuria can be associated with other physiological and pathological conditions such as exercise, diet, infections, and dehydration[3]. Serum creatinine levels vary according to age, gender, hydration, muscle mass, and kidney conditions, and are often elevated later in advancing disease processes. Therefore, the reliability of these markers in early renal damage detection is questionable[4-10].

SELECTION OF A RENAL BIOMARKER

The characteristics of a biomarker shall be considered to determine its usefulness. Its measurement should be easy and accurate, and results should be reproducible. It should also indicate an early renal injury, and the response to the treatment, cost-effectiveness, and availability should be taken into account. It should be able to be applied to a large population and augment the disease's clinical diagnosis and prognosis[11].

The commonly used markers for acute kidney injury (AKI) and renal dysfunctions are plenty, which may be extrapolated to DN. The biomarkers for oxidative stress include 8-hydroxy-2'-deoxyguanine (8-OHdG) as a novel but controversial marker for DNA damage; pentosidine, 2,4-dinitrophenylhydrazine, and advanced oxidation protein products for protein injury; and F2-α prostaglandin and 4-hydroxy-2-nonenal for lipid injury. The glutathione-s-transferase, an enzyme-like protein, is a marker for the glutathione antioxidant system. Some other biomarkers of inflammation, like cytokines and a variety of chemokines, are essential biomarkers for AKI and kidney dysfunction and include interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interferon-inducible protein-10 (IP-10). The renin-angiotensin-aldosterone system biomarkers are also used as kidney injury markers[12-14].

Biomarkers for damage to glomerular filtration membranes include urinary mRNA levels of podocin, synaptopodin, and nephrin. The levels of basement membrane injury markers like type IV collagen are substantially higher before microalbuminuria and and serum creatinine abnormality appear[15,16]. The biomarkers for endothelial cell injury, like vascular endothelial growth factor, von Willebrand factor (vWF), and intercellular adhesion molecule-1(ICAM-1), are found raised in patients with DN[17-20]. The biomarkers for mesangial expansion and fibrosis are also crucial, as DN is seen with extracellular matrix alterations and mesangial expansion, *e.g.*, transforming growth factor-β1 (TGF-β1) and pigment epithelial-derived factor[21,22]. The alteration of renal function is associated with glomerular and renal tubular dysfunction[23]. Transferrin, ceruloplasmin, and immunoglobulin G are early biomarkers for glomerular dysfunction. The renal tubular dysfunction markers include α-1 microglobulin, retinol-binding protein 4, lipocalin-2, N-acetyl-β-D-glucosidase, kidney injury molecule-1, and heart-type fatty acid binding protein[24-27].

Lipocalin-2

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a small protein purified from neutrophil granules and is considered a good marker for AKI and kidney disease. It belongs to the lipocalin family and is encoded by the lipocalin-2 (LCN2) gene on chromosome 9[28-30]. NGAL is a transporter protein responsible for many physiological processes, such as inflammation, the generation of an immune response, and metabolic homeostasis. Several studies have reported the role of lipocalin-2 in renal diseases, suggesting its role as a novel biomarker for acute renal injury and chronic kidney disorders. A few studies have also demonstrated its inverse relation with serum creatinine in T1D and T2D, although albuminuria was undetectable in these patients. In patients with DN, NGAL levels were significantly higher in serum and urine, which correlated with the estimated glomerular filtration rate (eGFR) inversely (Figure 1). However, these patients did not have albuminuria, implicating the potential role of NGAL as a diagnostic biomarker for DN[29-33].

EXPRESSION OF NGAL IN BODY TISSUES

NGAL is expressed in several body tissues, including the kidney, liver, lungs, trachea, small intestine, bone marrow, prostate, non-neoplastic breast tissue, macrophages, and fat tissues. Expression of NGAL is seen in fetal skin in the epidermis as early as the 20th week of intrauterine life and later concentrated around hair follicles only[32,34].

The normal concentration of NGAL in serum averages 20 ng/mL, while in urine also, it is 20 ng/mL. Its low molecular weight and positive charge make it undergo filtration, so renal clearance is seen as the primary regulator of the concentration of NGAL[35,36].

FUNCTIONS OF NGAL

As part of transport proteins, lipocalin-2 is also seen in many physiological conditions of the body involved in the innate immune response. It is generated through neutrophil degranulation and thus, released at the site of bacterial infection for bacterial sequestration. Iron transport is another role of NGAL as it is accumulated in the cytoplasm, and iron-responsive genes are stimulated in response to this increased concentration. Apo-NGAL is responsible for transporting chelated iron from the inside to the extracellular matrix. Apo-NGAL binds to the 24p3 receptor and internalizes to bind with the cellular siderophore, thus transporting it out of the cell. It signalizes the apoptotic cascade to start due to the expression of the pro-apoptotic protein Bim. The initiation of programmed cell death, whether under normal or abnormal circumstances, depends on the Bim protein. Its activation is precisely regulated at various levels to ensure its proper functioning. Bim is essential in preventing autoimmunity during normal immune responses; however, excessive activation can lead to chronic inflammation and tumor development. In nerve cells, the overexpression of Bim can result in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. On the other hand, cancer cells typically inhibit Bim expression from facilitating their proliferation and metastasis[29,37-44].

NGAL AND RENAL DAMAGE

The low molecular weight of NGAL makes it easily filterable through the glomerulus and later reabsorbed in the proximal tubules. If renal tubular damage starts, the reabsorption changes, and thus, excretion of NGAL starts early; epithelial damage thus results in increased NGAL concentration in serum and urine[45].

OVEREXPRESSION OF NGAL IN OTHER DISEASES

Several inflammatory and metabolic disorders are seen with altered concentrations of NGAL. Inflammatory conditions like pancreatitis, meningitis, psoriasis, and myocarditis are seen with increased NGAL expression. In certain autoimmune diseases like psoriasis, NGAL mRNA levels were found raised ten times or more. NGAL levels have been reported to be considerably higher in viral infective diseases but markedly lower in human immunodeficiency virus-infected patients who were not receiving therapy than in healthy controls[46,47]. Higher levels of NGAL were found to be associated with anemia independent of eGFR and other parameters like myeloperoxidase and high-sensitivity C-reactive protein[36].

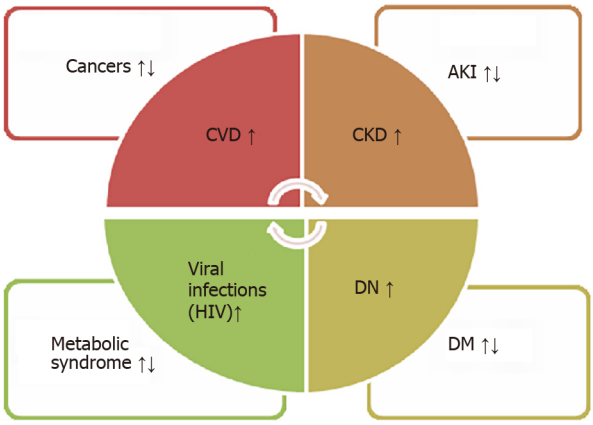

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Figure 1 Alteration of lipocalin-2 levels in different diseases. Lipocalin-2 levels increase in all except a few cancers where its levels are found to decrease. AKI: Acute kidney injury; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DM: Diabetes mellitus.

NGAL IN CANCERS

The possible role of NGAL in various cancer models has been studied and is suggested to be both beneficial and detrimental. The nuclear factor kappa B (NF-κB) signaling pathway regulates the transcription of NGAL, and the mitogen-activated protein kinase (MAPK) pathway may cooperate with NF-κB to upregulate the expression of NGAL. Moreover, epigenetic modifications might significantly initiate NGAL expression in tumor cells[28,48-56]. It may explain the increased levels of NGAL in most cancers. It remains to identify the specific molecular forms of NGAL (in serums and cells) associated with a particular cancer type (solid or liquid)[48]. Functionally, NGAL appears to exhibit all the significant events of tumorigenesis, including tumor proliferation, tumor cell survival, distant migration, local invasion, tumor angiogenesis, and resistance to anti-cancer drugs[57]. NGAL protein and mRNA levels are quantitatively measured in body fluids like blood, urine, and tissues and found overexpressed in various cancers like ovarian, endometrial, bladder, liver, breast, brain, lung, pancreatic, colorectal, and several other solid tumors[48-50,54]. The NGAL complex may help assess tumor stage in endometrial cancers before surgical treatment. The NGAL complex is found in blood tumor cells in patients with different types of leukemia[55,58-60].

METABOLIC DISORDERS AND NGAL

In metabolic diseases, including obesity, kidney disorders, and pre-eclamptic subjects, NGAL levels were significantly higher in animal models and obese human subjects[61-63]. T2D is characterized by inflammatory processes in the whole body, resulting in endothelial dysfunction. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as chemokines and adhesion molecules, have been shown to contribute to vascular complications in T2D. In T1D, an early predictive role of NGAL as a biomarker for nephropathy and incipient cardiovascular morbidity before and independent of microalbuminuria has been observed[6].

NGAL IN DN

The plasma NGAL (pNGAL) is filtered by the glomerulus and can be almost reabsorbed in the proximal tubules. The chance of detection of urinary NGAL (uNGAL) and pNGAL in animal and human subjects with renal injury has led to evaluating NGAL as an early noninvasive biomarker in human acute and chronic kidney injury in numerous research studies. Lipocalin-2 is, therefore, one of the most promising early, next-generation biomarkers for AKI. Glomerular basement thickening and mesangial expansion have been reported in several studies. The pathogenesis of DN is associated with glomerular and renal tubular interstitial injury. The primary mechanism of NGAL clearance from the blood is *via* megalin-dependent endocytosis in the proximal tubules of the kidney. Therefore, urinary excretion of NGAL is only expected when there is proximal renal tubular injury which prevents NGAL reabsorption or increased *de novo* NGAL synthesis. The NGAL protein secreted into the urine from the distal nephron segments is predominantly monomeric and differs from the dimeric NGAL originating from neutrophils. The overexpression of NGAL in the distal tubules and its rapid secretion into the urinary tract align with its role as an antimicrobial strategy. Furthermore, recent evidence suggests that NGAL

may also promote cell survival and proliferation, given the documented apoptotic cell death in distal nephron segments in various animal and human models of AKI[6,28,62]

Various proteomic and transcriptomic studies have identified NGAL as one of the most upregulated genes (LCN2 gene) and one of the most highly induced proteins in the kidney very early in the course of acute kidney disease in animal as well as human models[63,64]. NGAL is a novel marker for the diagnosis of DN. It is a marker for kidney injury or any other condition affecting the functions of the kidneys. Early diagnosis of AKI is often challenging and complicated, as suitable early markers for renal damage and kidney function are scarce. NGAL, being an early marker of AKI, overcomes such limitations and seems to demonstrate its role in the diagnosis at an early stage[65,66].

Various studies have reported increased urinary and serum levels of NGAL in AKI. NGAL as an early biomarker to diagnose DN, even earlier to incipient nephropathy, can be seen as a tubular injury marker. Both pNGAL and uNGAL can predict early tubular damage and can be used as a noninvasive tool for diagnosing, staging, and monitoring progressing DN[67]. Subclinical and early kidney injury can be seen in children with T1D with normal renal function. The pNGAL and uNGAL derangement, low-range albuminuria, and normal eGFR can indicate early kidney injury even in optimal glycaemic control. pNGAL and uNGAL in these changes result from tubular injury[68].

In non-terminal chronic kidney disease, NGAL can be used as a novel, independent renal predictor of CKD progression along with the severity of the renal disease. The urinary NGAL can be used as a marker for the early detection of DN, and its mean value has been observed to correlate with the degree of renal impairment. The parallel elevation in uNGAL with disease severity or with increasing stages of CKD supports the hypothesis of active tubular production, excluding a passive consequence of reduced renal clearance capacity. Urinary NGAL has been reported to correlate positively with urine albumin/creatinine ratio, duration of diabetes, hemoglobin A1C, and dyslipidemia. As the positive urine NGAL results were found even in normoalbuminuric patients, uNGAL can be used as an early biomarker for DN in normoalbuminuric patients, especially those with long-standing and uncontrolled diabetes[28,69-72]. Urinary NGAL levels may help monitor the status and treatment of diverse renal diseases reflecting defects in the glomerular filtration barrier, proximal tubule reabsorption, and distal nephrons[34].

It was appreciated that uNGAL is produced in response to ischemia, toxins, or inflammation in the tubular epithelial cells. For each 300 ng/mL increase in uNGAL, an increased risk for the resultant outcome of CKD (due to T1D and T2D) progression, end-stage kidney disease, or death in CKD patients is seen. Urinary NGAL of the microalbuminuric group increased way higher than the normoalbuminuric group[73-75].

The plasma levels of NGAL and IGFBP4 have been appreciated to be higher in patients with DN. Regular follow-up and monitoring before the symptomatic presentation of DN can be carried out with serial monitoring of uNGAL levels, but defining the baseline concentration of NGAL in patients is required[76-78].

The uNGAL may be a more specific marker of active renal tubular epithelial damage and tubulointerstitial inflammation, whereas pNGAL may be more indicative of the renal (and possibly extra-renal) vasculature state, including glomerular filtration ability. Increased level of NGAL as an endogenous filtration biomarker in type 2 diabetic patients is considered a predictive biomarker for early detection of DN. The uNGAL was found to be higher in patients with microalbuminuria than normoalbuminuria, especially in those with long-standing, uncontrolled diabetes and dyslipidemia[79-82]. The serum NGAL (sNGAL) showed an excellent diagnostic value comparable to uNGAL[83].

Urinary NGAL has a positive association with microalbuminuria and can be a noninvasive tool for diagnosing and monitoring the progression of DN. Urinary NGAL measurement is more sensitive than microalbumin, detecting early renal involvement in patients with diabetes mellitus. The uNGAL and creatinine ratio (uNCR) might prove promising in identifying cases with a high clinical suspicion of diabetic kidney disease and in patients with confirmatory biopsy. T2D patients with increased uNCR may have worse outcomes and higher chances of DN complications. However, pNGAL rises markedly with the reduction in GFR, resulting in many false positive inclusions of AKI in chronic patients. So along with eGFR, the uNGAL and plasma brain natriuretic peptide should be used in chronic kidney disease patients to assess AKI[69,84,85].

The increase in uNGAL and cystatin-C levels was directly proportional to microalbuminuria in diabetic patients. T2D patients with early DN had high uNGAL and cystatin-C levels. NGAL reflects tubular damage, and nitric oxide may be used as an angiogenic and oxidative stress marker. Using specific biomarkers along with NGAL can increase its diagnostic efficacy in differentiating renal causes from other clinical conditions[85-88]. uNGAL may be a more specific marker for active renal tubular epithelial damage and tubulointerstitial inflammation, whereas pNGAL may be more indicative of the renal (and possibly extra-renal) vasculature state, including glomerular filtration ability[89].

However, some studies have shown that exosomal-NGAL (NGAL-E) is a better marker than free-NGAL in T1D. NGAL was present in subjects' urinary enriched extracellular vesicle fraction (NGAL-E); however, NGAL-E did not correlate with glycated hemoglobin and albumin/creatinine ratio in the early stages[90].

NGAL was readily detected in the urine after anti-neoplastic drug administration in a dose- and duration-dependent manner. By comparison, uNGAL excretion following cisplatin administration was quantified within 96 h of drug administration so that it can be used as an early marker of kidney injury

in cancer subjects very early, showing its efficacy as an early marker in other pathologies leading to renal dysfunction[91,92].

A metanalytical study also concluded that NGAL is a potential diagnostic marker for patients with DN and that its diagnostic value for microalbuminuria and macroalbuminuria is superior to that for microalbuminuria alone[93]. Several studies collectively and strongly support using NGAL as a biomarker for predicting AKI. However, the lack of published studies that adhere to diagnostic study guidelines, heterogeneity in AKI definition, the lack of uniformly applicable cut-off values, and variability in the performance of commercially available NGAL assays are big challenges to establish its role concretely[94]. The specificity and sensitivity of NGAL were found to be moderate to excellent in various studies in various conditions, including indoor and outdoor patients, as a good predictor of AKI [10,63,95-98]. Although some limitations are reported, NGAL (sNGAL and uNGAL) can be prognostic of renal damage even in the case of subclinical or modest renal damage that can only be diagnosed by creatinine studies late in the course of the disease[99].

CONCLUSION

The studies reported in the present review describe the role of NGAL in nephropathy, particularly DN. Early detection of renal changes is vital for diagnostic and prognostic purposes. NGAL is an important renal dysfunction marker. Although its role in other conditions like infections, metabolic disorders, and cancers is already established, its function in nephropathy is also promising, as it increases significantly before other usual markers appear in the urine and blood.

FOOTNOTES

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MINIREVIEWS

Dehydroepiandrosterone sulfate supplementation in health and diseases

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Abstract

Dehydroepiandrosterone sulfate (DHEAS) is a hormone produced by the zona reticularis of the adrenal gland and the ovaries. Initially considered as an inert compound merely serving as an intermediate in the conversion of cholesterol to androgens, interest in DHEA began to grow in the 1960s when it was found that DHEAS is the most abundant steroid hormone in human plasma and that its levels decline with age. In many countries, DHEA is considered a nutritional supplement. It has been used for a multitude of conditions which include sexual dysfunction, infertility, genitourinary syndrome of menopause, musculoskeletal disorders, cardiovascular diseases, ageing, neurological diseases, autoimmune conditions, adrenal insufficiency, and anorexia nervosa. We describe an overview of the historical evolution of DHEA, its physiology, and the disease states where it has been evaluated as a supplement.

Key Words: Dehydroepiandrosterone; Adrenal; Health supplements; Hypothyroidism; Autoimmunity; Depression; Cardiovascular disease

Core Tip: In this review we discuss the current evidence for the nutraceutical utility of dehydroepiandrosterone sulfate (DHEAS). Initially regarded as a panacea for a multitude of human diseases, studies conducted with DHEA supplementation have yielded largely inconclusive results, with the possible exception as an alternative agent in adrenal insufficiency patients with low energy and low libido (in affected females), and genitourinary syndrome of menopause (vaginal preparation). However, with its easy availability as a relatively inexpensive over-the-counter supplement in many countries, DHEA, like vitamin D, has continued to evoke curiosity in the scientific community. Hence, the subject of DHEA supplementation requires a pragmatic approach, backed by robust evidence, with careful weighing of potential benefits (or lack thereof) and possible adverse effects.

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INTRODUCTION

Dehydroepiandrosterone (DHEA) was first isolated and characterized by Adolf Butenandt in 1934, and he was subsequently awarded the Nobel Prize in 1939 for his "work on sex hormones". The sulfated form of DHEA, dehydroepiandrosterone sulfate (DHEAS), was then isolated in 1944 by Munson, Gallagher, and Koch in 1944[1]. The hormone was named dehydroepiandrostenedione by Lieberman in 1949[1].

In the 1980s, despite a lack of human studies and information on its function, efficacy, and safety, DHEA began to be marketed as a non-prescription drug in the United States (US) for multiple indications such as anti-ageing, anti-cancer, and anti-obesity. It gained limelight as a "super hormone" and an "anti-ageing" wonder drug which led to multiple studies around its use in various conditions.

Soon thereafter in 1985, the US FDA predictably banned over-the-counter sales of DHEA considering the lack of health benefits and long-term safety data. However, in 1994, DHEA was re-introduced in the market with the dietary supplement health and education act, which allowed certain substances to be marketed as dietary supplements not requiring FDA approval. Marketing as a cure-all elixir and the lack of regulation led to skyrocketing production of DHEA and it became easily available as an over-the-counter supplement. However, research around the hormone has made rapid strides ever since with implications for the diagnosis and treatment of a host of human diseases (Table 1).

SEARCH STRATEGY

The following databases were used to identify the relevant studies: PubMed/Medline, Scopus, and Cochrane. We also applied Reference Citation Analysis (RCA) to further enhance our search results. All the databases were searched from their inception till December 10, 2022. We did a search again and the search was extended up till February 7, 2023 to look for any additional articles. Keywords used were mainly related to the topics of interest, including "DHEA," "adrenal insufficiency"," menopause"," autoimmunity", "immunity", "cognition", "infertility", "sexual function", "genitourinary", "anorexia", "bone", "muscle", "musculoskeletal" "systemic lupus erythematosus" or "SLE", "schizophrenia", "depression", "cardiovascular disease", "rheumatoid arthritis", and "hypothyroidism".

There was no restriction for study design and language (where English language translation was available). All articles related to DHEA supplementation were reviewed and relevant articles were considered for inclusion in this scoping review.

NORMAL PHYSIOLOGY

About 75%-90% of DHEA is produced by the zona reticularis of the adrenal gland while the rest is produced in the ovaries and the brain. Its sulfated form, DHEAS, is exclusively synthesized by the adrenals. DHEA has a shorter half-life and is secreted in a pulsatile manner, mirroring the circadian rhythm of corticotrophin. In contrast, DHEAS has a longer half-life and relatively more stable levels across the day, providing a continuous reservoir of DHEA.

DHEA and DHEAS start increasing in boys and girls around the age of six to eight years, and this increase in adrenal androgens is known as adrenarche and the concomitant clinical appearance of pubic hair is known as pubarche. The levels rise steadily and peak in the second to third decade of life.

Table 1 Proposed therapeutic indications of dehydroepiandrosterone

Indication	Current evidence
Sexual dysfunction	Equivocal[6]
Infertility	Equivocal[13]
Genitourinary symptoms (alternative agent)	Positive[7,9]
Peri-menopausal and menopausal women	Equivocal[5]
Adrenal insufficiency (alternative agent)	Positive[17]
Anorexia nervosa	Equivocal[19]
Autoimmune diseases	Equivocal[24,27]
Musculoskeletal	Equivocal[43]
Neuropsychiatric diseases	Equivocal[48]
Anti-ageing agent	Negative[35,36]
Cardiovascular disorders	Equivocal[54,55]

Thereafter there is a progressive decline by around 2%-5% each year with advancing age, such that levels decrease by 80%-90% in the eighth to ninth decade of life[2].

The exact mechanism of action of DHEA remains uncertain with some evidence suggesting that it has pleiotropic effects. As DHEA has minor steroidogenic activity, it acts predominantly by conversion to androgens and estrogens in peripheral target tissues (Figure 1). It also functions as a neurosteroid and acts *via* receptors for N methyl-D aspartate receptors (NMDA) and gamma amino butyric acid alpha (GABAα), peroxisome proliferator-activated receptor α (PPARα), or receptors for pregnane X, androstanol, and estrogen receptor β[3].

DHEA IN DISEASE STATES

DHEA and sexual dysfunction

Serum levels of DHEA and DHEAS start declining from the third decade, leading to decreased androgen levels. In a randomized, double-blind, placebo-controlled trial by Panjari *et al*[4], 93 post-menopausal women with low libido were included and the effect of DHEA on sexual function was assessed. They observed that there was no significant improvement in sexual function with regard to the primary outcome measures which included the change in total satisfying sexual events and the Sabbatsberg Sexual Self-Rating Scale total score. There was no significant change in secondary outcome measures as well, which included measures of well-being and quality of life.

In a systematic review and meta-analysis of 28 studies of DHEA therapy in 1273 post-menopausal women, DHEA therapy did not improve sexual function, quality of life, or menopausal symptoms and was associated with androgenic side effects[5]. It is to be noted that these studies had a duration less than 3 mo. Also, oral DHEA was used in all of these, and there are no studies on local DHEA (*see below*). Currently, the endocrine society guidelines recommend against the use of DHEA for sexual dysfunction and other related indications because of a lack of long-term safety efficacy data[6].

Genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM), a term first introduced in 2014, is a relatively common entity with a prevalence ranging from 27% to 82%. It encompasses symptoms ranging from vulvovaginal dryness and dyspareunia to urinary urgency and dysuria, and leads to significant impairment in quality of life and sexual function. In a randomized prospective double-blind placebo-controlled trial by Labrie *et al*[7], the efficacy of 0.5% intravaginal DHEA in women with GSM was assessed. They observed that vaginal DHEA (Prasterone) significantly relieved dyspareunia with improvement in vaginal secretions and epithelial integrity. Prasterone was first approved by the FDA in 2016 for the treatment of dyspareunia due to GSM[8]. Recent guidelines suggest vaginal DHEA as an alternative agent in individuals with GSM symptoms after the initial use of non-hormonal agents[9].

DHEA and infertility

DHEA has been found to improve ovarian steroidogenesis and also leads to an increase in IGF-1 which is speculated to have a favorable effect on oocyte quality and follicular development[10,11]. In a randomized prospective study by Wiser *et al*[12], they enrolled 33 women with poor ovarian reserve (17 in the DHEA group and 16 in the control group) and observed the effects of DHEA supplementation on

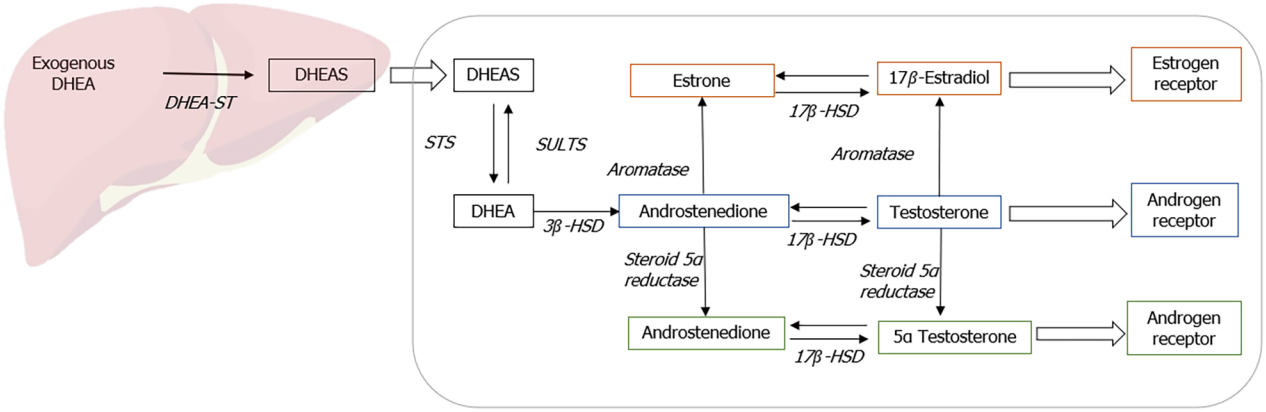

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Figure 1 Metabolism of exogenously administered dehydroepiandrosterone. DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; DHEA-ST: Dehydroepiandrosterone-sulphotransferase; HSD: Hydroxysteroid dehydrogenase; STS: Steryl-suplhatase; SULTS: Sulphotransferases.

in vitro fertilization. Patients in the DHEA group had a significantly higher live birth rate as compared to controls. In a meta-analysis by Qin *et al*[13], they included nine studies and observed that clinical pregnancy rates were significantly increased in women with diminished ovarian reserve supplemented with DHEA. However, when the analysis was restricted to randomized control trials, there was no significant difference in pregnancy rates. In a recent meta-analysis by Schwarze *et al*[14], they included five studies with a total of 910 individuals with diminished ovarian reserve, of which 413 received DHEA. They observed that DHEA supplementation was associated with significantly improved pregnancy rates and decreased abortion frequency. There was no effect on the number of oocytes retrieved. Hence, the results have been largely conflicting and it is difficult to draw any conclusions as the definitions for diminished ovarian reserve, stimulation protocols used, and dosing and duration of DHEA varied notably between studies. Taken together, it implies that DHEA may have a role in the peri-implantation period but have less impact on ovulation induction/ooscytes retrieval. Future randomised controlled trials planned with primary endpoints of implantation success in such group of subjects, may yield a favorable role for DHEA supplementation.

DHEA in adrenal insufficiency

Adrenal insufficiency is associated with reduced androgen levels which have been suggested to have multiple effects including loss of libido, reduced energy, and consequently decreased quality of life despite optimal glucocorticoid replacement. DHEA therapy has been suggested as a potential therapy to mitigate these effects. In a randomized double-blind placebo-controlled study by Binder *et al*[15], they included 23 young women with secondary hypoadrenalism and observed significant improvements in pubic hair growth and psychological well-being. In a subsequent meta-analysis by Alkatib *et al*[16] which included 10 studies in women with either primary or secondary adrenal insufficiency, DHEA supplementation lead to minor improvements in quality of life. However, there was no effect on sexual function or anxiety. Currently, the guidelines suggest that DHEA replacement (25–50 mg as a single oral dose in the morning) may be considered in individuals with low energy and in women with reduced libido despite optimized glucocorticoid and mineralocorticoid replacement[17]. Monitoring is done by clinical and biochemical markers such as measurement of DHEAS, testosterone, androstenedione, and sex hormone-binding globulin (SHBG) 24 h after the last DHEA dose. If the patient fails to report a sustained, beneficial effect of replacement after 6 mo, the treatment should be discontinued.

DHEA in anorexia nervosa

DHEA levels have also been implicated to play a role in low bone mass in anorexia nervosa. In a randomized control trial by Gordon *et al*[18] which compared the effects of DHEA *vs* conventional hormone replacement therapy in young women with anorexia nervosa, they observed that while hip bone mineral density (BMD) increased significantly with both therapies, DHEA therapy was associated with increased bone formation markers. DHEA therapy in addition was associated with significant improvement in psychological parameters. However, in a recent systematic review and meta-analysis, DHEA treatment was not found to be associated with improvement in BMD compared with placebo after adjustment for weight gain[19]. Therefore, while DHEA does play a role in the bone pathology in anorexia nervosa, evidence with treatment remains sparse and further randomized trials are needed.

DHEAS in autoimmune diseases

DHEA has been found to modulate inflammatory responses by blunting the production of pro-inflammatory cytokines, downregulating complement activation *via* the generation of C1 inhibitor, and

enhancing T-cell and NK cell cytotoxicity[20]. In accordance, DHEAS levels have also been found to be decreased in multiple autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hypothyroidism, fibromyalgia, and polymyalgia rheumatica[21-23].

In a randomized double-blind placebo-controlled study by Nordmark *et al*[24], they included 41 women with SLE on steroids and assessed the efficacy of DHEA supplementation. They observed significant improvement in some domains of health-related quality of outcome measures which included an improvement in mental health. There was also an improvement in sexual well-being while there was no improvement in other domains such as physical function, general health, or vitality.

Similarly, DHEA levels have also been found to be low in Sjogren's syndrome, which has been hypothesized as a potential cause of fatigue in these individuals. In a multicenter randomized controlled trial by Virkki *et al*[25], they included 107 individuals with primary Sjogren's syndrome and assessed the efficacy of DHEA administration on several measures of fatigue. They observed that DHEA supplementation at a dose of 50 mg significantly improved measures of fatigue but a similar improvement was observed with placebo as well. Their results were similar to an earlier study by Hartkamp *et al*[26], and hence the authors suggested cognitive behavioral interventions in these individuals. In autoimmune hypothyroidism, Shukla *et al*[27] investigated the relationship between DHEAS levels and arthralgias in individuals with primary hypothyroidism. They assessed 73 individuals with subclinical hypothyroidism and observed that DHEAS levels < 43.6 mcg/dL significantly predicted early rheumatoid changes in individuals with primary hypothyroidism. They postulated the inhibition of 11-β HSD1, a possible bystander effect due to hypothalamic-pituitary-axis suppression and its immunosuppressive effects as some of the mechanisms to explain the effects. Thus, there is some evidence to suggest a potential role of DHEA in multiple immunological diseases, and clinical interventions targeting this area merit further investigation.

Cognition

Ageing is associated with declining DHEA levels and deterioration in cognition. Several studies have explored the relationship of DHEA supplementation with cognitive outcomes. DHEA is synthesized in the brain and is the most abundant neurosteroid in humans. DHEA and DHEAS have multiple actions including neuroprotection, acting *via* AMPA and NMDA receptors, neuronal differentiation and apoptosis *via* tyrosine kinase receptors, inhibition of 11-β HSD1 activity, and anti-oxidant and anti-inflammatory actions[28,29]. In a study by Wolf *et al*[30], the authors studied the effect of DHEA supplementation on cognition in healthy elderly men and women. This was a double-blind placebo-controlled study and they observed that DHEA supplementation at a dose of 50 mg had no effect on cognitive abilities in these individuals. In a double-blind placebo-controlled study by Alhaj *et al*[31], they studied the effects of DHEA administration on episodic memory in 24 healthy young men and observed that DHEA was associated with both subjective and objective improvements in memory when given at a dose of 150 mg over a period of 7 d. In a Cochrane review by Grimley Evans *et al*[32] that included five trials, they observed that DHEA supplementation was not associated with any beneficial effects on cognitive outcomes in healthy individuals over 50 years of age. Subsequently, in a double-blind placebo-controlled cross-over study by Merritt *et al*[33], 50 mg of oral DHEA supplementation did not improve short-term memory in post-menopausal women. Hence, although DHEA does seem to play a role in cognitive function, there is little evidence to support its role as therapy for the same. Therefore, large-scale clinical studies are needed to assess whether DHEA could be used as a diagnostic and therapeutic tool for clinical implications.

Anti-ageing agent

Concomitant to its potential multiple actions on well-being, sexual function, and cognition, early interest in DHEA came about with it being promoted as the "fountain of youth hormone." In the DHEAge study by Baulieu and colleagues, they observed the effects of DHEA supplementation at 50 mg daily for a year in 280 older men and women (age 60-79, 140 each). While there was some improvement in some parameters such as sexual function in women over 70 years of age, BMD at the femoral neck, and skin indices, there was no difference in libido, BMD, or sexual function in men[34]. Moreover, there was no difference in body composition or muscle strength in women. Thereafter, in a double-blind randomized placebo-controlled study by Nair *et al*[35], they investigated the effects of DHEA administration in 87 elderly men with low levels of DHEAS and bioavailable testosterone and 57 elderly women with low DHEAS levels. There was no improvement in body composition, quality of life, physical performance, or insulin supplementation with DHEA supplementation. Similarly, there have been studies that have found no effects of DHEA supplementation on sexual function or well-being parameters[36,37]. Taken together, studies have argued against the use of DHEA as a cure-all elixir and the lack of long-term safety data does not justify the use of DHEA in healthy elderly individuals.

DHEA and the musculoskeletal system

As age-related decline in androgens and estrogens is said to contribute to the loss of muscle mass and bone mineral density in older adults, DHEA has been suggested as a potential agent for minimizing these losses. Moreover, the peak and nadir of BMD mirror the rise and fall in levels of DHEA,

respectively, and this has led to multiple studies of DHEA supplementation for bone health.

In bone, DHEA has been postulated to have a dual, pro-anabolic, and anti-catabolic effect. The anabolic effect of DHEA comes from its ability to increase the activity of osteoblasts secondary to raised IGF-1 levels *via* the GH/IGF-1 pathway. The anti-catabolic action involves its ability to inhibit the overall function of osteoclasts *via* direct and indirect actions on the estrogen receptor. DHEA also results in increased osteoprotegerin levels, which contributed to reduced resorption by osteoclasts.

In a recent pooled analysis of four double-blind randomized control trials by Jankowski *et al*[38], they examined the efficacy of DHEA in 295 women and 290 men aged 55 years or elder given DHEA or placebo daily for 12 mo. They observed that men had a significant increase in DHEAS, estradiol, and IGF-1 while women in addition had a significant increase in testosterone levels as well. There was no effect of DHEA on BMD in men, while there was a small increase in lumbar spine (1.0% ± 3.4%) and trochanter (0.5% ± 3.8%) with maintained hip BMD in women. This modest increase in BMD is less than that found with other anti-osteoporotic agents including bisphosphonates, denosumab, and teriparatide. However, these trials did not primarily involve women with osteoporosis which may explain these findings.

DHEA is also said to contribute to muscle growth and strength through an anabolic effect augmenting protein synthesis. The mechanisms suggested involve the ability of the skeletal muscle to metabolize DHEA to active androgens and increased bioavailability of insulin-like growth factor-1 (IGF-1). IGF-1 is said to be involved in the proliferation of myogenic cells leading to muscle growth and repair[39,40].

Scattered studies have found some positive effects of DHEA on muscle strength, muscle mass, and mobility, as well as physical function[41,42]. However, in a systematic review by Baker *et al*[43], they included eight randomized control trials and observed that the effects of DHEA on muscle strength and physical performance were inconclusive.

DHEA supplementation in schizophrenia

DHEA has also been found to play a role in the pathophysiology of schizophrenia. It has been suggested to modulate neuronal differentiation and synaptogenesis. Additionally, it also interacts with multiple hormone receptor systems including gamma-aminobutyric acid, glutamate, and dopamine[44]. In a systematic review and meta-analysis by Misiak *et al*[45] which included 19 studies, DHEAS levels were found to be significantly elevated in individuals with schizophrenia.

DHEA supplementation in depression

DHEA being a neurosteroid has also been evaluated in depression on account of its multiple actions. Its direct actions involve its ability to regulate neuronal excitability by interactions with neurotransmitter receptors known to modulate mood. Other indirect actions involve its ability to regulate cortisol levels and its potential to increase IGF-1 levels.

In one of the initial studies by Wolkowitz *et al*[46], they included 22 individuals with major depression and observed that DHEA was associated with a significant improvement in depressive score compared to placebo. Thereafter in 2005, Schmidt *et al*[47] evaluated the efficacy of DHEA in 46 individuals (23 men and 23 women) aged 45 to 65 years with depression in a randomized double-blind placebo-controlled study. They observed that 6 wk of DHEA supplementation was associated with a significant improvement in measures of depression. In a recent meta-analysis by Peixoto *et al*[48] which included 14 studies, DHEA was associated with a beneficial effect on depressive symptoms compared to placebo. However, the quality of evidence was low due to high clinical heterogeneity in clinical studies. Hence, although DHEA has been found to have some beneficial effect on depressive symptoms, the results should be interpreted with caution and further well-designed larger clinical trials will help in assessing these findings.

DHEA and cardiovascular disease

DHEAS levels have also been found to be decreased in cardiovascular disease in a few studies, suggesting a possible therapeutic role in atherosclerosis and coronary artery disease[49,50]. The mechanisms suggested to explain these effects include inhibition of platelet aggregation, smooth muscle cell proliferation and plasminogen activator inhibitor-1 generation, increased nitric oxide generation, and vasodilation[51,52]. In the Women's Ischemia Syndrome Evaluation study, lower DHEAS levels were associated with higher cardiovascular mortality and all-cause mortality and this was independent of other major cardiovascular risk factors. However, when adjusted for the presence or severity of obstructive coronary artery disease, the risk became non-significant[49]. DHEAS levels have also been found to be associated with arrhythmias. In the Rotterdam study which involved 1180 individuals without atrial fibrillation at baseline, after a mean follow-up of 12.3 years, DHEAS levels were found to be inversely associated with the risk of atrial fibrillation[53]. However, several studies have also failed to show an association between DHEA levels and cardiovascular disease[54,55]. In a case-control study by Golden *et al*[54], they assessed the correlation between DHEAS levels and atherosclerosis in 364 postmenopausal women and observed that DHEAS levels were not associated with the risk of atherosclerosis which was assessed by carotid artery intimal medial thickness. In a recent study by Zhao *et al*

[56], they observed that while increased testosterone levels were associated with an increased risk of cardiovascular diseases, DHEAS levels were not associated with these outcomes. In fact, some studies have found DHEA supplementation to be associated with increased cardiovascular risk. DHEA supplementation has been found to be associated with a pro-atherogenic state *via* upregulation of lipoprotein processing genes leading to macrophage foam cell formation[57]. Similarly, DHEA supplementation has also been found to be associated with deranged lipid profiles[58,59]. In a double-blind randomized cross-over study by Srinivasan *et al*[58], they assessed the effect of 50 mg DHEA supplementation for 3 mo on lipid parameters, they observed significantly decreased levels of high-density lipoprotein (HDL) in women supplemented with DHEA. Hence, the association of lower DHEAS levels with increased cardiovascular risk remains uncertain. On the contrary, evidence suggests a cautionary approach in using DHEA supplementation in view of a possible association with adverse cardiovascular profile.

ADVERSE EFFECTS

The major concerns with DHEA revolve around its ability to convert to androgen and estrogen metabolites. Reported androgenic side effects involve mild acne, facial hair growth, and seborrhea[60]. DHEA has also been associated with a pro-atherogenic state with decreased HDL levels[57,58]. It has also been seen that DHEA leads to proliferation of breast cancer cells *via* stimulation of estrogen receptors[61]. Hence, there have been concerns with the use of DHEA in hormone dependent cancers including breast cancer, endometrial cancer, and prostate cancer[62,63]. Currently, there is limited evidence with a paucity of long-term safety data and caution needs to exercised.

CONCLUSION

Initially marketed as a magic bullet for a myriad of human diseases, its clinical utility remains limited with conflicting results across multiple studies. Nevertheless, it remains an important physiological precursor in the synthesis of androgens and estrogens. While there is considerable evidence to suggest the role of DHEA in adrenal insufficiency and GSM, its role in menopausal females, elderly individuals, and other conditions such as sexual dysfunction, infertility, autoimmunity, and neurological and cardiovascular diseases remains to be fully elucidated. The studies done till date are limited by variations in diagnostic thresholds, DHEA dosing and timing of treatment, relatively small sample size, and shorter duration. Further large-scale, multicentric, robust randomized control trials to assess the effects of DHEA supplementation going forward will help gain a foothold in this untapped research area.

FOOTNOTES

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SYSTEMATIC REVIEWS

Current approach for Boerhaaves syndrome: A systematic review of case reports

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Abstract

BACKGROUND

There is no consensus on the appropriate therapeutic strategy for Boerhaave syndrome due to its rarity and changing therapeutic approaches. We conducted a systematic review of case reports documenting Boerhaave syndrome.

AIM

To assess the therapeutic methods and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

METHODS

We searched PubMed, Google scholar, MEDLINE, and The Cochrane Library for studies concerning Boerhaave syndrome published between 2017 and 2022.

RESULTS

Of the included studies, 49 were case reports, including a total of 56 cases. The mean age was 55.8 ± 16 years old. Initial conservative treatment was performed in 25 cases, while operation was performed in 31 cases. The rate of conservative treatment was significantly higher than that of operation in cases of shock vital on admission (9.7% *vs* 44.0%; P = 0.005). Seventeen out of 25 conservative cases (68.0%) were initially treated endoscopic esophageal stenting; 2 of those 17 cases subsequently underwent operation due to poor infection control. Twelve cases developed postoperative leakage (38.7%), and 4 of those 12 cases underwent endoscopic esophageal stenting to stop the leakage. The length of the hospital stay was not significantly different between the conservative treatment and operation cases (operation *vs* conservation: 33.52 ± 22.69 *vs* 38.81 ± 35.28 days; P = 0.553).

CONCLUSION

In the treatment of Boerhaave syndrome, it is most important to diagnose the

issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

Key Words: Boerhaave syndrome; Esophageal perforation; Self expandable metalic stent; Minimally invasive surgical procedures; Anastomotic leakage; Shock

Core Tip: Totally 49 published case reports concerning the Boerhaave syndrome were systematically reviewed. In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

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INTRODUCTION

Since Herman Boerhaave first recognized the disease in 1724, spontaneous esophageal perforation has been described as a medical emergency in the relevant literature[1]. The annual incidence of spontaneous esophageal perforation, also called Boerhaave syndrome, is 3.1 per 1000000; although rare, this condition is associated with high rates of misdiagnosis and mortality[2].

Boerhaave syndrome can be caused by vomiting and is frequently associated with alcohol intoxication[3]. A long period of time between perforation and treatment often results in mediastinitis, followed by septic shock and multiorgan failure[4-10]. Surgery and conservative management are the major treatment options for Boerhaave syndrome. However, few reports have examined whether operation or conservation is the preferred treatment method. Indeed, in the past five years, only one systematic review of Australasian literature on Boerhaave syndrome has been reported[11]. At present, there is no consensus on the optimal therapeutic strategy due to the rarity of Boerhaave syndrome and changing therapeutic approaches.

We therefore reviewed and evaluated 56 cases published in 49 case report articles in PubMed, Google scholar, MEDLINE, and The Cochrane Library in the past 5 years to assess the therapeutic methods and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

MATERIALS AND METHODS

Study selection

A case report literature review was conducted using Pubmed, Google scholar, Cochrane Library, and MEDLINE for articles published between October 2017 and October 2022. The search was limited to articles in English. “Boerhaave syndrome” or “spontaneous esophageal perforation” were key words in the search. All titles and abstracts of publications were screened to select articles describing Boerhaave syndrome or spontaneous esophageal perforation. The searches were further broadened by extensively checking all references in the articles retrieved that met the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criterion was patients who underwent operation or conservative therapy for Boerhaave syndrome. The exclusion criteria were meta-analyses, reviews, articles without outcomes reported, articles without the operation method reported, articles involving cases of treatment refusal, articles involving recurrent cases of esophageal perforation, articles involving best supportive care, articles involving pediatric cases, articles focusing on other diseases, and articles in non-English languages.

Data extraction

The study design, and data on the patients' demographics, interventions, and outcomes were extracted from the included studies. An independent researcher collected the study data using a standard Excel™ data collection sheet (Microsoft Corporation, Japan). This spreadsheet was used to calculate the descriptive statistics of all parameters that were evaluated in the present study. Continuous and categorical variables were shown as the mean and standard deviation (SD) and range.

Quality appraisal

The overall quality of the cases was classified as good to moderate. The majority of patients adequately described the chief complaint (100%), the patient's medical history (82.1%), the sex (98.2%), the length from symptom onset (98.2%), the length of the hospital stay (76.8%), imaging findings (100%), treatments (100%), and outcomes (100%).

Statistical analyses

All values were presented as the mean ± SD. Intergroup differences were evaluated by an analysis of variance, while a nonparametric analysis was conducted for data with a skewed distribution. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University)[12]. EZR for R (The R Foundation for Statistical Computing, version 2.13.0) is a modified version of the R commander (version 1.6–3) that includes statistical functions that are frequently used in biostatistics. P values of < 0.05 were considered statistically significant.

RESULTS

The results of the literature search are shown in Figure 1. Through our search, we identified 1310 studies. Of these, 990 studies were excluded by title and abstract. Of the remaining 115 potentially relevant articles, we excluded 48 concerning other diseases, 11 with insufficient data, 3 concerning recurrence cases, 2 involving best supportive care, and 2 pediatric cases. This resulted in the inclusion of 49 case report articles involving 56 cases for this study.

Patients' characteristics

Table 1 shows the details of the included studies. Of the 55 patients whose sex was mentioned, 51 were male, and 4 were female (1 case with no information). The mean age was 55.8 ± 16 years old. Thirty-six of the 55 cases (65.5%) were referred to the hospital within 24 h after symptom onset (1 case with no information). The most common method of the diagnosis was computed tomography (n = 31), followed by esophagography (n = 15), endoscopy (n = 9), and exploratory laparotomy (n = 1). A total of 42 cases (75%) were accurately diagnosed on admission. Fourteen patients (25%) showed shock vitals when they arrived at the hospital. Twelve (21.4%) were intra-mediastinum type, and 44 (78.6%) were extra-mediastinum type. The mean (range) size of the laceration in the 30 cases for which such details were described was 3.8 (1-12) cm (Table 2).

Initial treatment for Boerhaave syndrome

Conservative treatment was performed in 25 cases, while operation was performed in 31 cases. Conservative treatment included endoscopic esophageal stents in 17 cases, endoscopic clipping in 5, thoracic drainage in 21, and endoluminal vacuum-assisted (EVAC) therapy in 1. The operation approach was trans-thoracic and trans-abdominal approaches in 18 and 10 cases, respectively; a combined trans-abdominal and trans-thoracic approach was performed in 3 cases. In the trans-thoracic approach, minimally invasive surgery was performed in 5 cases (23.8%). In the trans-abdominal approach, minimally invasive surgery was performed in 8 cases (61.5%). The operation methods were primary repair only in eight cases, primary repair with omentoplasty in six cases, primary repair with fundus pouch in six cases, primary repair with intercostal muscle pouch in five cases, primary repair with pericardial fat pouch in five cases, T tube in two cases, esophagectomy in one case, and esophagostomy in one case. Twelve out of 31 cases (38.7%) developed postoperative leakage. Two of those cases underwent EVAC therapy, and four of the cases underwent endoscopic esophageal stenting. Seven out of the 56 total cases (12.5%) died following treatment for Boerhaave syndrome; notably, 4 of those 7 cases (57.1%) had already had shock vitals on arrival at the hospital (Table 3).

Endoscopic esophageal stenting

Seventeen cases underwent endoscopic esophageal stenting initially, and 14 of them (82.4%) had severe comorbidities. Ten of the 17 cases (58.8%) who underwent endoscopic esophageal stenting had had shock vitals on arrival at the hospital. One case (14.3%) was the intra-mediastinum type, while the other 16 (85.7%) were the extra-mediastinum type. Two of the 17 cases who underwent endoscopic esophageal stenting had initially undergone operation due to poor infection control.

Table 1 Descriptive comparative characteristics of all included 49 studies

Ref.	Age	Sex	Accurate diagnosis	Rupture type	Shock vital	Laceration size (cm)	Treatment	Prognosis
Jahangir *et al*[4], 2021	64	M	Yes	Intrapleural type	Yes	1	Stent, thoracic drainage	Death
Issa *et al*[23], 2019	32	M	Yes	Intrapleural type	No	2	Stent, thoracic drainage	Alive
Tan *et al*[5], 2022	84	M	No	Intrapleural type	No	Unknown	Thoracotomy, primary repair only	Death
Chang *et al*[13], 2021	67	M	Yes	Intrapleural type	No	3	Thoracopy, primary repair only, feeding jejunostomy	Alive
Chang *et al*[13], 2021	62	M	Yes	Intrapleural type	No	2	Thoracopy, primary repair only, feeding jejunostomy	Alive
Sheshala *et al* [24], 2021	39	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Matsumoto *et al* [25], 2019	60	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Ayazi *et al*[6], 2021	22	M	Yes	Intrapleural type	Yes	Unknown	Thoracotomy, esophagectomy, gastrostomy	Death
Maki *et al*[44], 2022	76	M	Yes	Intramediastinal type	No	7	Transhiatal approach, primary repair plus omentoplasty, feeding jejunostomy	Alive
Ioannidis *et al* [39], 2021	83	F	Yes	Intrapleural type	No	Unknown	Thoracic drainage	Alive
Y K *et al*[26], 2018	86	M	Yes	Intrapleural type	Yes	5	Stent, thoracic drainage, feeding jejunostomy	Alive
Czopnik *et al* [3], 2017	47	M	Yes	Intrapleural type	No	5	Transhiatal approach, primary repair, gastrostomy	Alive
Awadelkarim *et al*[27], 2021	36	M	Yes	Intrapleural type	Yes	2	Stent, thoracic drainage	Alive
Chalikonda *et al* [28], 2019	74	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Śnieżyński *et al* [29], 2021	53	M	Yes	Intrapleural type	No	3	Stent, thoracic drainage	Alive
Matsuura *et al* [21], 2022	69	M	Yes	Intramediastinal type	No	Unknown	Endoscopic clipping	Alive
Chen *et al*[19], 2021	57	M	No	Intramediastinal type	No	Unknown	Transhiatal approach, primary repair only, feeding jejunostomy	Alive
Truyens *et al* [30], 2020	66	M	Yes	Intramediastinal type	Yes	Unknown	Antibiotic administration	Alive
Truyens *et al* [30], 2020	77	M	Yes	Intramediastinal type	No	Unknown	Stent	Alive
Swol *et al*[7], 2019	70	M	Yes	Intramediastinal type	No	2	Transhiatal approach, primary repair plus fundus pauch	Death
Park *et al*[45], 2021	Unknown	Unknown	Yes	Intramediastinal type	No	5	Laparoscopic transhiatal approch, primary repair plus omentoplasty → endoscopic clipping, stent	Alive
Rahman *et al* [49], 2021	53	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus intercostal muscle pauch, gastro-jujuno tube → stent	Alive
Nachiappan *et al*[46], 2022	59	M	No	Intrapleural type	No	1,5	Endscopic clipping, stent → laparo-scopic transhiatal approach, primary repair plus omentoplasty	Alive
Pasternak *et al* [14], 2019	37	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only, gastrostomy	Alive
Kita *et al*[55], 2022	46	M	Yes	Intramediastinal type	No	4	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive

Kita *et al*[55], 2022	48	M	Yes	Intramediastinal type	No	3	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive
Kita *et al*[55], 2022	65	M	Yes	Intramediastinal type	No	5	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive
Saffo *et al*[8], 2021	76	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Death
Kochar *et al*[50], 2019	40	M	Yes	Intrapleural type	Yes	Unknown	Thoracotomy, primary repair plus intercostal muscle pauch, intraoperative stent, thoracic drainage	Alive
Bury *et al*[51], 2022	50	M	No	Intrapleural type	No	4	Thoracotomy, primary repair plus intercostal muscle pauch, thoracic drainage	Alive
Aref *et al*[47], 2019	32	M	Yes	Intramediastinal type	No	2	Laparoscopic transhiatal approach, primary repair plus omentoplasty	Alive
Bani Fawwaz *et al*[15], 2022	63	M	Yes	Intrapleural type	Yes	3	Stent, thoracic drainage	Alive
Bani Fawwaz *et al*[15], 2022	56	F	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus T tube, Belsey fundoplication, intraoperative stent, thoracic drainage, gastrostpomy	Alive
Xu *et al*[22], 2021	63	M	Yes	Intrapleural type	No	Unknown	Endoscopic clipping	Alive
Tuñon *et al*[57], 2021	24	M	Yes	Intrapleural type	No	4	Endoluminal vacuum therapy → endoscopic clipping	Alive
Lee *et al*[58], 2018	52	M	Yes	Intrapleural type	No	Unknown	Thoracoscopic approach, primary repair only → endoluminal vacuum therapy, thoracic drainage	Alive
He *et al*[54], 2018	57	M	Yes	Intramediastinal type	No	6	Endoscopic clipping	Death
Kim *et al*[59], 2019	56	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only → endoluminal vacuum therapy, thoracic drainage	Alive
Shennib *et al* [52], 2021	47	M	No	Intrapleural type	Yes	5	Thoracotomy, primary repair plus pericardial pauch, gastrostomy, feeding jejunostomy	Alive
Agrawal *et al* [40], 2019	26	M	No	Intrapleural type	No	Unknown	thoracic drainage	Alive
Sato *et al*[31], 2018	52	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only → stent, thoracic drainage	Alive
Sato *et al*[31], 2018	53	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Ali *et al*[16], 2020	30	F	No	Intrapleural type	No	4	Thoracotomy, primary repair only	Alive
Anand *et al*[48], 2022	64	M	Yes	Intrapleural type	No	2	Thoracotomy, primary repair plus intercostal muscle pauch, thoracic drainage	Alive
Barakat *et al* [32], 2017	62	M	Yes	Intrapleural type	No	1	Stent, endoscopic clipping	Alive
Alakkari *et al* [17], 2019	69	F	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus T tube	Alive
Zhu *et al*[18], 2021	33	M	No	Intrapleural type	No	Unknown	Stent, PEG →thoracotomy, drainage	Alive
Sekiya *et al*[56], 2019	61	M	Yes	Intrapleural type	No	3	Thoracoscopic and laparoscopic approach, primary repair plus pericardial pauch, gastrostomy	Alive
Sekiya *et al*[56], 2019	64	M	Yes	Intrapleural type	No	4	Thoracoscopic and laparoscopic approach, primary repair plus pericardial pauch, feeding jejunostomy	Alive
Olivero *et al*	67	M	No	Intrapleural type	No	2	Thoracotomy, primary repair plus	Alive

[53], 2019							pericardial pauch, thoracic drainage	
Felipe *et al*[38], 2021	47	M	Yes	Intrapleural type	No	12	Thoracotomy and laparotomy approach, esophagostomy, gastrostomy → stent	Alive
Ahmad *et al* [33], 2018	63	M	Yes	Intrapleural type	No	2.5	Stent, thoracic drainage	Alive
Hashmi *et al* [10], 2021	83	M	Yes	Intrapleural type	Yes	Unknown	Antibiotic administration	Death
Teblick *et al*[34], 2018	74	M	Yes	Intrapleural type	No	Unknown	Stent, thoracic drainage	Alive
He *et al*[9], 2018	27	M	Yes	Intrapleural type	No	6	Thoracotomy, primary repair plus pleural flap, feeding jejunostomy	Alive

PEG: Percutaneous endoscopic gastrostomy; M: Male; F: Female.

Table 2 Characteristics of the patients with Boerhaave syndrome included in the review, *n* (%)

Sex		[a]Male 51, female 4
Age		55.8 ± 16
The length from symptom within 24 h		[b]36 (65.5)
The method of diagnosis	CT	31
	Esophagography	15
	Endoscopy	9
	Exploratory laparotomy	1
Accurate diagnosis on admission		42 (75)
Shock vital on admission		14 (25)
Rupture type	Intramediastinal	12 (21.4)
	Extramediatinal	44 (78.6)
Lacelation size (cm) (range)		[c]3.8 (1-12)

[a]One case with no information.
[b]One case with no information.
[c]26 cases with no information.
CT: Computed tomography.

Four of the cases who initially underwent operation consequently underwent endoscopic esophageal stenting to stop leakage.

Minimally invasive surgery

Eleven out of 31 cases (35.5%) underwent minimally invasive surgery. Seven of the 13 cases (53.8%) who underwent the trans-abdominal approach received the trans-hiatal approach specifically with laparoscopic surgery. Five of the 21 cases (23.8%) who underwent the trans-thoracic approach received thoracoscopic surgery. The length of the hospital stay after surgery tended to be shorter with minimally invasive surgery than with non-minimally invasive surgery [minimally invasive surgery (n = 10) *vs* non-minimally invasive surgery (n = 15): 25.5 ± 17.1 *vs* 38.86 ± 24.85 d; P = 0.153] (Figure 2A).

Conservative treatment vs surgery

Table 4 shows the differences in details between patients who underwent an operation and those who received conservative treatment. The sex, age, rate of patients admitting within 24h after symptom onset, rupture type, and rate of survival did not significantly differ between patients who underwent an operation and those who received conservative treatment. The rate of patients with shock vitals on admission did differ significantly between patients who underwent an operation and those who received conservative treatment (9.7% *vs* 44.0%; P = 0.005). The length of hospital stay was not significantly different among the 43 cases (operation *vs* conservative treatment: 33.52 ± 22.09 *vs* 38.81 ± 35.28 d; P = 0.55) (Figure 2B).

Table 3 Initial treatment for Boerhaave syndrome

			The number do not add up because of duplication case
Conservation (n = 25)[a]	Esophageal stent		17
	Clipping		5
	Thoracic drainage		21
	EVAC[b]		1
Operation (n = 31)	Approach	Trans-thoracic approach	18
		Trans-abdominal approach	10
		Trans-thoracic and abdominal approach	3
	Method	Primary repair only	8
		Primary repair with omentoplasty	6
		Primary repair with fundus pauch	6
		Primary repair with intercostal muscle pauch	5
		Primary repair with pericardial fat pauch	5
		T tube	2
		Esophagectomy	1
		Esophagostomy and gastrostomy	1

[a]Duplication exist.
[b]Endoluminal vacuum-assisted therapy.
EVAC: Endoluminal vacuum-assisted.

Table 4 The length of hospital stay was not significantly different among the 43 cases

Factor	Group	Operation (n = 31)	Conservation (n = 25)	P value
Sex (%)	M	27 (90.0)	24 (96.0)	0.617
	F	3 (10.0)	1 (4.0)	
mean ± SD		53.17 (14.68)	59.00 (18.14)	0.193
The length from symptom within 24 h (%)	Yes	10 (32.3)	9 (36.0)	1
	No	20 (64.5)	16 (64.0)	
Shock vital on admission (%)	Yes	3 (9.7)	11 (44.0)	0.005
	No	28 (90.3)	14 (56.0)	
rupture type	Intramediastinal (%)	8 (25.8)	4 (16.0)	0.516
	Extramediastinal (%)	23 (74.2)	21 (84.0)	
Alive (%)	Yes	28 (90.3)	21 (84.0)	0.688
	No	3 (9.7)	4 (16.0)	

F: Female; M: Male.

DISCUSSION

Primary surgical repair has been the gold-standard treatment for esophageal perforation for a long time [13-19]. Primary repair of the esophagus conducted with mediastinal and thoracic drainage is reported to have a 90% success rate. Cases in which esophageal rupture is diagnosed at an early stage (within 24 h) without associated esophageal disease are reported to show a particularly high success rate[20].

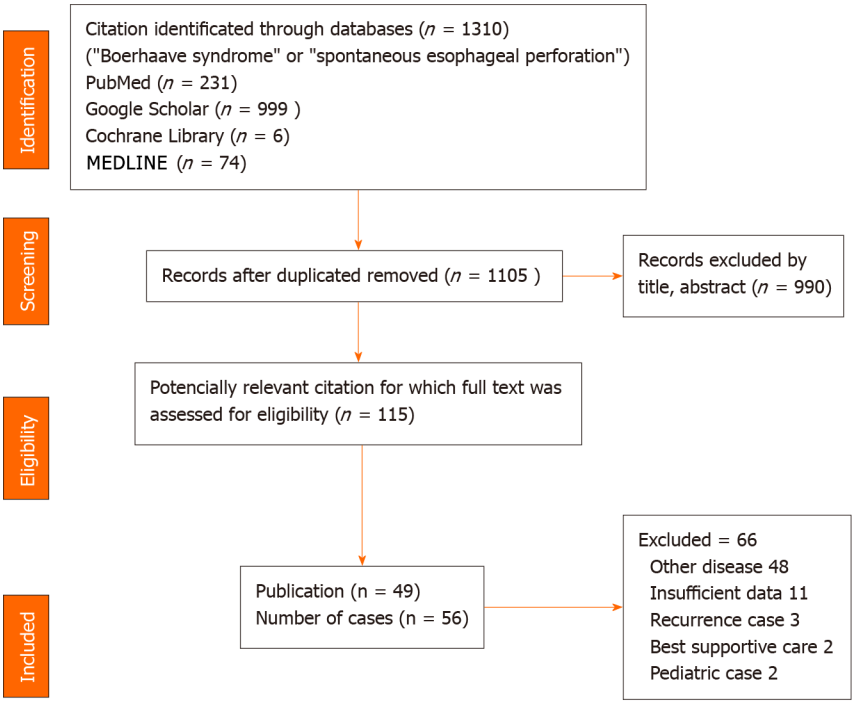

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Figure 1 PRISMA flow diagram demonstrating articles selection process.

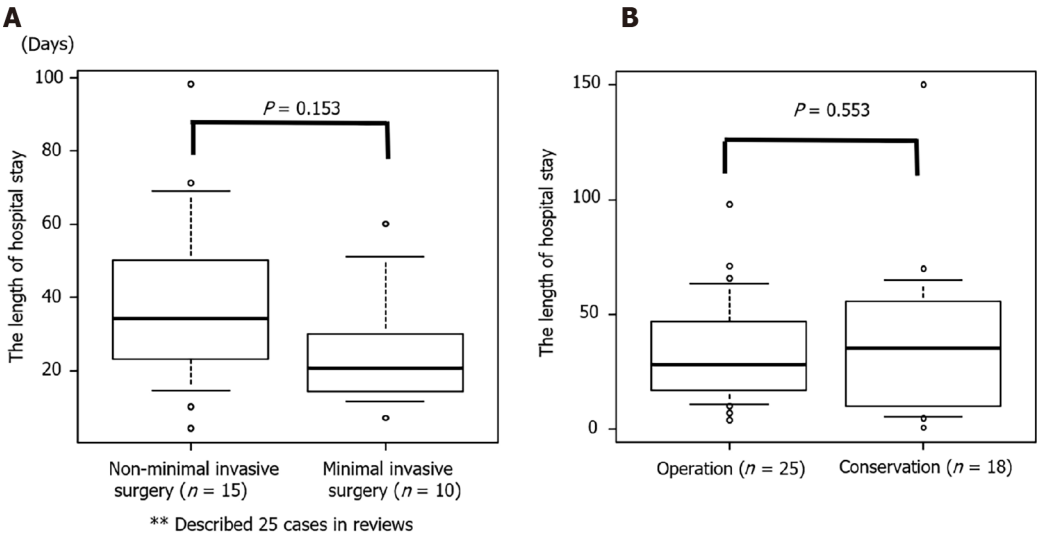

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Figure 2 Comparison of length of hospital stay. A: The length of hospital stay in the non-minimally and minimally invasive surgery groups; B: The length of hospital stay in the operation and conservative treatment groups.

There has been a recent trend toward more non-operative management[21,22], such as esophageal stent replacement *via* an endoscopic approach[23-32]. The indications for esophageal stenting include multiple comorbidities, advanced mediastinal sepsis, hemodynamic compromise, and clinical intolerance of extensive surgical repair[33]. In our review, the rate of conservation was significantly higher than that of operation in instances of shock vital on admission (44.0% *vs* 9.7%; $P = 0.005$).

Esophageal stenting was able to be attempted for patients who were in a bad general condition or intolerant to surgery[34]. Endoscopic esophageal stenting was also performed for cases of postoperative leakage. Kauer *et al*[35] in 2008 first described the usefulness of stent placement in the management of thoracic anastomotic leakage after esophagectomy. An interval approach utilizing covered metallic stent was then introduced for the management of anastomotic leakage after esophagectomy[36]. However, no prospective clinical study comparing the outcomes of esophageal stenting to that of conservative/surgical treatment has yet been performed. Bi *et al*[37] reported that the efficacy of the three-tube method, (tube drainage of the abscess, placement of a jejunal feeding tube, and placement of a

gastrointestinal decompression tube, with implantation of a covered metallic stent) for the management of anastomotic leakage following esophagectomy. This means that it is important not only to place esophageal stents but also to provide adequate drainage, a concept that can also be applied for treating Boerhaave syndrome.

Surgical approaches differed among facilities in our review. The operation approach in our evaluated studies was the trans-thoracic approach in 18 cases, trans-abdominal approach in 10 cases, and combined trans-thoracic and trans-abdominal approach in 3 cases. The approach seemed to differ depending on laceration site, the patient's general condition, and whether the operator was a thoracic surgeon or a gastrointestinal surgeon. The reported operative methods for Boerhaave syndrome include primary repair (with/without reinforcement), an exclusion diversion operation[38], esophageal resection, and simple thoracic drainage[39-40]. Previous reports mentioned that reinforcement with vascularized tissue was associated with reduced fistula formation and mortality rates in comparison to repair without reinforcement[41-43]. In the case of friability of the tissue, primary repair with reinforcement, such as omental flaps[44-47], intercostal muscle flaps[48-51], and pericardial flaps[52-54], should be performed. A comprehensive evaluation of the degree of laceration, extent of laceration, and general condition required for deciding the repair method should be conducted.

There have been a few recent reports concerning minimally invasive surgery for Boerhaave syndrome. Kita *et al*[55] suggested that a good clinical course can be obtained by laparoscopic trans-hiatal esophageal repair for Boerhaave's syndrome with localized mediastinal collections to avoid surgical invasion due to thoracotomy. Sekiya *et al*[56] reported the convenience and usefulness of minimally invasive surgery *via* an abdominal and left thoracic approach, which provides excellent visualization of the abdominal and thoracic cavities and facilitates quick switching between views. The authors further suggested that, in cases with an interval to the diagnosis < 24 h, no severe comorbidities, and a perforation site in the left lower esophagus, a trans-hiatal approach for minimally invasive surgery is feasible to repair the laceration and ameliorate the infection[56]. In our systematic review, the length of hospital stay after minimally invasive surgery tended to be shorter than after non-minimally invasive surgery (25.5 ± 17.1 *vs* 38.86 ± 24.85 d; $P = 0.153$). Minimally invasive surgery is useful for its cosmetic aspect, camera magnification effect, and ease of suturing, especially a laparoscopic trans-hiatal approach.

In our systematic review, 12 out of 31 cases (38.7%) developed postoperative leakage. Two of those 13 Leakage cases underwent EVAC therapy. Recently, the efficacy of EVAC therapy for esophago-pleural fistula after an operation for Boerhaave syndrome was reported[57-59]. EVAC therapy can be applied in postoperative management according to the principle applied for external wounds that provide wound drainage and tissue granulation. EVAC therapy can be applied to conservatively treat cases where primary surgical repair of esophageal perforation is unsuccessful. Moreover, with the use of an S-B tube, the patient can simultaneously receive intraluminal EVAC therapy with enteral nutrition in a non-invasive manner[58]. This may accelerate the healing of the injured esophagus and reduce the duration of hospitalization.

We suggest an algorithm that might be useful in the treatment of Boerhaave syndrome in Figure 3, with reference to our systematic review. If Boerhaave syndrome is suspected on computed tomography, esophagography or upper gastrointestinal endoscopy should be performed immediately. The treatment of Boerhaave syndrome is basically primary repair with reinforcement. If postoperative leakage occurs, endoscopic esophageal stenting or EVAC therapy should be considered. If the patient is inoperable (severe shock vitals, super-elderly patients, severe comorbidities, *etc.*), endoscopic esophageal stenting and thoracic drainage should be considered.

Several limitations associated with the present study warrant mention. Importantly, due to its rarity, there are few large case series on Boerhaave syndrome. Furthermore, the therapeutic strategies for Boerhaave syndrome have changed over time, with new approaches being developed recently. We reviewed and analyzed 49 articles; however, the review process may have included various publication biases.

CONCLUSION

In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The optimal treatment should be determined according to the etiology, general physical condition of the patient, and site of perforation, as well as the extent of contamination, as determined by radiology. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

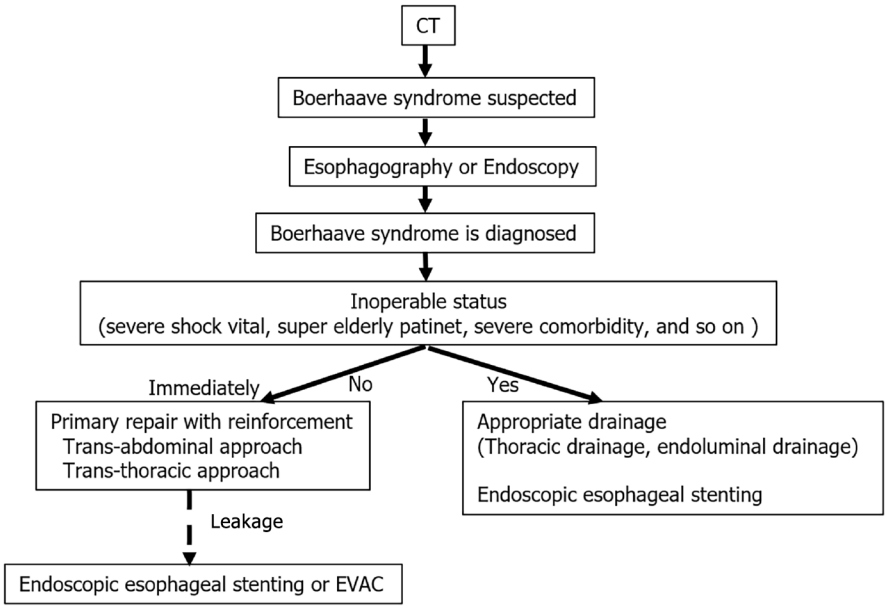

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Figure 3 Algorithm for the treatment of Boerhaave syndrome with reference to the systematic review findings. CT: Computed tomography; EVAC: Endoluminal vacuum-assisted.

ARTICLE HIGHLIGHTS

Research perspectives

As far, it has long been reported that Boerhaave syndrome has a poor prognosis when diagnosed late. However, no consensus has been reached concerning the appropriate therapeutic strategy for Boerhaave syndrome because of the rarity of the disease and the changing therapeutic trends.

Research conclusions

We assess the therapeutic methods [operation *vs* drainage *vs* stent *vs* endoluminal vacuum-assisted (EVAC), *etc.*] and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

Research results

We believe that this systematic review will be useful in future treatment of Boerhaave syndrome when there is doubt as to whether conservative treatment or surgery should be done, as well as the method of surgery.

Research methods

We searched PubMed, Google scholar, MEDLINE, and The Cochrane Library for studies concerning Boerhaave syndrome published between 2017 and 2022.

Research objectives

In results, the key to treatment of Boerhaave syndrome was early diagnosis. In addition, although surgery was the basic treatment, esophageal stents and drainage may be useful for patients with intolerance. Furthermore, for postoperative leakage, esophageal stents, drainage, and EVAC were useful.

Research motivation

In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

Research background

Because Boerhaave syndrome is a rare disease, observational studies should be conducted in collaboration with other centers. We hope that this will result in a high-quality strategy.

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FOOTNOTES

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META-ANALYSIS

Role of baricitinib in COVID-19 patients: A systematic review and meta-analysis

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Abstract

BACKGROUND

Recent studies have indicated the use of baricitinib in coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

AIM

To determine the precise role of baricitinib in the mortality of COVID-19 patients.

METHODS

The relevant studies were searched in PubMed, Google scholar, and Clinical trials registries till July 13, 2021 and sorted out based on inclusion and exclusion criteria. The quality of studies was assessed using Newcastle-Ottawa Scale. A random-effect model was used, and the pooled estimate was calculated as the odds ratio with a 95% confidence interval using Rev Man 5.

RESULTS

A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group.

CONCLUSION

More studies are required to confirm the role of baricitinib in the deaths of COVID-19 patients.

Key Words: Janus kinase inhibitors; Baricitinib; COVID-19; Mortality; Systematic Review; Meta-analysis

Core Tip: Emerging reports have indicated the use of baricitinib in hospitalized coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far. Current study aimed to find out the exact association of baricitinib in the mortality of COVID-19 patients.

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INTRODUCTION

According to the World Health Organization (WHO), multiple pneumonia episodes of unknown cause were reported in the central Metropolitan area of Wuhan in December 2019 in China. The causal infection was later identified as a novel coronavirus, tentatively termed coronavirus disease 2019 (COVID-19). This virus has been causing havoc on public health across the world since its outbreak in December 2019. More than 2000 incidents of COVID-19 infection were reported as of January 26, 2020, the majority of which were individuals living in or traveling Wuhan. The WHO claimed the COVID-19 pandemic was a Public Health Emergency of International Concern on January 30, 2020[1]. The cases of infection were highly associated with the seafood market in Wuhan[2]. Chinese officials announced 2835 confirmed cases in 2020, with 81 deaths. The causal agent has been identified as a novel coronavirus, COVID-19, a pathogen linked to severe acute respiratory syndrome (SARS), was quickly identified as the cause (SARS-CoV) by Chinese officials[3,4]. Coronaviruses (CoV) belongs to the family "coronaviridae". Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to be spread directly from bats to humans or by a single or several host species[3,5]. The treatment is based on the symptoms of the patients. Various classes of drugs are repurposed and are being used in the management of this infection.

Janus Kinase Inhibitors (JAKi) are also one of the repurposed drugs which are being used in the management of hospitalized COVID-19 patients due to their anti-inflammatory (inhibition of IL-6) and anti-viral effects (inhibit the entry of virus)[6]. Baricitinib is one of the JAKi approved for the treatment of rheumatoid arthritis. It has been observed that most SARS-CoV-2 infected patients were died due to cytokine storms, specifically the excess release of IL-6. Thus, baricitinib might be useful in the reduction of deaths of COVID-19 patients[7,8]. Meta-analysis is one of the quantitative analyses that help in clinical decision-making. The results of the individual studies are pooled and integrated using suitable statistical procedures[9-11]. In the current study, we performed a systematic review of clinical studies to determine the role of baricitinib in the deaths of COVID-19 hospitalised patients.

MATERIALS AND METHODS

The study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Figure 1). The study is registered with the International prospective register of systematic reviews (PROSPERO, Registration number: CRD42021281366).

Search strategy

A search was conducted in PubMed, Google scholar, and Clinical trial registry for observational, randomized, and non-randomized controlled studies, cohort studies, and comparative cross-sectional studies with the following search strategies: "baricitinib", OR "immunosuppressants", OR "anti-rheumatoid", OR "Janus kinase inhibitor" OR "Disease-modifying antirheumatic drug" AND "COVID-19" OR "Coronavirus" OR "Acute respiratory distress syndrome" OR "SARS-CoV-2". The references of included studies were screened to boost the search.

Study selection

Two reviewers (MT and AB) separately screened all the titles and abstracts as per the inclusion and

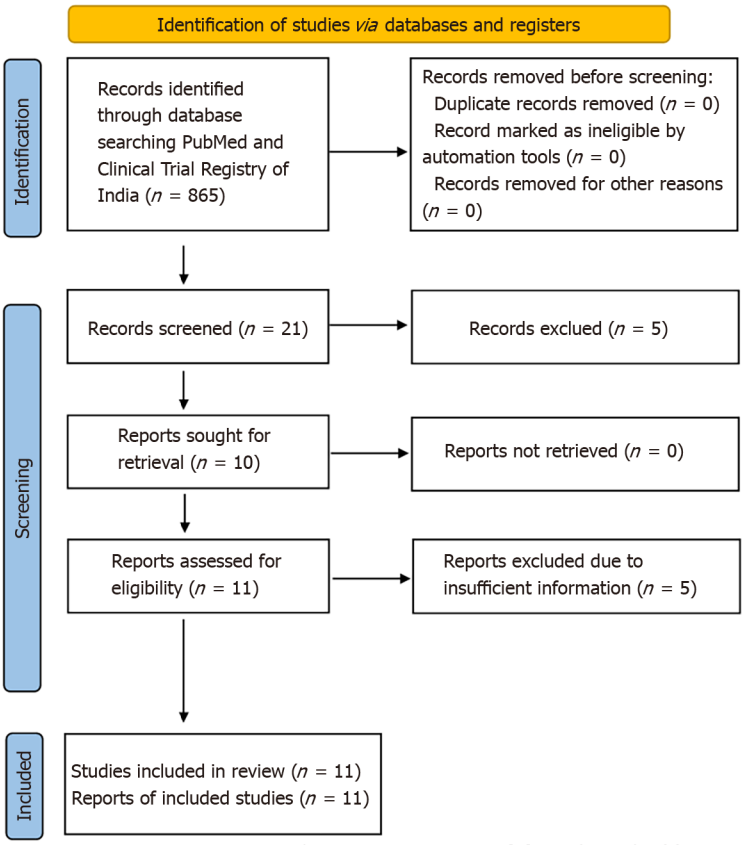

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Figure 1 Selection of studies as per the PRISMA guidelines.

exclusion criteria. The studies were included if participants were on baricitinib therapy, with all age groups, and all sexes. The case reports, case series, narrative review, systematic review, meta-analysis, studies of poor quality as per standard scale were excluded. The reviewers (MT and AB) separately screened the full-text studies for final inclusion. In the case of conflicts over the inclusion, the third reviewer (AK) was consulted.

Quality assessment

The quality assessment of eligible observational studies was done using Newcastle-Ottawa Scale whereas quality assessment of clinical trials was done using NIH quality assessment scale for quality assessment of controlled intervention studies. The assessment was done by two reviewers (MT and AB) separately. The disagreement among authors was resolved after a discussion with four reviewers (GLK, AKD, RK, and AK). The studies were categorized into three categories, *i.e.*, good, fair, and poor quality.

Data extraction

The data was extracted from studies by two reviewers (MT and AB) in an excel sheet. The information includes the name of the first author with publication year, the country where the study has been conducted, gender, study design, the total number of subjects, number of subjects, and deaths in baricitinib, non-baricitinib group.

Sensitivity analysis

The sensitivity analysis was done to check the effect of high or low sample size on the outcome to address the degree of heterogeneity.

Statistical analysis

RevMan 5 was used for all of the analyses. Using a random-effect model, the overall estimate was calculated as an odds ratio with 95% confidence intervals. Cochrane Q and I square statistics were used to calculate study heterogeneity.

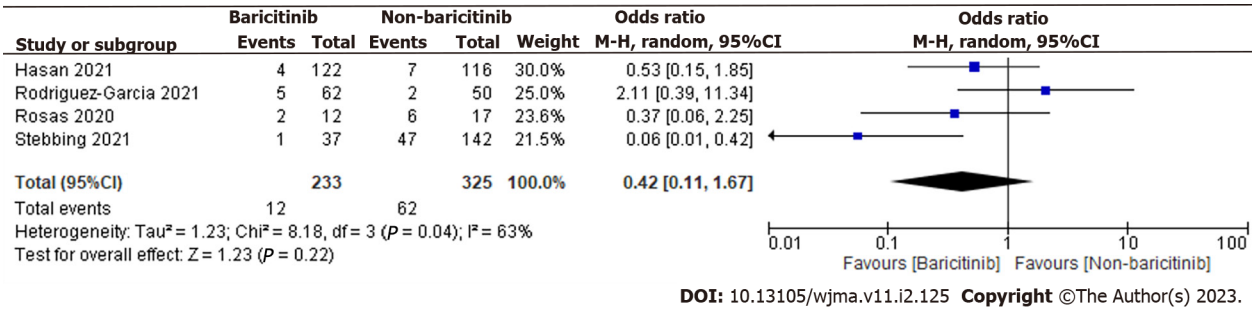

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Figure 2 Forest Plot showing overall estimate measure of observational studies as odds ratio using random-effect model.

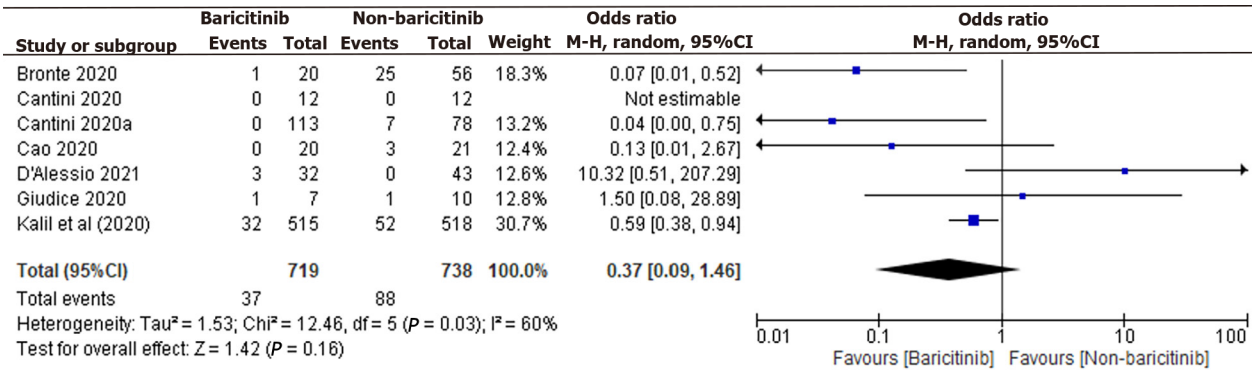

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Figure 3 Forest Plot showing overall estimate measure of clinical trials as odds ratio using random-effect model.

RESULTS

Search results and study characteristics

We found 865 articles after the initial search. After primarily screening of titles, 21 relevant articles were found. Further, based on the screening of abstracts, 16 were retrieved, out of which 05 articles were excluded due to insufficient information. Finally, 11 articles[11-22] were included for qualitative and quantitative analysis. Figure 1 depicts the selection of articles. The full-text or secondary screening with bibliography searches yielded no additional articles for inclusion. Out of the 11 studies, 4 were observational studies whereas the remaining 7 studies were clinical trials. The four studies were conducted in Italy, two in Spain, one in Italy and Spain, and one each at, Omaha, Bangladesh, Germany, Wuhan. The characteristics of included observational studies were compiled in Table 1 whereas the characteristics of included clinical trials were compiled in Table 2.

Quality assessment

All observational studies on the Newcastle-Ottawa Scale were found to be of good to fair quality based on their scores in the selection, comparability, and outcome subscales. Three of the four studies were of high quality, while the fourth was of fair quality (Table 3). According to the NIH quality assessment scale, 5 studies were of good quality, while the remaining two were of fair quality (Table 4).

Analysis of observational studies

A total of 558 patients were found in selected 4 observational studies. 233 of the 558 coronavirus disease 2019 (COVID-19) cases were taking baricitinib, while the remaining 325 were not. The overall estimate was 0.42 [0.11, 1.67], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 2).

Analysis of clinical trials

In total, 1457 patients were found in 7 clinical trials. 719 of the 1457 COVID-19 cases were taking baricitinib, while the remaining 738 were not. The overall estimate was 0.37 [0.09, 1.46], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 3).

Table 1 Characteristics of included observational studies

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Hasan *et al*[14], 2021	Bangladesh	Cohort study	238	159	79	122	4	116	7
Stebbing *et al*[15], 2021	Italy, Spain	Observational	790	438	352	37	1	142	47
Rodriguez-Garcia *et al*[16], 2020	Spain	Cohort study	112	78	34	62	5	50	2
Rosas *et al*[19], 2020	Spain	Case control study	29	20	9	12	2	17	6

Table 2 Characteristics of included clinical trials

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Bronte *et al*[13], 2020	Italy	Clinical trial	76	38	38	20	1	56	25
Kalil *et al*[12], 2020	Omaha	Clinical trial	1033	652	381	515	32	518	52
Cantini *et al*[17], 2020	Germany	Clinical trial	24	20	4	12	0	12	0
Cantini *et al*[18], 2020	Italy	Clinical trial	191	119	72	113	0	78	7
Cao *et al*[20],2020	Wuhan	Clinical trial	41	24	17	20	0	21	3
D'Alessio *et al*[21],2021	Italy	Clinical trial	75	52	23	32	3	43	0
Giudice *et al*[22], 2020	Italy	Clinical trial	17	13	4	7	1	10	1

Table 3 Quality assessment of observational studies using new castle Ottawa scale

Ref.	Selection	Comparability	Exposure	Total score	Quality of the study
Hasan *et al*[14], 2021	****	**	***	9	Good
Stebbing *et al*[15], 2021	***	*	***	7	Good
Rodriguez-Garcia *et al*[16], 2020	****	*	***	8	Good
Rosas *et al*[19], 2020	**	**	***	7	Fair

*For each numbered item within the selection and outcome categories.

Heterogeneity

The I^2 (90%) and chi^2 statics have shown high heterogeneity among studies.

Sensitivity analysis

We have analyzed the forest plots of both observational and clinical trials and found that there is a study with high and low sample sizes, particularly in clinical trials. Therefore, analysis was also done again to check the effect of these studies on the outcome. The studies with a high and low sample sizes *i.e.*, Kalil *et al*[12] and Giudice *et al*[22], were excluded, and analysis was done again. The overall estimate was 0.23 [0.02, 2.37], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group (Figure 4). Overall, results were not affected by the studies with high and low sample sizes.

DISCUSSION

The current analysis was done to find out the role of baricitinib in the reduction of deaths of COVID-19 hospitalized patients. To the best of our knowledge, very few meta-analyses have been done so far on the use of baricitinib in COVID-19 treatment. Recently, Chen *et al*[23], have performed a meta-analysis

Table 4 Quality assessment of clinical trials using NIH scale

No.	Ref.	Type of study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality of the study
1	Bronte *et al*[13], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
2	Kalil *et al*[12], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Good
3	Cantini *et al*[17], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
4	Cantini *et al*[18], 2020	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	Fair
5	Cao *et al*[20], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
6	D'Alessio *et al*[21], 2021	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
7	Giudice *et al*[22], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	NO	Yes	NR	Good

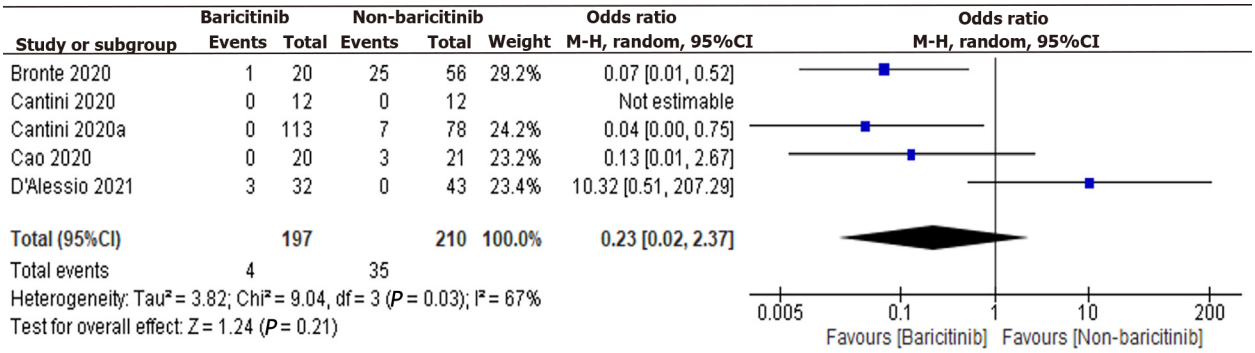

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Figure 4 Forest Plot showing overall estimate measure of clinical trials as odds ratio after exclusion of studies with high (Kalil *et al*[12], 2020) and low sample size (Giudice *et al*[22], 2020) using random-effect model.

of 11 studies and reported the safety and efficacy of JAK-inhibitors including baricitinib in COVID-19 patients. Another JAK inhibitor *i.e.*, ruxolitinib is also used in hospitalized patients. The meta-analysis results of Wijaya *et al*[24], have demonstrated a significant clinical improvement and decrease in the risk of mortality of COVID-19 patients. The potential of baricitinib in the reduction of deaths of hospitalized COVID 19 patients is also indicated by a meta-analysis conducted by Walz *et al*[25]. Recently, Putman *et al*[26], have also performed a meta-analysis to find out the efficacy of anti-rheumatoid therapy, including baricitinib and steroids for the treatment of COVID-19. However, number of available studies regarding the use of baricitinib in COVID-19 patients at that time was very less. The already published meta-analysis have also analyzed different design of studies together which make less valid conclusion. In the current meta-analysis, we have analyzed observational and clinical trials separately. However, the results of both observational and clinical trials have shown the non-significant deaths of COVID-19 hospitalized patients in the baricitinib group as compared to non-baricitinib group. Further, the sensitivity analysis results have also shown no effect of outliers on the outcome.

CONCLUSION

In conclusion, more research is needed to draw a valid conclusion about the use of baricitinib in the reduction of COVID-19 patient deaths.

ARTICLE HIGHLIGHTS

Research background

More research is needed to draw a valid conclusion about the use of baricitinib in the reduction of coronavirus disease 2019 (COVID-19) patient deaths.

Research motivation
More research is needed to confirm the role of baricitinib in COVID-19 patient deaths.

Research objectives
A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group. The degree of heterogeneity among studies was also discovered to be high.

Research methods
The study was conducted as per the PRISMA guideline using RevMan 5 software.

Research results
To investigate the role of baricitininb in the reduction of COVID-19 patient deaths.

Research conclusions
Can baricitinib reduce the deaths of COVID-19 patients?

Research perspectives
Emerging reports have indicated the use of baricitinib in hospitalized COVID-19 patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

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FOOTNOTES

Author contributions: Thakur M and Babu A contributed to searching and selection of studies, extraction of data; Khatik GL, Datusalia AK, and Khatri R contributed to cross verification of data; Khatik GL contributed to first draft of the manuscript; Datusalia AK and Khatri R contributed to revision; Kumar A contributed to design, analysis and final rthe evision of manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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

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MINIREVIEWS

Diabetes mellitus: An overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment

Adekunle Sanyaolu, Aleksandra Marinkovic, Stephanie Prakash, Martina Williams, Yashika Dixon, Chuku Okorie, Verner N Orish, Ricardo Izurieta

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Abstract

Diabetes is one of the deadliest diseases. Due to its effects on the lives of people, it has attracted a lot of attention recently. The causes of the various forms of diabetes, including type 1 and type 2, were discussed along with how they affect those who have the disease. Younger people are more prone to type 1 diabetes than older people, who are more likely to develop type 2. The treatment options and strategies for the two forms of diabetes were also discussed in addition to how the disease affects the quality of life of people. Among several factors that were explained, it has been shown that people from low and middle-income countries are more prone to having diabetes. Additionally, the condition is more likely to affect some races more than others. It is associated with obesity. According to statistics, those who are poor are more severely affected by the disease. The progression of the disease over time has been associated with an increase in disability and mortality.

Key Words: Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Diabetes; Insulin; Blood glucose

Core Tip: Diabetes is a disease that has significant financial consequences in the patients and can also be lethal. There are two types: type 1 and type 2 diabetes. The former is more prevalent among children, whereas the latter is more prevalent among adults. Diabetes is known to cause severe complications, resulting in misery and premature death. Fortunately, interventions and treatment options are available.

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INTRODUCTION

Diabetes is a chronic condition characterized by abnormalities in insulin secretion or action, or sometimes both[1]. Insulin is a hormone released by the pancreas that works as the primary messenger for moving glucose from consumed meals to flow from the bloodstream into the body's cells where it is used for energy[2]. Diabetes affects the entire system and causes issues in specific organs such as the eyes, nerves, and kidneys[3]. It affects 9.0% of the adult population globally, according to the World Health Organization[2,4,5]. It is a developing pandemic that may be traced back to the fast rise in obesity and inactivity[3], being classified into two types: Type 1 (insulin-dependent) and type 2 (non-insulin-dependent) (adult-onset)[1]. Diabetes causes serious health problems globally, primarily increasing the risk of heart disease and other complications[4]. It affects 80.0% of the population in low and middle-income nations, and in wealthy countries, adults between the ages of 35 and 64 years are most affected[4].

Furthermore, the most economically and socially marginalized persons have the heaviest burden of living with the condition and are most financially impacted[4,5]. Its consequences are assessed not only by the rise in the prevalence presented every year per capita, but also through the rising number of complications and deaths[4]. While the prevalence of most infectious illness continues to diminish as technology improves and life expectancy increases, the impacts of diabetes continue to increase[4]. This article reviews diabetes mellitus with an overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment.

METHODOLOGY

The electronic databases PubMed, Google Scholar, and Med Line Plus were searched for the review of literature. The search was limited to peer-reviewed publications between January 1994 and November 2022 for the compiled data. Publications that had keywords including "diabetes mellitus" were chosen. The articles were then included after being evaluated for relevance to the topic (Figure 1).

DIFFERENT TYPES OF DIABETES

Diabetes is a metabolic illness in which insulin plays a central role. There are several pathogenic pathways at work in the etiology of this illness[1]. They vary from autoimmune death of pancreatic beta cells, resulting in chronic insulin insufficiency, to a disease inhibiting insulin action[1]. The cause of this condition is an aberrant carbohydrate, lipid, and protein metabolism caused by insufficient or even defective insulin activity[1]. The major cause of hyperglycemia is a deficiency in either secretion or effect of insulin at one or more sites along its route of action[1].

TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (T1DM) is triggered by an autoimmune response in which the body targets

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Figure 1 Article selection.

insulin-producing cells[1]. The level of beta cell breakdown in T1DM varies among patients, being fast in some and exceedingly sluggish in others[1]. Keto-acidosis is the most common initial symptom of the illness in most people[1]. Others exhibit symptoms such as fasting hyperglycemia as well as keto-acidosis in the context of environmental variables[1]. Although some people may preserve adequate beta-cell activity to prevent keto-acidosis, many individuals eventually become insulin dependent and develop keto-acidosis[1]. As the condition advances, insulin production decreases, and C-peptide levels become low, and often may become undetectable[1]. A variety of reasons, including heredity, environmental factors, and idiopathic causes have been linked to the autoimmune degradation of beta cells[1]. Some cases of T1DM have an unclear origin as seen in some people of African or Asian descent[1].

TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM) affects 90.0%-95.0% of the diabetic population. T2DM is characterized by a complicated process in which the fundamental issue is a balance between insulin production by beta cells and insulin action, resulting in insulin resistance to insulin-stimulated glucose in the blood[3]. Impaired glucose tolerance is the illness' intermediate stage that determines the risk of heart disease[1]. Many individuals with T2DM are obese, indicating that obesity may induce some sort of insulin resistance[1]. Keto-acidosis occurs spontaneously and gradually in this type of diabetes, and it is frequently triggered by the same conditions that cause T1DM such as stress and illness. Because of the absence of apparent symptoms, T2DM is commonly undiagnosed[3]. Most of the symptoms develop slowly and are frequently not severe enough to be detected[1].

REGIONAL OVERVIEWS

The diversity of socioeconomic and geographical parameters, prevalence, associated death, and health expenditure may all be used to assess the Global Perspective[1,2,5]. Most diabetics reside in less developed and economically disadvantaged parts of the world[5]. Eighty percent of the population is from low- to middle-income nations[1,2,5]. Different forms of diabetes are prevalent across the world, yet each has a distinctive impact on different populations[5,6]. Infectious diseases, such as human immunodeficiency virus and malaria, as well as poverty are prevalent in Africa[5]. A shift in lifestyle in urban and rural regions, has resulted to an increase in obesity. "Diabetes has taken precedence in this region" and others[5,6]. Europe is grouped into 56 countries, with socioeconomic levels ranging from low to high[7]. Age is the most important risk factor for diabetics. Diabetes is expected to affect 56 million people in Europe, with adults accounting for 8.5%[7]. The top three nations in the Middle East and North Africa with the highest comparative frequency are Saudi Arabia, Kuwait, and Qatar[6,7]. The rapid rise in economic growth, along with an aging population, has led to a substantial rise in the prevalence of T2DM[4]. Rapid urbanization, lower infant mortality, and increasing life expectancy are the primary drivers of the increase in T2DM prevalence[4]. North America and the Caribbean have the second-highest comparative prevalence of adult diabetes (9.6%)[4]. If the main North American countries of the United States (US), Mexico, and Canada were included in the figure because of their large population, the Caribbean islands would still have the greatest occurrence[4,7]. Diabetes affects 38.6 million individuals in this region, with the number anticipated to climb to over 50 million by 2035 [7]. The US had the highest number of diabetics, at 24.4 million[4].

DIABETES IN CHILDREN AND ADOLESCENTS

Diabetes is one of the most common disorders affecting school-aged children[8]. In 2012, around 208000 young persons under the age of 20 years in the US developed diabetes[8]. Additionally, during the COVID-19 pandemic, children with newly diagnosed T1DM had higher glucose and HbA1c levels, necessitating specific actions to increase clinician and public awareness[9]. T1DM had a global incidence rate of 19.73 per 100000 children in 2019 and 32.39 per 100000 in 2020[9]. The number of pediatric cases of new-onset T1DM, diabetic ketoacidosis, and severe diabetic ketoacidosis increased by 9.5% (T1DM), 25.0% (DKA), and 19.5% (severe DKA), respectively, during the first year of the COVID-19 pandemic compared to pre-pandemic levels[9].

A high proportion of children and adolescents with type 2 diabetes are also susceptible to insulin resistance and have a family history of T2DM[8,10]. Certain racial and ethnic groups, including African Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans, have higher rates of T2DM[10]. Some children and adolescents with T2DM may not exhibit any signs or symptoms at all[10]. Other individuals' symptoms may resemble those of T1DM[10]. A toddler or teenager may feel tired, thirsty, or sick and urinate more frequently[10]. Weight loss, hazy vision, recurring infections, and delayed wound/sore healing are all possible symptoms[10]. Because symptoms vary so much, healthcare practitioners must identify and evaluate children and adolescents who are at high risk for the condition[10]. The key to controlling T2DM in children is a balanced diet and quantity management, as well as increased physical activity[10,11]. Metformin should also be recommended when T2DM is diagnosed[11]. However, data indicate that 50.0% of young people with T2DM will be unable to keep their hemoglobin A1c (HbA1c) below 8.0% on metformin alone, with or without lifestyle changes[11]. If metformin alone is insufficient to normalize blood glucose levels, insulin may be required[11,12]. At the time of diagnosis, blood pressure, lipid profile, microalbuminuria evaluation, and dilated eye examination are suggested[12].

DIABETES IN ADULTS

In 2021, diabetes was the eighth leading cause of mortality in the US, affecting more than 100000 people [13]. Nearly one-fourth of all US persons with diabetes are undiagnosed, according to the Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report[14]. Table 1 shows that this is particularly evident in younger adults aged 18-44 years[14]. More than 1/3 of the population with diabetes in this age range are unaware of or did not report having diabetes[14].

Though the trend in the incidence of diabetes among adults has been decreasing significantly since 2008, Table 2 shows that there were still 1.4 million new cases in 2019[15]. It is also worth noting that incidence rates are significantly higher among those with a high school education or less[16]. This indicates that more effort should be made on health education among those with lower scholastic achievements[15,16].

TREATMENT OF DIABETES AMONG PEOPLE AGED 18 YEARS OR OLDER WITH DIAGNOSED DIABETES IN THE UNITED STATES, 2015-2016

Diabetes management begins with healthy eating habits and physical activity. Since this may be challenging, medications are available to augment the achievement of better treatment results[17]. A retrospective, cross-sectional analysis of the 2003-2016 National Health and Nutrition Examination Survey data was carried out to investigate trends in the use of diabetes medications[17]. The study sampled 6323 patients[17]. Furthermore, those 18 years and older with an HbA1c greater than 6.4%, or a fasting plasma glucose greater than 125 mg/dL were included [17]. The percentage of patients taking any medication increased from 58.0% in 2003-2004 to 67.0% in 2015-2016[17]. The use of metformin and insulin analogs increased following American Diabetes Association recommendations in 2007 when metformin was and continues to be the preferred first-line therapy for T2DM[17]. Among patients on one therapeutic agent, the use of metformin increased from 33.0% in 2003-2004 to 74.0% in 2015-2016 [17]. Risk factors for T2DM in adults include: Overweight or obesity, age of 45 years or older, a family history of diabetes, decreased physical inactivity, and history of gestational diabetes[18]. Figure 2 shows the distribution of diabetes across races/ethnicity. Diabetes is most prevalent among American Indians and Alaska Natives (14.5%), followed by Blacks (12.1%), people of Hispanic origin (11.8%), Asians (9.5%), and Whites (7.4%)[19].

Table 1 Diagnosed and undiagnosed diabetes among people aged 18 years or older in the United States, 2019

Characteristics		Undiagnosed diabetics (number in millions)	Total diabetics (number in millions)
Total	28.5	8.5	37.1
Age (year)			
18-44	3.5	2.1	5.6
45-64	11.8	3.8	15.5
≥ 65	13.2	2.6	15.9
Sex			
Men	15.4	3.6	19.1
Women	13.1	4.9	18.0

Data sources: 2017–March 2020 National Health and Nutrition Examination Survey; 2019 United States Census Bureau data[14].

Table 2 New cases of diagnosed diabetes among people aged 18 years or older in the United States, 2018-2019

Characteristics	Population estimates, number in thousands	Incidence estimates, rate per 1000
Total	1398	5.9
Age in year		
18-44	401	3.2
45-64	703	10.1
≥ 65	293	5.8
Sex		
Men	723	6.6
Women	675	5.2

Data sources: 2018–2019 National Health Interview Survey and 2019 United States Census Bureau data[14].

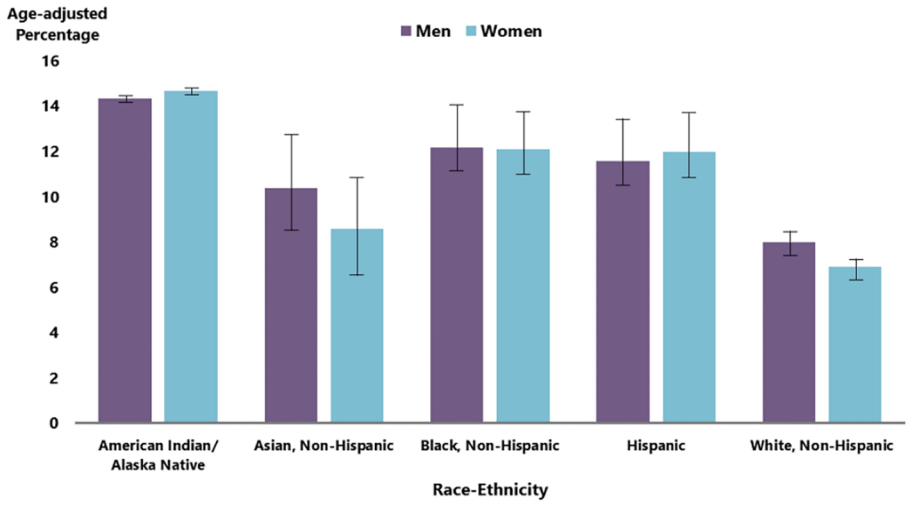

Figure 2 Diabetes by race/ethnicity. The age-adjusted estimated prevalence of diagnosed diabetes by race/ethnicity group and sex for adults aged 18 years or older in the United States, 2018–2019. Data sources: 2018–2019 National Health Interview Survey; 2019 Indian Health Service National Data Warehouse (for American Indian/Alaska Native group only)[19].

CO-MORBID CONDITIONS

The autoimmune diseases such as autoimmune thyroiditis (AIT), celiac disease (CD), Addison's disease,

and vitiligo are frequently linked to T1DM[19]. In comparison to 0.5% of the general population, CD prevalence in T1DM patients ranges from 1.5% to 10.0%[20]. It is important to note that people who develop both illnesses have an earlier age onset for TIDM than patients who just have T1DM[20]. Furthermore, 3.4% - 50.0% of people with T1DM also have AIT[20]. Anti-thyroid antibodies are developed in 11.0% - 16.9% of T1DM patients within the first year of diagnosis, with females being more frequently impacted[20]. Up to 2.0% of T1DM patients may have anti-adrenal autoantibodies[20]. It is commonly known that autoimmune diseases like diabetes and vitiligo are related. About 6.0% of diabetic children have vitiligo[20]. Additionally, T1DM has been linked to non-autoimmune diseases such as eating disorders[20].

The most common conditions seen in T2DM, according to previous research and American Diabetes Association guidelines, are hyperlipidemia, hypertension, obesity, depression, chronic obstructive pulmonary disease/asthma, coronary artery disease (CAD), chronic kidney disease (CKD), arthritis, cancers, neuropathy, heart failure, fractures, peripheral arterial disease, and retinopathy[21]. According to a study by Lin *et al*[21], persons over 65 years of age are more likely than those under 65 years to have multiple co-morbid conditions. Additionally, they discovered that older persons were less likely to be obese and depressed but more likely to have hyperlipidemia, hypertension, CAD, CKD, arthritis, malignancy, and heart failure[21]. With this information in mind, customized management plans should be created for frequent comorbidity clusters.

COMPLICATIONS

Diabetes can cause long-term harm to the heart, blood vessels, eyes, kidneys, and nerves. Smoking cigarettes, being overweight or obese, doing little or no physical activity, having high blood pressure, and hyperlipidemia are risk factors for developing diabetes complications[22]. According to a multi-national study, heart disease and stroke account for 50.0% of diabetes-related deaths[23]. In comparison to adults without diabetes, patients with diabetes over the age of 18 years have 1.7 times higher risk of dying from cardiovascular disease[24]. In 2011, the CDC found that nearly one-third of diabetics aged 35 years or older had a history of heart disease or stroke. It has been reported that coronary heart disease (21.9%) affects more people than stroke (9.1%)[22].

Diabetes has major complications that may be fatal, such as hyperglycemic crises, which include diabetic ketoacidosis and hyperglycemic hyperosmolar condition[20]. Death rates have progressively decreased over time, but 17.3 per 100000 people still die each year[24]. In 2011, 44.0% of all new cases of renal failure were caused by diabetes. In the same year, 228924 people of all ages were undergoing diabetes-related dialysis or a kidney transplant, while 49677 people of all ages started therapy for kidney failure[24]. The minor blood vessels in the retina are harmed by diabetic retinopathy, which causes blindness. Diabetes is responsible for 1.0% of blindness worldwide[23]. Furthermore, diabetes may result in amputations. Foot neuropathy raises the risk of developing foot ulcers, getting infected, and ultimately leading to an amputation[23]. Around 73000 non-traumatic lower limb amputations occurred in 2010 for adult diabetics. Overall, these patients comprise about 60.0% of all non-traumatic lower-limb amputations in adults over the age of 20 years[24].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 1 DIABETES MELLITUS

One of the factors associated with the risk of T1DM is genetic variation. Some families have an inherited propensity for T1DM development[25]. It has been shown that the immune system can distinguish between proteins produced by the body's own cells and those produced by foreign invaders with the aid of the human leukocyte antigen (HLA) complex[25]. An increased risk of T1DM exists with some HLA variations on chromosome 6[25]. Hundreds of genes that are known to play a role in the immune system are found in the genetic sequence area. The genes frequently linked to T1DM have been identified to be part of the HLA class II genes. These genes include *HLA-DQA1, HLA-DQB1,* and *HLA-DRB1*[25].

An estimated 40.0%–50.0% of the heritable risk for T1DM is attributed to HLA class II genes[26]. Researchers discovered a significant link between T1DM and the haplotypes DQA1*0501-DQB1*0201 and DQA1*0301-DQB1*0302 in Caucasian populations[26]. A haplotype is a group of single nucleotide polymorphisms that are located on the same chromosome[26]. Further research revealed that different races have different high-risk haplotypes for T1DM, such as DRB1*07-DQA1*0301-DQB1*0201 for African Americans, DRB1*09-DQA1*0301-DQB1*0303 for Japanese people, and DRB1*04-DQA1*0401-DQB1*0302 for Chinese people[26]. Additionally, it was discovered that DRB1*15-DQA1*0602-DQB1*0102 were protective and linked to a lower incidence of T1DM in most populations[26]. Recent studies reveal that independent of HLA class II genes, other genes in the central, class I, and extended class I areas may also enhance the risk of T1DM[26].

People with high-risk DRB1-DQA1-DQB1 haplotypes are substantially more likely to develop T1DM than people without such a haplotype[25]. It is reported that there is an approximately 6.0% absolute risk for Caucasian people with two susceptibility haplotypes to develop T1DM by the time they are 35 years old. However, in populations where T1DM is uncommon, this number is much lower (1.0% among Asians). Two other genes, insulin (INS) and cytotoxic T lymphocyte-associated 4 (CTLA-4), are also known to affect the risk of T1DM as shown in Table 3[27,28].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 2 DIABETES MELLITUS

The metabolic illness T2DM is characterized by hyperglycemia and a lack of insulin in the blood. One of the many factors contributing to T2DM is a genetic anomaly[26]. In 2011, several studies found that about 36 genes were connected to an elevated risk of T2DM. Due to these hereditary variables, only 10.0% of T2DM cases are clinically present[26]. Table 4 lists the genes that are susceptible to T2DM[29].

Due to its function in adipose tissue and lipid metabolism, the peroxisome proliferator-activated receptors γ (PPARγ) gene is crucial for study[30]. The PPARγ gene's (Pro) function lowers insulin sensitivity while simultaneously raising the risk of T2DM[30]. In most populations, this gene is regarded as being prevalent[30]. At least one copy of the Pro allele is carried by 98.0% of Europeans. As a result, it probably accounts for a sizable part (25.0%) of T2DM in the Caucasian population[30].

Humans and most other mammals contain the proteins known as ATP binding cassette, subfamily C, member 8 (ABCC8)[31]. Sulfonylurea receptor 1 (SUR1) protein is made with the help of this gene[31]. This protein and the Kir6.2 sub-unit, which is encoded by KCNJ1, are components of the ATP-sensitive potassium channel, which participate in a wide range of physiologic responses, such as controlling the release of insulin and glucagon from the beta cells of the pancreas[31]. Insulin secretion and potassium channel function can both be impacted by a gene abnormality[31], finally leading to T2DM. Intriguingly, the distance between ABCC8 and KCNJ11—which is only 4.5 KB—is close to that of the INS gene[31]. *ABCC8 (Ala) and KCNJ11 (Lys)* gene variants have been linked to T2DM[30].

A ubiquitously expressed intracellular calcium-dependent cysteine protease known as calpain 10, which is prevalent in humans, is encoded by the CAPN10 gene[32]. An intrinsic adenine (A) to glycine (G) mutation at position 43 of a haplotype that was previously associated with T2DM appears to be important in CAPN10 transcription[32]. According to physiological research, the differences in chaplain 10 activities' effects on insulin secretion increase the risk of T2DM[32]. Studies from various ethnic groups suggest that Mexican American communities may be considerably more likely than Caucasian populations to have an increase in T2DM risks because of this locus[32].

COST OF DIABETES

Diabetes economic expenses in the US rose by 26.0% between 2012 and 2017, after accounting for inflation, because of rising diabetes prevalence and per-person costs[33]. The population aged 65 and older is most affected by the rise in diabetes prevalence and medical expenses, which adds to the rising financial burden on the Medicare program[33]. The estimated $327 billion total cost of diabetes diagnosis in 2017 includes $237 billion in direct medical expenses and $90 billion in lost productivity [33]. Average annual medical costs for individuals with diabetes are $16750, of which diabetes-related expenses account for $9000 of that total[33]. Medical costs for those with diabetes are, on average, 2.3 times more expensive than that for people without the disease[33]. The indirect costs of diabetes include increased absenteeism ($3.3 billion) and decreased productivity at work ($26.9 billion) for the employed population, as well as decreased productivity for those who are not in the labor force ($2.3 billion)[33]. In addition, indirect costs include the inability to work due to disease-related disability ($37.5 billion) and lost output as a result of 277000 premature deaths that can be directly linked to diabetes ($19.9 billion)[33].

TREATMENT

The course of treatment for diabetes varies from patient to patient depending on the laboratory test results, particularly the levels of blood glucose[34]. Blood glucose control is the main objective of every treatment plan to avoid associated problems[34]. The primary treatment modalities targeting T1DM are insulin therapy, oral hypoglycemic agents, exercise, and a regulation/monitoring of diet[34]. The primary goals of T2DM are weight loss and dietary advice. In the severe event where the aforementioned techniques fail to regulate blood glucose levels, oral medication will be administered [34].

Table 3 Estimated relative risk of genes that affect type I diabetes mellitus

Gene	Locus	Variant	Estimated relative risk
HLA-DQB1	6p21.3	*0201 & *0302	3-45
INS	11p15.5	Class I	1-2
CTLA4	2q31-35	Thr17Ala	1-2

CTLA4: Cytotoxic T lymphocyte-associated 4; HLA: Human leukocyte antigen; INS: Insulin.

Table 4 Estimated relative risk of genes that affect type II diabetes mellitus

Gene	Locus	Variant	Estimated relative risk
PPARγ	3p25	Pro12Ala	1-3
ABCC8	11p15.1	Ser1369Ala	2-4
KCNJ11	11p15.1	Glu23Lys	1-2
CALPN10	2q37.3	A43G 1	1-4

ABCC8: ATP binding cassette, subfamily C, member 8; PPARγ: Peroxisome proliferator-activated receptors γ.

CONCLUSION

Diabetes has been associated with significant financial loss for the families that are affected. It has also been associated with severe complications which could leads to death. l. T1DM and T2DM are the two types of diabetes mellitus. The former is more prevalent among children, whereas the latter is more prevalent among adults. However, there are risk factors that have been identified in children that could lead to the development of T2DM and have a negative impact on their health. Diabetes is known to cause other severe complications in patients, resulting in even more misery and premature death. Individuals' chances of developing diabetes are also affected by their race, ethnicity and lifestyle. Perhaps this is related to the social and economic factors among these races. In people suffering from this disease, fortunately, interventions as well as treatment options are available.

FOOTNOTES

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MINIREVIEWS

Advances in the mechanism of action of metformin in pituitary tumors

Long-Yao Zhang, Yu-Hua Yin, Xue-Jian Wang

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Abstract

Pituitary tumors are common intracranial tumors, but when faced with drug-resistant or aggressive tumors, existing medical measures may not provide good control, leading to progression and deterioration. Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is uncertain whether it will provide new adjuvant or alternative therapies for the treatment of these tumors. We analyzed the potential mechanisms of action of metformin with respect to the inhibition of pituitary tumor growth and hormone secretion by reviewing the available literature.

Key Words: Metformin; Pituitary tumor; Mechanism; Treatment; Study; Review

Core Tip: Pituitary tumors are common intracranial tumors, but when faced with drug-resistant or aggressive tumors, existing medical measures may not provide good control, leading to progression and deterioration. Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is uncertain whether it will provide new adjuvant or alternative therapies for the treatment of these tumors. We analyzed the potential mechanisms of action of metformin on the inhibition of pituitary tumor growth and hormone secretion by reviewing the available literature.

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INTRODUCTION

Pituitary adenoma is a common intracranial tumor, accounting for approximately 10% to 15% of neurological tumors, and its incidence is second only to glioma and meningioma[1-5]. Pituitary tumors originate in the anterior pituitary gland and are usually benign lesions with slow growth. They are classified according to their size: Pituitary microadenomas (< 1 cm in diameter), macroadenomas (≥ 1 cm in diameter) and giant adenomas (> 4 cm in diameter)[6,7]. According to their different growth sites, they can secrete different hormones such as growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), and thyrotropin, or they can be nonfunctional adenomas that do not secrete hormones. Clinical manifestations mainly include the mass effect of the tumor and endocrine symptoms due to hyper- or hypofunction of the pituitary or target gland[8-10]. Although most pituitary tumors can be controlled by drug therapy, surgery, and radiation therapy, some of these tumors may become drug resistant or recurrent, or even invade surrounding tissue structures, which may make treatment more difficult or prevent effective control of the tumor to achieve the desired therapeutic goals. A such, it is critical to find alternative therapies or new technologies to control the growth and hormone secretion of resistant or invasive pituitary tumors.

Metformin is a drug widely used in the treatment of diabetes mellitus, given its ability to reduce liver damage, promote insulin production, and increase insulin sensitivity and peripheral glucose utilization. In recent years, a number of *in vitro* and *in vivo* studies and reviews have shown that metformin has the effect of inhibiting the growth of various types of tumors or cancers, including neuroendocrine tumors, through various mechanisms[11-19]. This indicates that metformin may help to reduce the possibility of tumor or cancer occurrence and provide treatment benefits in patients. Although there are some epidemiological data demonstrating the relationship between metformin and risk reduction in patients suffering from multiple tumors or cancers, the role of metformin in cancer treatment is not yet fully clear[3,11,17,20-23]. Here, we review the available literature on the role of metformin in pituitary tumors and discuss the potential mechanisms of action of this drug with respect to the treatment of these tumors (Figure 1).

MECHANISM OF ACTION STUDY

Mitochondria-mediated pathways

The B-cell lymphoma 2 (Bcl-2) family is a key regulatory member of the mitochondrial-mediated apoptotic pathway, activating the downstream death program, which in turn leads to caspase-3 enzyme cleavage and ultimately apoptosis, characterized by a decrease in mitochondrial membrane potential (MMP).

In one study, decreased MMP, increased expression of pro-apoptotic proteins, and decreased expression of anti-apoptotic proteins were observed in GH3 cells treated with metformin. This finding suggests the involvement of the mitochondria-mediated apoptotic pathway, indicating that metformin may induce apoptosis in GH3 cells by downregulating the Bcl-2/BAX ratio and inducing caspase-3 cleavage activation and thus achieve anti-tumor effects[24]. In another study, metformin was observed to inhibit the proliferation of MMQ, cells and similar mitochondria-mediated apoptosis and experimental results were observed[25].

Another study observed that metformin inhibited the proliferation of ACTH-secreting mouse pituitary cortical dystrophoma cells AtT20, promoted apoptosis, and reduced ACTH secretion, but did not prevent progression of the cell cycle. Metformin-induced apoptosis was accompanied by an increase in caspase-3 activity, while metformin downregulated the anti-apoptotic protein Bcl-2 but upregulated the pro-apoptotic protein BAX, suggesting the involvement of a mitochondria-mediated apoptotic pathway[26]. However, a different study suggested that metformin does not increase apoptosis in GH3 pituitary tumor cells, possibly due to the experimental design or the nutritional environment used; this effect of metformin needs further investigation[27].

AMPK-mediated related pathways

In one study, adenosine monophosphate activated protein kinase (AMPK) was found to mediate growth inhibition or apoptosis of many types of tumor cells[2,28-30]. As metformin is an activator of the AMPK pathway[2], it has been suggested that it activates AMPK by restricting complex I in the mitochondrial respiratory chain, generating cellular energy stress, and thus activating AMPK[27,31-33] and indirectly

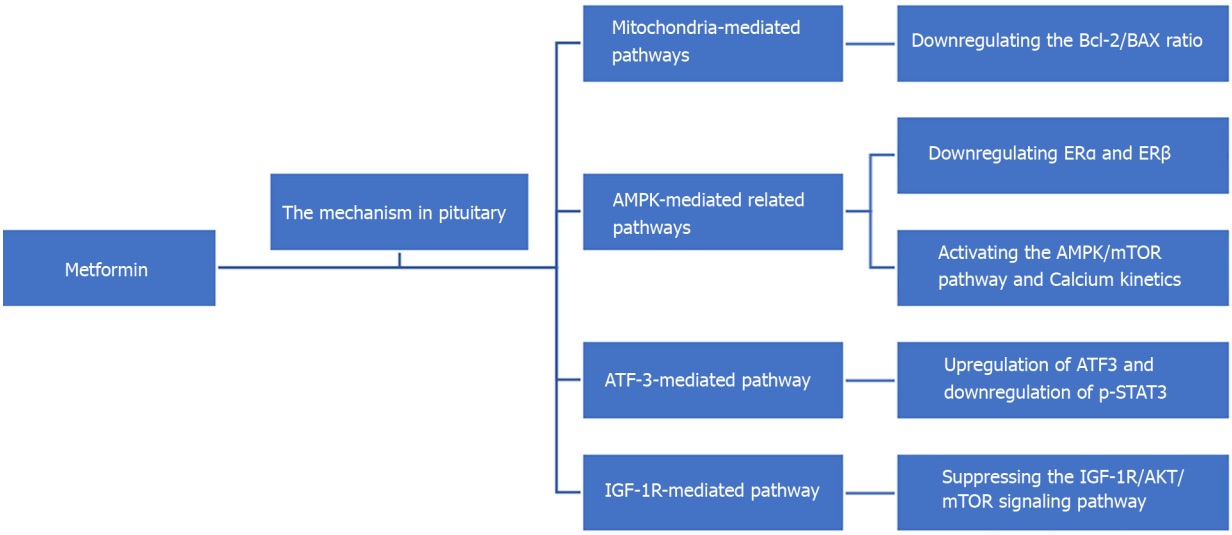

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Figure 1 Potential mechanisms of metformin in the treatment of pituitary tumors. AMPK: Adenosine monophosphate activated protein kinase; ATF: Activating transcription factor; AKT: Protein kinase B; BAX: Bcl-associated X, IGF: Insulin-like growth factor; mTOR: Mammalian target of rapamycin.

by increasing the [AMP]:[ADP] ratio[28]. However, it is not clear what the role of metformin may be in pituitary tumors, raising concerns about its mechanism of action in pituitary tumor cells.

Previous work has noted sex-dependent effects of mesenchymal epithelial transition (MET) on serum PRL levels, suggesting that the hypothalamic-pituitary-gonadal axis may be a target of metformin. One study investigated the AMPK agonist by measuring AMPK phosphorylation in human primary prolactinoma samples using bromocriptine (BC)-sensitive MMQ cells and BC-resistant GH3 cells and their xenografts as models. The role of MET in prolactinoma and the downstream effectors were investigated. It was proposed that AMPK signaling is inhibited in D2R-positive BC-resistant human prolactinomas. The AMPK activator MET inhibited the proliferation of BC-sensitive (MMQ) and drug-resistant (GH3) prolactinoma cells. It has also been shown that bromocriptine resistance is associated with downregulation of AMPK activity and high estrogen receptor (ER) expression, and that MET downregulates ERα and ERβ by activating the AMPK signaling pathway and inhibits prolactinoma growth and PRL secretion[34]. Overall, MET inhibits prolactinoma growth and PRL secretion by activating the AMPK signaling pathway.

It has been shown that metformin enhances phosphorylated AMPK expression and decreases phosphorylation levels of mammalian target of rapamycin (p-mTOR) expression in MMQ cells. Additionally, compound C, an AMPK inhibitor, reduces the inhibitory effect of metformin on p-mTOR expression. It has been suggested that metformin activates the AMPK/mTOR pathway, which may be part of the mechanism to inhibit MMQ cell proliferation and induce apoptosis and G0/G1 phase block [25]. Meanwhile, metformin significantly increased the levels of phosphorylated AMPK, phosphorylated protein kinase B, and phosphorylated mTOR in AtT20 cells in a dose-dependent manner, demonstrating that metformin activated AMPK and inhibited mTOR in AtT20 cells, suggesting that the activation of AMPK/mTOR signaling pathway may be related to metformin-induced proliferation inhibition and apoptosis promotion in AtT20 cells. However, it remains to be verified whether the activation of AMPK is related to the reduction of hormone secretion[26].

However, another study found that in GH-secreting PitNET cells, metformin induced GH3 cells to inhibit the target of epidermal growth factor (EGF) -induced mTOR-p70S6 6 kinase signaling pathway. As a potential mechanism, it was suggested that downstream EGF receptors were incorporated into AMPK substrates, indicating that membrane receptors are direct targets and may be involved in mediating their inhibitory effects on cell growth. In this study, the presence of AMPK targets, including cell surface receptors in GH3 cell membranes, was demonstrated using protein fractions[27].

Calcium has been reported to be a relevant second messenger for pituitary cell physiology. It has been shown that the effect of metformin on PitNET may involve AMP-activated protein kinase-dependent calcium kinetics, thereby altering cell viability. However, the altered calcium kinetics induced in different pituitary tumor cells are variable, suggesting that metformin inhibits different types of pituitary tumor cells differently, and that the observed altered calcium kinetics appear to be related to hormone secretion[35].

Activating transcription factor-3-mediated pathway

Activating transcription factor 3 (ATF3) is a stress response transcription factor belonging to the ATF/CREB family. In one study, ATF3 was found to be upregulated by metformin, and its knockdown

significantly reduced metformin-induced apoptosis, suggesting that ATF-3 may mediate the pro-apoptotic effect of metformin. The inhibitory effect of compound C on AMPK did not alter the inhibitory effect of metformin on STAT3 activity, suggesting that metformin may reduce GH secretion by inhibiting non-AMPK-dependent STAT3 activity. Metformin also significantly inhibited cell proliferation and GH secretion in primary human growth hormone-secreting pituitary adenoma (GH-PA) cells. Upregulation of ATF3 and downregulation of p-STAT3 were also demonstrated in xenografts. It was revealed that metformin inhibited the growth of somatic dystrophic adenoma cells both *in vitro* and *in vivo* through ATF-3-mediated pro-apoptotic effects. These findings suggest that metformin is a potentially promising therapeutic agent for the treatment of GH-PA[24].

Insulin-like growth factor -1R-mediated pathway

Insulin-like growth factor (IGF) -1R is an important growth factor receptor that activates the downstream phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway upon binding to IGF-1. The overactivation of this pathway is associated with tumor development. It has been observed that IGF-1R, p-AKT (S473), and p-ERK levels decreased with increasing metformin concentration after treatment. The IGF-1R inhibitor PPP inhibited MMQ cell proliferation, suggesting that metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells[25]. These results suggest that metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells.

In another study, metformin decreased IGF-1R expression, AKT (S473) phosphorylation, and mTOR (Ser2448) phosphorylation, which inhibited AtT20 cell proliferation, Moreover, PPP (an IGF-1R inhibitor) significantly inhibited AtT20 cell proliferation in a dose-dependent manner, suggesting that IGF-1R plays a role in tumor progression. Taken together, these findings suggest that metformin may inhibit AtT20 cell proliferation by suppressing the IGF-1R/AKT/mTOR signaling pathway[26].

DISCUSSION

It is known from the above studies that there may be multiple pathways for the effect of metformin on pituitary tumors, but the complete mechanisms of these different pathways are not entirely clear. Moreover, the findings and opinions on the same pathway are not consistent. The effects of metformin have been attributed to its actions on different cells or in different environments. Indeed, it has been pointed out that the effect of metformin at the cellular level depends on the metabolic characteristics and metabolic demands of the cells, and the tumor microenvironment may influence this response. Pyruvate metabolism branching points are likely to play a major role in the variability of the cellular response to metformin, a role supported by significant differences in pyruvate dehydrogenase complex expression levels between myogenic cells and pituitary tumor cells[36]. Research conducted *in vitro* and in and clinical trials are still limited or unavailable; as such, more evidence is needed to verify the accuracy of these ideas.

There is *in vitro* evidence suggesting that it may not be feasible to achieve high concentrations of metformin in humans[37,38]. The observation that the prevalence of various tumor types is lower in patients with type 2 diabetes on regular metformin doses and that serum concentrations of metformin are much lower than those that inhibit cancer cells *in vitro* raises the possibility that the mechanism of tumor prevention *in vivo* with regular therapeutic doses of metformin may be largely indirect and related to metformin ameliorating such metabolic or hormonal abnormalities such as obesity, hyperglycemia, and hypertension. It is also important to consider that there may be physiological metabolic differences between rat pituitary tumor cell lines and human pituitary tumor cell lines, among others.

Despite these studies, metformin has not been formally used as a clinical treatment for pituitary tumors. There have been case reports of reduced prolactin levels and tumor size in 2 patients treated with a combination of bromocriptine and metformin, whereas bromocriptine alone was not sufficient to reduce prolactin levels or slow tumor growth[39]. In another case report, the combination of bromocriptine and metformin reduced prolactin levels and tumor size. In a third case report, the combination of metformin and capsaicin did not show consistent inhibition of serum prolactin levels in either the short- or long-term in 10 patients with prolactinoma resistant to capsaicin[40]. Additional studies have evaluated the effects of metformin on cell viability and hormone secretion when combined with other agents; for example, metformin/somatostatin (SSA) analog combination therapy did not increase the effectiveness of SSA monotherapy[34]. Metformin/SSA combination therapy did not increase the effectiveness of SSA monotherapy, but did appear to enhance the role of octreotide in GHomas, and MET + BC significantly inhibited PRL secretion, further reducing tumor growth and serum PRL levels in xenografts when compared to BC treatment alone[35]. However, in the face of metformin treatment, the tumor growth and serum PRL levels in xenografts were further reduced.

The heterogeneity among patients with pituitary tumors and the diversity of drug treatment options add to the complexity of disease treatment, and further studies are needed to demonstrate whether treatment with metformin alters the risk of pituitary tumor morbidity and mortality and to determine

the dose and duration of treatment and the effect when combined with other drugs. It is also important to consider whether it is reasonable to use metformin to treat pituitary tumors in patients without diabetes and to pay mind to the potential side effects or complications of using different concentrations of metformin in humans. Attention to these possible issues could help to improve the management of pituitary tumor patients in a more individualized manner. Given the available data, the use of metformin may be a promising and clinically relevant option for patients with pituitary tumors. Further studies are needed to confirm metformin's clinical relevance as an adjuvant or novel therapy and to further develop a comprehensive understanding of the potential antitumor mechanisms of this drug in the treatment of pituitary tumors.

CONCLUSION

Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been several studies on the mechanism of metformin for the treatment of pituitary tumors, but it remains to be investigated whether it will be incorporated as an alternative therapy for the treatment of these tumors.

FOOTNOTES

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SYSTEMATIC REVIEWS

Pulmonary cytomegalovirus infection: A case report and systematic review

Awotar Kanika, Jonathan Soldera

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Abstract

BACKGROUND

Cytomegalovirus (CMV) is a common virus that can cause the first infection in childhood or adolescence and reactivate later in life due to immunosuppression. CMV pneumonia is a rare illness in immunocompetent patients but is one of the most significant opportunistic infections in immunocompromised patients.

AIM

To report a case and review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

METHODS

We conducted a systematic search on the MEDLINE (PubMed) database, without date or language restrictions, to identify relevant studies using Medical Subject Headings and Health Science Descriptors. We manually searched the reference lists of the included studies. Simple descriptive analysis was used to summarize the results.

RESULTS

Our search identified 445 references, and after screening, 43 studies reporting 45 cases were included in the final analysis, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever (82%) and dyspnea (75%) were the most common clinical findings. Thoracic computed tomography showed bilateral ground-glass opacities, a relevant differential diagnosis for severe acute respiratory syndrome coronavirus 2 infection. The majority of patients (85%) received antiviral therapy, and 89% of patients recovered, while 9% of patients died.

CONCLUSION

CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients. Clinicians should be aware of the clinical presentation, management, and outcomes of CMV

pneumonia to guide appropriate treatment decisions.

Key Words: Cytomegalovirus; Immunocompromised; Immunocompetent; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019; Ganciclovir

Core Tip: The paper reports a case of disseminated cytomegalovirus (CMV) infection in an immunocompetent patient who presented with cough, dyspnea, high-grade fever, and jaundice. The patient was diagnosed with CMV pneumonia after developing sepsis and being admitted to the intensive care unit. The study conducted a systematic search on the MEDLINE database to identify published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients. The search identified 43 studies reporting 45 cases, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever and dyspnea were the most common clinical findings, and thoracic computed tomography showed bilateral ground-glass opacities. The majority of patients received antiviral therapy, and 89% of patients recovered, while 9% of patients died. The study highlights that CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients, and clinicians should be aware of the clinical presentation, management, and outcomes of CMV pneumonia to guide appropriate treatment decisions.

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INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus that belongs to the herpesviridae family and shares similarities with other herpes viruses. In immunocompetent adults, CMV infection is usually asymptomatic and causes mild mononucleosis-like syndrome, typically in childhood or adolescence. However, CMV can cause severe disease and pneumonia in immunocompetent individuals, albeit rarely[1,2]. CMV infection may lead to severe viral pneumonitis in immunocompromised patients, such as those with autoimmune deficiency syndrome (AIDS), allogeneic bone marrow transplantation recipients, or those on immunosuppressive drugs or high-dose steroids. The incidence of CMV infection is approximately 25%-30% in recipients of hematopoietic stem cell transplantation[3]. The gastrointestinal tract and central nervous system are the most frequent sites of severe CMV infection. CMV was one of the three most common causes of severe viral community-acquired pneumonia (CAP), along with influenza and adenovirus. However, this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020[4]. The pulmonary manifestations of CMV infection may vary from a dry cough to severe interstitial pneumonia, with patients presenting with diffuse pulmonary infiltrates resembling a ground glass appearance. The diagnosis of CMV pneumonia is based on radiological patterns and serology (CMV IgM antibody) or polymerase chain reaction (PCR)[4]. In 1968, the first case of CMV CAP was reported by Carlstorm and colleagues in their case series of CMV infection in immunocompetent hosts[5]. CMV CAP in immunocompetent hosts presents as prolonged fever and interstitial infiltrates on chest X-ray that resolved slowly over 6 wk. Patients with CMV CAP present with relative lymphopenia, atypical lymphocytes, and mildly elevated serum transaminases. Primary CMV infection persists for life and is generally acquired through close physical contact involving direct inoculation with infected cells or body fluids. The spread of viral infection is through coughing, direct contact with body fluids such as blood, urine, feces, semen, vaginal fluid, and breast milk, or *via* mucous membranes, including the mouth or genitals. CMV infection following transplantation can be acquired if the transmission is from the organ from a CMV-seropositive donor. Mothers infected with CMV during pregnancy may transmit this infection to their newborn baby, leading to congenital CMV. CMV infection is one of the leading causes of miscarriage[1,6]. Babies with congenital CMV sometimes may be healthy for months or years after birth but may have late occurring signs such as hearing loss, and develop vision problems and developmental delay. Latent CMV can reactivate and replicate rapidly when the immune system is suppressed. It can lead to high levels of CMV viremia, and infection of multiple organ systems can cause severe illness such as retinitis, colitis, hepatitis, pneumonia, or encephalitis. Fatal CMV pneumonia is more common in patients who have received marrow transplants than those who received transplant of solid organs like the lung, heart, liver, or kidney[7,8]. CMV accentuates the sepsis-induced immunologic effects, leading to an increase in the risk for secondary

infections. CMV infection in critically ill patients is associated with prolonged ventilator support, nosocomial infections, prolonged hospital/intensive care unit (ICU) stay, and increased mortality rates [9].

As the coronavirus disease 2019 (COVID-19) pandemic continues and becomes an endemic, it is crucial to recognize that not all clinical and radiological presentations are solely attributable to COVID-19[10]. Therefore, diagnostic differentiation is essential, and ground-glass opacities (GGOs) must be evaluated in conjunction with other imaging findings, laboratory tests, and clinical features to reach a definitive diagnosis. CMV pneumonia can be diagnosed by detecting the virus in serum and/or respiratory samples such as bronchoalveolar lavage (BAL) or tracheal aspiration[10]. Quantitative real-time PCR (qRT-PCR) can be utilized to measure viral loads in blood and BAL fluid[11]. Lung biopsy histopathology is considered the gold standard for diagnosing pulmonary CMV infections, with the presence of CMV inclusion bodies (owl's eye) in biopsy specimens being confirmatory of lung infection [12]. However, the diagnostic yield of lung biopsy for diagnosing lung CMV infections can vary as inclusions may not always be visualized. Immunohistochemical (IHC) staining for CMV in cytological specimens of bronchial washing fluid can also detect CMV[13,14].

The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir, which inhibits viral deoxyribonucleic acid (DNA) polymerase, thereby interfering with DNA elongation. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, whereas severe illness requires initial treatment with intravenous ganciclovir or foscarnet at full doses (adjusted for renal function)[15]. Treatment at full doses should be continued until symptom resolution and blood antigenemia (or DNAemia) clears. Adjuvant treatment with intravenous immunoglobulin or CMV hyper-immunoglobulin is recommended in immunocompromised patients and may be used in cases of severe CMV disease and hypogammaglobinemia[12].

This study aimed to report a case of disseminated CMV in an immunocompetent patient, and systematically review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

Case report

Chief complaints: A 32-year-old man presented with a cough, dyspnea, high-grade fever, and jaundice.

History of present illness: The patient had no significant medical history and was not taking any medication. Physical examination revealed a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy. The initial blood tests showed pancytopenia, elevated liver enzymes, elevated bilirubin, and hypoalbuminemia. CT of the thorax showed GGOs, while CT of the face showed sinusitis, raising suspicion of an infectious etiology.

History of past illness: The patient had no significant past medical history.

Personal and family history: No significant personal or family history was reported.

Physical examination: The patient presented with a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy.

Laboratory examinations: Complete blood count revealed a platelet count of 87000/mm^3, hemoglobin level of 8.2 g/dL, and leukocyte count of 4830/mm^3. Liver function tests showed alkaline phosphatase of 1174 U/L, gamma-glutamyl transferase of 804 U/L, aspartate aminotransferase of 403 U/L, total bilirubin of 17.2 mg/dL, albumin of 1.7 g/dL, and international normalized ratio of 1.11. Autoimmune antibody testing for fluorescence antinuclear antibody was negative. COVID-19 antigen swab test was negative.

Imaging examinations: After a liver biopsy, the patient's results were suggestive of drug-induced liver injury, and subsequent immunochemistry testing returned negative results for CMV. Magnetic resonance imaging (MRI) of the abdomen showed a liver with enlarged dimensions, regular contours, and heterogeneous signal intensity, with predominance of hyper signal in the T2-weighted sequences, suggestive of an inflammatory process (hepatitis), and splenomegaly and pancreatic edema suggestive of pancreatitis. CT of the thorax showed GGOs (Figure 1), while CT of the face showed sinusitis.

Final diagnosis: The patient's clinical condition worsened, and he developed hypotension and sepsis, requiring admission to the ICU. Broad-spectrum antibiotics were started, and he was investigated for possible Wegener's granulomatosis. However, auto-antibodies were negative and his final diagnosis was disseminated CMV infection, confirmed by the high viral load of 325192.5 copies/mL.

Treatment: The patient was started on ganciclovir therapy.

Outcome and follow-up: After 6 wk of treatment, the patient recovered completely from his symptoms, achieving a sustained undetectable viral load.

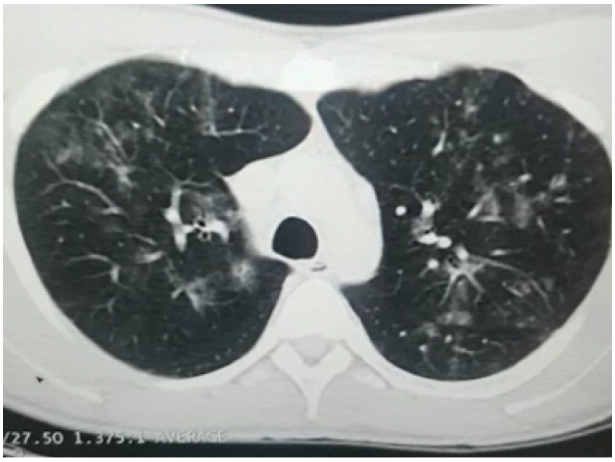

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Figure 1 Computed tomography of the thorax showing ground glass opacities.

MATERIALS AND METHODS

This study followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16].

Data sources

The electronic database MEDLINE (PubMed) was searched using the terms described in the Supplementary material. The searches were conducted in September and October 2022, with no date of publication restrictions and language restricted to English. References of included studies were screened for relevant records, and the reference lists of the retrieved studies were submitted to a manual search.

Inclusion and exclusion criteria

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 also included, as long as the data available made data collection possible. Studies written in languages other than English were excluded. Studies having other co-existing causes of pneumonia were excluded from our study, for example, superimposed bacterial, parasitic, or fungal infections in existing CMV pneumonia, and other lung pathologies.

Study selection and data extraction

Titles were screened initially to select the cases of pulmonary complications of CMV infection and filter out non-relevant studies. Then, abstracts of chosen studies were read to select potentially relevant papers. The third step was the analysis of the full-length papers, and those which were not case reports of pulmonary CMV were filtered out. Data was extracted on the characteristics of the subjects and the outcomes measured from each eligible study. A table of extracted data on eligible studies was made in order to measure and identify patterns.

RESULTS

Using the search strategy, a total of 435 references were retrieved. After reviewing titles, 232 studies were found to be relevant for our topic and 203 studies were excluded. By analyzing abstracts, 172 studies were found to be potential relevant papers for our topic and therefore 60 studies were excluded. After reading and analyzing full length papers, 43 studies with 45 case reports of pulmonary CMV infection were included. The data of 45 case reports was extracted and prepared in Table 1 to measure and identify the patterns to get the results to reach a conclusion. Figure 2 shows the PRISMA search strategy. Every study included was a case report.

The baseline features are described in Table 2 and Table 3 for the 45 patients who were included for data extraction. All patients were diagnosed with CMV pneumonia. The majority of patients were males (58%) and in the age group of 16-45 years (55.6%). The most common symptoms reported were fever (82%), dyspnea (76%), and cough (53%). Respiratory distress was observed in 58% of the patients. Almost two-thirds of the patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients by chest X-ray and 69% by CT. Blood/serum was the most commonly used method for serology testing (89%), and bronchoalveolar fluid was used in 45% of the cases.

Table 1 Summary of systematically reviewed clinical cases of cytomegalovirus pneumonia

Ref.	Age	Sex	Clinical findings	Immune status	Radiographic findings	Serology	Immunohistochemistry & biopsy	Treatment	Out-come
Luís *et al*[22], 2021	42	M	Fever, headache, odynophagia, bilateral otalgia	Immunocompetent	CXR – B/L infiltrates; Thoracic CT – B/L GGO	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Balakrishnan *et al* [23], 2022	41	M	Fever, cough, weight loss	Immunocompromised; chronic glomerulo- nephritis, IgA nephropathy; on immunosup-pressive drugs	CXR – B/L infiltrates; Thoracic CT – B/L GGO, patchy consolidation, nodular opacities	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Valganciclovir	Recovery
Basinger *et al*[24], 2022	70	M	Rapid decline in general condition, resp. distress	Immunocompromised; a history of allogenic hematopoietic stem cell transplant	Rapidly progressive bilateral pulmonary nodules	Not done	Post mortem cytopatholog. Change, consistent with CMV infection, confirmed by IHC	Not initiated	Died
Gonçalves *et al* [2], 2018	29	M	Fever, headache, malaise, cough, thoracic pleuritic pain	Immunocompetent	Thoracic CT showed bilateral infiltrates	Blood – positive for CMV IgG and IgM; BAL – CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Wong *et al*[25], 2022	37	M	Fever, cough, dyspnea	Immunocompromised; X-linked agammaglobulinemia is a hereditary immune disorder		CMV positive		Antiviral and immune globulin therapy	Recovery
Gangemi *et al* [26], 2021	72	M	Non-healing buccal ulcer, fever, acute hypoxic respiratory failure, worsening odynophagia, weight loss	Immunocomromised; oropharyngeal Ca in remission	Chest X-ray – patchy opacities of B/L lung fields; Thoracic CT – bilateral upper and lower lobe consolidations, B/L pleural effusions	Positive for both CMV IgG and IgM		Ganciclovir and valganciclovir	Recovery
Patil *et al*[27], 2020	23	F	Worsening dyspnea, high grade fever, dry cough	Immunocompetent	Chest X-ray – mild bilateral interstitial infiltrates with small bilateral pleural effusions; CT chest - worsening of bilateral interstitial infiltrates	BAL CMV PCR and blood CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Alyssa *et al*[28], 2017	63	F	Fever, hypotension, dyspnoea on exertion, hypoxemia, weakness	Immunocompromised; diagnosis of dermatomyositis - history of prolonged use of glucocorticoids and treatment with rituximab	CT chest - bilateral GGOs in a mosaic distribution and consolidations of B/L lower lobes	CMV DNA PCR quantitation in whole blood was positive and shell-vial culture for CMV positive		Ganciclovir and valganciclovir	Recovery
Fragkiadakis *et al* [29], 2018	36	F	Fever, respiratory distress	Immunocompromised; undergone multiple transfusions, and splenectomy was done for homozygous β-thalassemia	CT chest demonstrated pneumonitis	Serology and molecular blood testing reports – CMV infection and viremia		Ganciclovir	Recovery
Waqas *et al*[30], 2019	36	M	Fever, cough, malaise	Immunocompetent	CXR – B/L infiltrates	Diagnosed with CMV infection		Ganciclovir	Recovery
Xie *et al*[31], 2021	22	M	Fever, progressive dyspnea,	Immunocompromised; newly	Chest CT – extensive GGOs of	CMV quantitative PCR		Ganciclovir	Recovery

			dry cough	diagnosed HIV infection	bilateral lungs with multiple cavity lesions in the left upper lung	positive			
Al-Eyadhy *et al* [32], 2017	12	M	Tachycardia, tachypnea, fever, severe ARDS with multi-organ failure	Immunocompetent; CMV infection associated morbidity and mortality among immune-competent children	CXR and chest CT – ARDS features	CMV PCR positive in blood	HPE of lung biopsy CMV positive	Ganciclovir	Recovery
Reesi *et al*[33], 2014	3	M	Fever, dyspnea	Immunocompromised; acute lymphoblastic leukaemia on chemotherapy	CXR - pulmonary infiltrates; CT chest - diffuse GGOs of B/L lung fields, few pleural-based nodules	BAL CMV PCR was positive; CMV IgG and IgM positive		Ganciclovir and valganciclovir	Recovery
Cunha *et al*[34], 2008	64	M	"Flu-like illness", fever, myalgias, progressive dyspnoea, and required mechanical ventilation	Immunocompetent; slowly improved over 14 d and was eventually extubated	Chest X-ray showed B/L interstitial markings that rapidly progressed over 24 h	Initially IgG, IgM and CMV PCR negative; 10 d later, IgG, IgM, and CMV PCR were positive	BAL cytology was negative for viral inclusions	Did not receive CMV antiviral therapy	Recovery
Demirkol *et al* [35], 2018	2	M	Respiratory distress, fever, multiple organ dysfunction secondary to sepsis	Immunocompetent; developed necrotizing pneumonia	Thoracic CT – features of necrotising pneumonia	Serological tests indicated that the patient had CMV reactivation	Excised lung tissue, features of CMV infection	Ganciclovir	Recovery
Margery *et al*[36], 2009	43	F	Fever, dyspnoea	Immunocompetent	Thoracic CT – diffuse GGOs	Anti-CMV IgM and PCR detection of viral DNA in serum		Not treated	Recovery
Bansal *et al*[37], 2012	45	F	Nausea and vomiting. CMV infection can present with only atypical symptoms in liver transplant patients	Immunocompromised; liver transplant due to anti- tubercular drug induced acute liver failure	CXR showed B/L infiltrates	Testing of CMV viral load showed a viral load of 9640 copies/mL		Ganciclovir	Recovery
Sunnetcioglu *et al* [38], 2016	24	M	Cough, fever dyspnoea, haemoptysis, shortness of breath, and was intubated	Immunocompromised; on immunesuppressive therapy for polyarteritis nodosa	Chest X-ray showed right-sided opacity in the middle and lower lung zones Thoracic CT showed B/L alveolar opacity	Positive test for serum CMV IgM antibodies		NA	NA
Liatsos *et al*[39], 2017	40	F	Acutely ill with fever, dry cough, and mild shortness of breath	Immunocompromised; β-thalassemia major with splenectomy, regularly transfused with packed and leukocyte-depleted red blood cells	Thoracic CT - B/L interstitial lung infiltrates and small nodules marked toward the lower lobes, with a few ground-glass areas and bilateral pulmonary effusions	Positive RT-PCR for CMV in both blood and BAL		Ganciclovir and valganciclovir	Recovery
Wickramasinghe *et al*[40], 2022	32	M	Headache, fever, cough, and shortness of breath. The patient was in respiratory distress, shifted to ICU and electively intubated	Immunocompromised; Tuberculosis meningitis	Chest X-ray showed left-sided consolidation. CT chest revealed lower lobe (left more than right) consolidation and nodules	Positive CMV IgM and negative IgG, suggesting acute infection		Antitubercular drugs and ganciclovir	Recovery
Barclay *et al*[41], 2011	38	F	Fever and non-specific symptoms & increasingly hypoxaemic	Immunocompetent	Thoracic HRCT showed diffuse multilobular ground glass appearance with	CMV IgM antibody was positive and CMV PCR was positive		Valganciclovir	Recovery

					peripheral nodular opacities				
Coussement *et al* [42], 2016	64	F	Fever, cough, dyspnea, hypoxemia	Immunocompromised; bilateral lung transplant for chronic obstructive pulmonary disease	Thoracic CT demonstrated bilateral infiltrates; abdominal CT showed peri-colic infiltration compatible with a recurrence of diverticulitis	CMV VL observed both in blood and BAL samples; a diagnosis of CMV pneumonitis using BAL sample; a macrophage characteristic of CMV viral infection	Resected colon revealed HPE CMV colitis, viral inclusions, and positive immunohistochemistry	Ganciclovir	Recovery
Kanhere *et al*[43], 2014	3 1/2	M	Fever, respiratory distress, hepatosplenomegaly	Immunocompromised; hemophagocytic lymphohistiocytosis		CMV IgM serology was reactive in both infant and mother		Ganciclovir	Recovery
Suresh *et al*[44], 2013	7/12	M	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	Chest XR -prominent bronchovascular markings	CMV IgM serology was positive and CMV PCR based on BAL was also positive		Ganciclovir and valganciclovir	Recovery
Suresh *et al*[44], 2013, Case 2	3/12	F	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	CXR normal	CMV IgM blood was raised; BAL positive for CMV PCR		Ganciclovir and valganciclovir	Recovery
Yu *et al*[45], 2017	64	M	Acute respiratory failure with renal failure	Immunocompromised; diabetic; severe CMV pneumonia with slow resolution or persistent viremia on treatment	Chest X-ray -predominately right lung infiltrates; chest CT showed multiple consolidative patches with air bronchograms	Positive CMV PCR in blood and BAL	Lung biopsy was done. Inclusion bodies, positive for CMV IHC	Ganciclovir and valganciclovir	Died
Tollitt *et al*[46], 2016	71	F	Hemoptysis	Immunocompromised; antineutrophil cytoplasmic antibody-associated vasculitis; on therapy with cyclophosphamide, steroids, and plasma exchange	Pulmonary CMV disease mimics pulmonary disease associated with vasculitis on CXR	BAL demonstrated positivity for CMV DNA and serum CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Vetter *et al*[47], 2010	70	F	Fever, nausea, dyspnea	Immunocompromised; immunosuppressive therapy with methotrexate and prednisone for large-vessel vasculitis	Chest X-ray showed no interstitial pneumonitis; chest and abdominal CT showed no signs of inflammation	CMV IgG and IgM antibodies positive; CMV PCR positive in BAL fluid		Ganciclovir	Recovery
Snape *et al*[48], 2011	28	F	Fever, cough tender sinuses, frontal headache	Immunecompetent	CXR showed consolidation of the middle and right upper lobe; Pulmonary CT angiography revealed no pulmonary embolus and patchy consolidation of B/L lungs	Positivity for CMV IgM		Valganciclovir	Recovery
Karakelides *et al* [49], 2003	47	M	Cough, hemoptysis, weight loss	Immunocompetent	CXR and chest CECT showed a 3.5-cm cavitary mass, upper lobe of left lung and mild left mediastinal and hilar adenopathy	Transbronchial biopsy - CMV inclusions	Wedge excision of left upper lung mass; HPE -nuclear & cytoplasmic inclusions of CMV	NR	Recovery

Shimada *et al*[50], 2004	27	F	Fever	Immunocompromised; on immunosuppressive treatment for viral-associated hemophagocytic syndrome	CXR and chest HRCT – diffuse small pulmonary nodules	CMV DNA PCR was positive on bronchoalveolar lavage cells; immunoassay pp65 CMV antigen positive	Lung biopsy inclusion-bearing cells for CMV	Gancyclovir	Recovery
Simsir *et al*[51], 2001	43	M	Malaise, fever, pleuritic chest pain, epigastric pain, diarrhea, nausea, vomiting	Immunocompromised; underwent renal transplant secondary to diabetic nephropathy	CXR showed a nodule in the upper lobe of the right lung; chest CT revealed bilateral smaller pulmonary nodules	CMV antigen test was positive, with negative CMV IgG	CMV was established by fine-needle aspiration biopsy of the lung nodule	Gancyclovir	Recovery
Abbey *et al*[52], 2014	51	M	Fever, dry, cough, dyspnoea, general malaise	Immunocompromised; Crohn's disease on azathioprine; also had mild pancreatic insufficiency and bile salt malabsorption	CXR showed bilateral infiltrates in middle and lower zones; chest CT showed B/L small pleural effusions and B/L basal lung consolidation	CMV IgM positive, acute CMV infection		Ganciclovir and valganciclovir	Recovery
Belin *et al*[53], 2003	47	F	Shortness of breath, fever, stomatitis, genital ulcerations, burning sensations	Immunocompromised; severe rheumatoid arthritis, on prednisolone, methotrexate, and cyclosporine	CXR showed interstitial infiltrates in both lung bases	BAL showed CMV mRNA		Ganciclovir	Recovery
Kaşifoğlu *et al* [54], 2006	21	F	Polyarthralgias, fatigue, fever, muscle weakness, non-productive cough, dyspnea	Immunocompromised; dermatomyo-sitis, treated with azathioprine, prednisolone, and cyclosporine	Chest XR showed bilateral interstitial infiltration; chest HRCT - bilaterally ill-defined multifocal GGOs	Positivity for anti-CMV, IgM, and anti-CMV IgG antibodies and presence of CMV DNA by PCR		Ganciclovir	Recovery
Chen *et al*[55], 2010	5	M	Fever, cough, dyspnea, hypoxemia, ARDS	Immunocompetent; the patient developed ventilator-associated pneumonia, and died of burkhoderia sepsis	Chest XR – multiple parenchymal consolidations; chest XR disclosed "white lung" during the second week	Positive PCR; bronchoal-veolar and seroconversion of CMV IgM and IgG		NR	Died
Tambe *et al*[56], 2019	32	F	Fever, dyspnea, generalized rash, weakness	Immunocompromised; stage IV, classical Hodgkin's lymphoma, treated with chemotherapy	Chest CT revealed bilateral pulmonary infiltrates and bilateral pleural effusion	CMV was detected on BAL culture; serum quantitative CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Boussouar *et al* [57], 2018	47	F	Dry cough, chest pain and fever	Immunocompromised; orthotopic heart transplant and immunosup-pressive treatment was initiated with corticosteroids, cyclosporine, and mycophenolate	Chest XR - alveolar opacities with upper lobe predom-inance; chest CT revealed consolidation in the right upper lobe associated with septal thickening and multiple nodules	Blood CMV PCR, which has been undetectable	Lung biopsy showed nuclear inclusions suggestive of CMV infection; IHC showed nuclear positivity for CMV	Ganciclovir and valganciclovir	Recovery
Haddad *et al*[58], 1984	18	M	Fever, chills, non-productive cough, severe hypoxia requiring intubation	Immunocompromised; sickle cell thalassemia	Chest XR suggested early pulmonary edema and cardiomegaly	On postmortem culture of lung parenchyma, CMV grew in 5 d		NR	Died
Katagiri *et al*[59], 2008	35	F	Deterioration of lupus nephritis and received treatment with a high dose of steroid and cyclosporine	Immunocompromised; SLE with increased risk of opportunistic infection	Chest X-ray showed bilateral pleural effusion; chest CT revealed a cavitary lesion in the right middle lobe of the lung	Positive for CMV; antigenemia		Ganciclovir	Recovery

Ayyappan *et al* [60], 2006	72	M	Fever, productive cough, worsening breathlessness and tenderness in epigastrium	Immunocompromised; rheumatoid arthritis-related interstitial lung disease, on corticosteroids and cyclophosphamide	Chest XR showed bilateral consolidation; chest CT revealed cavitating masses in the right upper lobe & lingula and diffuse interstitial fibrosis	PCR assay of BAL fluid was positive for CMV	Gastric biopsy - intracytoplasmic viral inclusions consistent with CMV gastritis; transbronchial lung biopsy showed intracytoplasmic viral inclusion	Gancyclovir	Recovery
Manian *et al*[61], 1993	32	F	Fever, non-productive cough, worsening oxygenation	Immunocompetent	Chest X ray - bilateral interstitial infiltrates	Enzyme immune-assay showed that CMV IgG and CMV IgM were positive		Ganciclovir	Recovery
McCormack *et al* [62], 1998	31	M	Fever, abdominal pain, jaundice, cough, palpitations, shortness of breath with atrial fibrillation	Immunocompetent	Chest radiograph showed bilateral interstitial pulmonary infiltrates	EIA for antibodies to CMV showed a strong reaction to IgM and a weak reaction to IgG	A urine culture yielded CMV; a cytopathic effect was observed and con-firmed by immunofluorescence	Ganciclovir	Recovery
Najjar *et al*[63], 2004, Case 1	34	F	Fever	Immunocompromised; SLE with renal failure on haemodialysis	Chest XR - bilateral infiltrates; chest CT - bilateral peripheral parenchymal infiltrates and a cavitating mass in right lower lobe	A CMV antigenaemia assay was positive and CMV isolation in blood	Histological findings included numerous intranuclear and intracytoplasmic CMV inclusions confirmed by IHC	IV ganciclovir and IV IgG	Recovery
Najjar *et al*[63], 2004, Case 2	33	M	Fever, dyspnoea, worsening renal function	Immunocompromised; SLE, class IV lupus, nephritis treated with chronic steroid therapy, azathioprine, and cyclophosphamide	Chest CT revealed a right upper lobe thick-walled cavitary lesion	Serology revealed raised CMV IgM & IgG	HPE - evidence of focal interstitial fibrosis, accumulation of intraalveolar macrophages, and CMV with intracytoplasmic and nuclear inclusions in the lining alveolar cells	Gancyclovir	Recovery
Kanika *et al*	32	M	Fever, dyspneia, hypotension, jaundice	Immunocompetent	MRI showed hepatitis and pancreatitis; CT showed GGO	Serum PCR with a high viral load	Liver biopsy suggestive of drug induced liver injury and immunochemistry negative for CMV	Ganciclovir	Recorvery

B/L: Bilateral; GGOs: Ground glass opacities; CT: Computed tomography; ARDS: Acute respiratory distress syndrome; SLE: Systemic lupus erythematosus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; HRCT: High resolution CT; IHC: Immunohistochemistry; BAL: Bronchoalveolar lavage; HPE: Histopathological examination; EIA: Enzyme immune assay; PCR: Polymerase chain reaction.

Immunohistochemistry (IHC) was reported in 24% of the cases, and biopsy-histopathology was performed in 27% of the patients. The treatment was reported in 84% of the cases, with a high recovery rate of 89%. Unfortunately, the mortality rate was 9%, with four patients reported to have died.

DISCUSSION

This paper analyzed 45 cases of CMV-induced pneumonia. Patients were divided into two main categories: Immunocompetent and immunocompromised. Twenty-nine (64%) patients were immunocompromised, and 16 (36%) were immunocompetent and developed CMV pneumonia. This suggests that CMV infection prevalence is higher in immunocompromised patients[2]. The reported case highlights the importance of considering CMV infection in patients who present with fever, respiratory symptoms, and abnormal liver function tests. Although CMV infection is more common in immunocompromised patients, this case demonstrates that it can also occur in immunocompetent individuals. It

Table 2 Baseline features of 45 patients with cytomegalovirus pneumonia

Variable	Patients, *n* = 45 (100%)
Age group	
0–15 yr	7 (15.6)
16–45 yr	25 (55.6)
46–75 yr	13 (28.8)
Sex	
Male	26 (58)
Female	19 (42)
Symptoms	
Fever	37 (82)
Cough	24 (53)
Dyspnoea	34 (76)
Resp. distress	26 (58)
Immune status	
Immunocompetent	16 (36)
Immunocompromised	29 (64)
Radiograhic findings	
Chest X-ray	32 (71)
Thoracic CT	31 (69)
Serology	
Blood/serum	40 (89)
Bronchoalveolar fluid (BAL)	18 (45)
Specific tests	
Immunohistochemistry	11 (24)
Biopsy - histopathology	12 (27)
Treatment	38 (84)
Recovery	40 (89)
Died	4 (9)

Table 3 Summary of data collected

	Immunocompetent	Immunocompromised
Total	16	29
Fever	13	24
Cough	11	13
Dyspnoea	12	22
Respiratory distress	10	16
Treatment	12	26
Recovered	15 (94%)	25 (86%)

is important to note that CMV is a common cause of pneumonia, particularly in immunocompromised patients, and should be considered in the differential diagnosis of patients with respiratory symptoms who do not respond to standard treatment. Early diagnosis and treatment are essential in improving patient outcomes, especially in severe cases. Therefore, clinicians should be aware of the clinical features

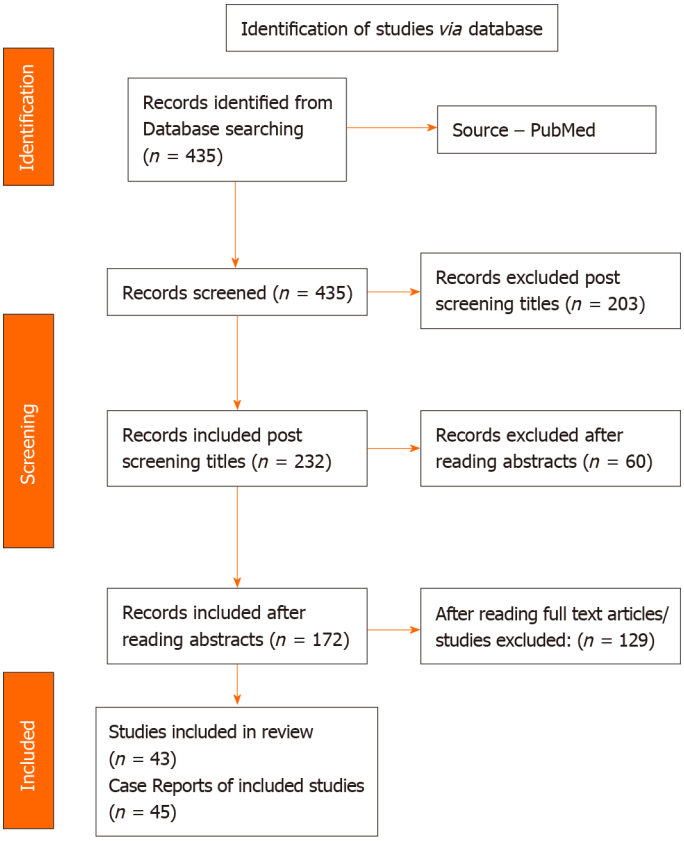

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Figure 2 PRISMA search strategy for systematic review.

and radiological findings of CMV pneumonia to enable early diagnosis and appropriate management [17-20].

The differential diagnosis of this case includes severe COVID-19 infection, which shares some clinical features with CMV pneumonia, such as cough, dyspnea, and fever. However, some features of the case, such as jaundice, hepatosplenomegaly, and pancytopenia, are not typically seen in severe COVID-19 cases. Additionally, GGOs on CT imaging can be seen in both CMV pneumonia and COVID-19. Therefore, it is important to consider other infectious and non-infectious etiologies in patients with respiratory symptoms and abnormal liver function tests.

A systematic review was performed a total of 45 patients, of which 26 (58%) were male and 19 (42%) were female. Infection was more prevalent in males, with 11 immunocompetent and 15 immunocompromised male patients and 5 immunocompetent and 14 immunocompromised female patients. This suggests that CMV infection is more prevalent in immunosuppressed patients in both males and females. Immunocompromised states are an important host-associated risk factor to get CMV infection [2].

Regarding age, 25 patients were adults (13 males and 12 females), indicating that the adult population is more prone to developing pulmonary CMV infection. As it is estimated that more than half of the adult population are infected with CMV in the United States, and 80% of the adult population have this infection by the age of 40 years, the prevalence of CMV-induced pneumonia may increase with age[1]. The clinical findings of most patients were fever (82%), dyspnea (75%), cough (53%), and respiratory distress (53%) in both immunocompetent and immunocompromised patients. These findings are consistent with previous studies on CMV pneumonia[4].

Regarding radiological findings, 32 patients were submitted to a chest X-ray mostly showing bilateral diffuse pulmonary infiltrates. CT of the thorax was done in 31 patients, and the main finding was bilateral GGOs. In some patients, there were small bilateral pulmonary nodules, confluent consolidations, and bronchiectasis. In case of atypical radiological findings other than bilateral infiltrates and GGOs, further investigation, such as blood and BAL serology, lung biopsy histopathological examination (HPE), and IHC, should be considered to rule out CMV pneumonia[7].

Blood serology was done in 40 (89%) patients, and IgM and IgG were positive for CMV. Other tests, such as BAL fluid serology, lung biopsy histopathology, and IHC, were done to confirm the diagnosis in some patients. IgM CMV positive in blood represents acute CMV infection, and antiviral treatment was given to the patients with a successful outcome[2,5].

A study by Basinger *et al*[24] demonstrated that immunocompromised states, particularly those with a history of allogenic hematopoietic stem cell transplant, can result in rapidly deteriorating conditions and respiratory status post-CMV infection. Radiologically, patients may present with rapidly progressive bilateral pulmonary nodules approximately 2 mo after receiving a bone marrow transplant. This patient died shortly after admission, and the diagnosis was made on post-mortem microscopic examination of the pulmonary nodules that demonstrated viral cytopathologic changes consistent with CMV infection, confirmed by IHC. It is essential to note that the radiographic presentation is not always GGOs, and rapidly enlarging pulmonary nodules in an immunosuppressed patient are highly suggestive of an infectious process. Therefore, careful histologic examination for viral cytopathologic changes is essential[3].

Regarding treatment, 38 (85%) patients received antiviral therapy, and 2 patients recovered without receiving antiviral treatment. In total, 89% of patients recovered, indicating that the prognosis of CMV pneumonia is good if diagnosed early and treated in time, in both immunocompetent and immunocompromised patients[2]. A study by Al-Eyadhy *et al*[32] in 2017 presented the case of a 12-year-old immunocompetent patient who was admitted with severe ARDS and developed multi-organ failure, which is an important differential diagnosis from severe acute respiratory syndrome coronavirus 2 infection. Due to the correct diagnosis and treatment of CMV infection in time, the patient recovered. Another study by Coussement *et al*[42] in 2016 showed that a 63-year-old immunocompromised patient who did a bilateral lung transplant for chronic obstructive pulmonary disease admitted with severe CMV infection and due to timely diagnosis and antiviral treatment, the patient recovered well.

In immunocompetent patients, the recovery rate was 94%, while in immunocompromised patients, it was 86%. The study showed that there were four deaths, three of which were among immunocompromised patients. This suggests that immunocompromised patients may develop more severe CMV illness that deteriorates quickly, sometimes making it challenging to make a timely diagnosis. Therefore, it is crucial to consider CMV infection as one of the important differentials in immunocompromised patients[1,4].

The final result of this analysis showed that 89% of total patients recovered, indicating that the prognosis of CMV pneumonia is good if patients are diagnosed early and treated promptly, even for immunocompromised patients[1,4].

To reach a definitive diagnosis, clinical findings must be correlated with imaging tests and laboratory tests. Polymerase chain reaction (PCR) is the most sensitive method of detecting CMV, and qRT-PCR can be used to quantify viral loads in blood and BAL fluid. BAL CMV-PCR is considered the most accepted approach for viral isolation in the lungs due to its high sensitivity. Lung biopsy histopathology is considered the gold standard for the diagnosis of pulmonary CMV infections, and the presence of CMV inclusions in the HPE report is confirmatory of lung infection. Additionally, CMV can be detected by IHC staining for CMV in cytologic specimens of bronchial lavage fluid[1,2].

In critically ill patients, CMV infection is associated with prolonged mechanical ventilation, nosocomial infections, prolonged hospital and ICU stay, and increased mortality. The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, while severe illness is treated with IV ganciclovir or foscarnet at full doses (adjusted for renal function), followed by valganciclovir. Treatment at full doses should be continued until the resolution of symptoms and blood antigenemia (or DNAemia) is cleared. The prognosis of CMV pneumonia is good if patients are diagnosed and treated at an early stage[1,2,4]. This systematic review aimed to understand the pattern, presentations, clinical course, and outcome of patients with COVID-19 and CMV coinfection and analyzed data from 34 reports with 59 patients. The results showed that middle-aged and elderly patients with comorbidities were more susceptible to coinfection, and CMV colitis was the most common manifestation of end-organ involvement. The findings of this study may assist in detecting and treating patients with unusual clinical courses or severe, prolonged, or unexplained deterioration of end-organ function[64].

CONCLUSION

In conclusion, CMV pneumonia is a serious complication in both immunocompromised and immunocompetent patients, with a higher morbidity and mortality rate in the former group. The diagnosis of CMV pneumonia can be challenging as it may present with nonspecific clinical and radiological features similar to COVID-19 pneumonia. Therefore, it is crucial to consider CMV infection as a differential diagnosis in immunocompromised patients with respiratory symptoms. Early diagnosis and treatment with antiviral therapy can lead to a good prognosis, while delayed diagnosis and treatment can lead to a more severe illness and potentially fatal outcomes. Clinicians should have a high index of suspicion for CMV pneumonia in immunocompromised patients and perform appropriate diagnostic tests, such as PCR and histopathological examination. Further research is needed to better understand the pathogenesis, risk factors, and optimal management of CMV pneumonia.

ARTICLE HIGHLIGHTS

Research background

Cytomegalovirus (CMV) is a DNA virus that can cause severe disease in immunocompromised patients and is common in recipients of hematopoietic stem cell transplantation. CMV is acquired through direct contact with infected cells or body fluids, and transmission can occur from a CMV-seropositive donor organ. Congenital CMV, transmitted from infected mothers to their newborns, is a leading cause of miscarriage. CMV is one of the three most common causes of severe viral community-acquired pneumonia, but this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 in 2020.

Research motivation

During the COVID-19 pandemic, it is important to differentiate clinical and radiological presentations from other diseases. Ground-glass opacities (GGOs) require evaluation along with other tests to reach a diagnosis. To diagnose CMV pneumonia, the virus can be detected in serum or respiratory samples, and quantitative real-time PCR can measure viral loads in blood and BAL fluid. Lung biopsy histopathology is the gold standard for diagnosing pulmonary CMV infections. However, the diagnostic yield of lung biopsy varies, and the study of CMV pneumonia in immunocompetent patients with GGOs remains limited.

Research objectives

This study aimed to report a case of CMV pneumonia in an immunocompetent patient with GGOs on chest CT, to review the literature on the clinical, radiological, and laboratory features of CMV pneumonia in immunocompetent hosts, and to discuss the diagnostic workup and management of CMV pneumonia.

Research methods

This study followed PRISMA guidelines to identify case reports and case series studies on pulmonary complications of CMV infection. The selection criteria included studies that reported only CMV pneumonia without other co-existing causes of pneumonia. Data extraction involved identifying the characteristics of the subjects and the outcomes measured. The patient case report presented in the article was included in the study as it met the inclusion criteria, and the patient received ganciclovir therapy resulting in complete recovery from symptoms and sustained undetectable viral load after 6 wk of treatment.

Research results

The study found 45 case reports of pulmonary CMV infection after analyzing 435 references. The majority of the patients were males (58%) in the age group of 16-45 years (55.6%). Common symptoms included fever, dyspnea, and cough, with respiratory distress observed in 58% of the cases. Most patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients, and blood/serum was the most commonly used method for diagnosis. Treatment was reported in 84% of the cases, with a high recovery rate of 89%, but the mortality rate was 9%. Early diagnosis and prompt treatment are crucial to improve outcomes and reduce mortality rates, especially in immunocompromised individuals.

Research conclusions

The study analyzed 45 cases of CMV-induced pneumonia and found that it can occur in both immunocompetent and immunocompromised patients, with clinical findings of fever, dyspnea, cough, and respiratory distress. Radiological findings showed bilateral diffuse pulmonary infiltrates and bilateral GGOs. Blood serology was positive for CMV, and antiviral treatment was given with a successful outcome. The recovery rate was high, but four deaths were reported, with three among immunocompromised patients.

Research perspectives

Future studies can investigate the prevalence of CMV pneumonia in different age groups and genders, and the possible link between CMV and COVID-19. The effectiveness of antiviral therapy in preventing severe CMV illness and the optimal duration of treatment can be evaluated. Pathophysiology and immunology of CMV pneumonia in immunocompromised patients need further research.

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SYSTEMATIC REVIEWS

Real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the Delta and Omicron variants: Systematic review

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Abstract

BACKGROUND

As of 31 December 2022, there were over 6.6 million coronavirus disease 2019 (COVID-19) deaths and over 651 million cases across 200 countries worldwide. Despite the increase in vaccinations and booster shots, COVID-19 cases and deaths continue to remain high. While the effectiveness of these vaccines has already been established by different manufacturers, the fact remains that these vaccines were created quickly for global emergency use, tested under controlled clinical conditions from voluntary subjects and age groups whose general characteristics may differ from the actual general population.

AIM

To conduct a systematic review to determine the real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the predominance of Delta and Omicron variants in preventing COVID-19 related infection, hospital, intensive care unit (ICU) admission and intubation, and death.

METHODS

A combination of Medical Subject Headings and non–Medical Subject Headings was carried out to identify all relevant research articles that meets the inclusion and exclusion criteria from PubMed, Cochrane, CINAHL, Scopus, ProQuest, EMBASE, Web of Science, and Google Scholar databases, as well as qualified research studies from pre–print servers using medRxiv and Research Square, published from January 1, 2021 - December 31, 2022.

RESULTS

As per the inclusion and exclusion criteria, the effectiveness of Pfizer-BioNTech and Moderna vaccines were evaluated from an estimated total study population of 26535692 using infection, hospital, ICU admission and intubation, and death as outcome measures from studies published between 2021 and 2022, conducted in New York, Finland, Canada, Costa Rica, Qatar, Greece, and Brazil. The risk of bias was evaluated using risk of bias in nonrandomized studies of interventions

(ROBINS-I) tool for cohort, case-control, and cross-sectional studies. While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated 94% vaccine effectiveness in the elderly, the results in this study showed that vaccine effectiveness in real-world settings is marginally lower against infection (40%-89%), hospitalization (92%), ICU admission and intubation (98%-85%), and death (77%-87%) with an indication of diminished effectiveness of vaccine over time. Furthermore, 2 doses of mRNA vaccines are inadequate and only provides interim protection.

CONCLUSION

Because of the natural diminishing effectiveness of the vaccine, the need for booster dose to restore its efficacy is vital. From a research perspective, the use of highly heterogeneous outcome measures inhibits the comparison, contrast, and integration of the results which makes data pooling across different studies problematic. While pharmaceutical intervention like vaccination is important to fight an epidemic, utilizing common outcome measurements or carrying out studies with minimal heterogeneity in outcome measurements, is equally crucial to better understand and respond to an international health crisis.

Key Words: COVID-19; mRNA Vaccine; Effectiveness; Elderly; Delta; Omicron; Systematic review

Core Tip: This systematic review investigates the real-world effectiveness of mRNA coronavirus disease 2019 (COVID-19) vaccines in reducing morbidity and mortality in the elderly during the predominance of Delta and Omicron variants. This study found that the effectiveness of mRNA COVID-19 vaccines in the elderly against the Delta and Omicron variants is marginally lower than what was suggested in clinical trial data. Vaccine efficacy also diminishes over time, indicating the need for a booster dose to restore its effectiveness. Furthermore, to better understand and respond to an epidemic, studies should utilize common outcome measurements or minimize heterogeneity in outcome measures to facilitate data comparison and integration of results.

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INTRODUCTION

As of December 31, 2022, there were over 6.6 million coronavirus disease 2019 (COVID-19) deaths and over 651 million cases across 200 countries worldwide[1]. During the second half of 2021, COVID-19 cases and deaths were predominantly influenced by the Delta and Omicron variants, wreaking havoc even in countries with tough COVID-19 restrictions[2,3]. Epidemiological studies have shown that the contagious and highly transmissible nature of the Delta and Omicron variants has even put the elderly population in a more disadvantaged position, accounting roughly 14% of all COVID-19 cases and 70% of all COVID-19 deaths as of December 31, 2022[4-7]. While there is no broad consensus on the age at which a person can be considered elderly, the approved cutoff age as per the United Nations is 60+ years[8].

As a response to the extensive impact of COVID-19, which has become a public health concern and an international health crisis, the Centers for Disease Control and Prevention rolled out a global strategy response framework which outlined a combination of non-pharmaceutical and pharmaceutical interventions[9-11]. While the primary method of epidemic control has been non-pharmaceutical measures, pharmaceutical intervention, like vaccine, is expected to be the only effective, long-term defense against infection and death[12,13]. Vaccination is critical since the epidemic is still challenging to control due to the dormant symptoms and contagious nature of the virus especially during the incubation period which triggers late detection of infection[12,13].

Of the 356 vaccine candidates, over 12 billion vaccine doses have been administered by 34 different vaccines approved under Emergency Use Authorization[1,14]. Despite the increase in vaccinations and booster shots, COVID-19 cases and deaths continue to remain high[1]. While the effectiveness of these vaccines has already been established by different manufacturers, the fact remains that these vaccines were created quickly for global emergency use, tested under controlled clinical conditions from voluntary subjects and age groups whose general characteristics may differ from the actual general

population[15-17]. In spite of the many observational studies providing data on the effectiveness of vaccination in various populations, this study aims to compile the disparate data through systematic review[18-29]. This study carefully examines the effectiveness of COVID-19 vaccines in real-world settings in the elderly during the predominance of Delta and Omicron variants.

MATERIALS AND METHODS

The systematic review was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards to ensure a comprehensive and methodical approach[30].

Search strategy and selection criteria

The review searched for qualified studies using a combination of Medical Subject Headings (MeSH) and non–Medical Subject Headings from PubMed, Cochrane, CINAHL, Scopus, ProQuest, EMBASE, Web of Science, and Google Scholar databases, as well as qualified research studies from pre–print servers using medRxiv and Research Square, published from January 1, 2021 – December 31, 2022. The search was independently performed by a single researcher using the following keywords and search terms (Supplementary Table 1: Keywords and Search Terms using PICO): (1) Covid-19; covid 19; covid19; SARS CoV 2*; SARS-CoV-2*; SARS Coronavirus 2 Infection; sars virus; 2019 Novel Coronavirus*; nCoV; 2019-nCoV*; COVID-19 Pandemic*; COVID-19 Virus*; Coronavirus; Coronavirus Disease*; Severe Acute Respiratory Syndrome Coronavirus 2 Infection; CV-19; CV19; (2) covid 19 vaccine*; covid-19 vaccine*; Pfizer-BioNTech vaccine; Comirnaty; BNT162b2; Bnt-162b2; Bnt162b2; Tozinameran; Tozinameran [INN]; UNII-5085ZFP6SJ; Moderna vaccine; mRNA-1273; MRNA-1273; Spikevax; CX-024414; Elasomeran; Elasomeran [INN]; M-1273; Moderna covid-19 vaccine rna; TAK-919; UNII-EPK39PL4R4; Covid 19 booster; Covid-19 booster; SARS-CoV-2 vaccine; SARS-CoV-2 booster; vaccinated; inoculat*; immuni*; post-vaccination; antibody; protected; (3) unvaccinated; uninoculated; uninoculated; unimmunized; unprotected; susceptible; and (4) reduce incidence*; reduce admission*; reduce infection*; reduce hospitalization*; reduce morbidity*; reduce mortality*; reduce death*; lessen infection*; lessen admission*; lessen hospitalization*; lessen morbidity*; lessen mortality*; lessen death *; prevent incidence*; prevent infection*; prevent admission*; prevent hospitalization*; prevent morbidity*; prevent mortality*; prevent death*; minimize incidence*; minimize admission*; minimize infection*; minimize hospitalization*; minimize morbidity*; minimize mortality*; minimize death*; control incidence*; control admission*; control infection*; control hospitalization*; control morbidity*; control mortality*; control death*; combat incidence*; combat admission*; combat infection*; combat hospitalization*; combat morbidity*; combat mortality*; combat death*; eliminate incidence*; eliminate admission*; eliminate infection*; eliminate hospitalization*; eliminate morbidity*; eliminate mortality*; eliminate death*; diminish incidence*; diminish admission*; diminish infection*; diminish hospitalization*; diminish morbidity*; diminish mortality*; diminish death*; solve incidence*; solve admission* ; solve infection*; solve hospitalization*; solve morbidity*; solve mortality*; solve death*.

Eligibility standards: inclusion and exclusion criteria

In accordance to the inclusion criteria, the systematic review identified relevant English-published observational studies, which examined the effectiveness of COVID-19 vaccines among the: (1) Elderly populations who were ≥ 60 years old; (2) recipient of at least 2 doses of mRNA (Pfizer-BioNTech and Moderna) vaccines; (3) during the predominance of Delta (B.1.617.2) or Omicron (B.1.1.529/BA); and (4) studies which examined subjects as COVID-19 positive based on a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR or PCR) tests as well as studies which compared and examined the incidence of COVID-19, infection, hospitalization, admission to intensive care unit (ICU), intubation, and death. This systematic review, however, will not include: (1) Systematic review and meta-analysis studies, case reports, case series, reviews, editorials, conference papers, letters, and correspondence; (2) studies on animals; (3) studies with mathematical modelling analysis; (4) studies with insufficient data to calculate the prevention rate of COVID-19; (5) studies with immunocompromised subjects; (6) studies which did not have an unvaccinated subjects to compare; (7) studies that did not use SARS-CoV-2 vaccination as the exposure; (8) duplicate studies or studies with overlapping participants; and (9) studies that did not explain how COVID-19 subjects were determined (Figure 1).

Data extraction and outcomes

The review process underwent 4 stages: (1) All the papers found within the identified databases were examined and the publication year, study titles, authors, and abstracts were imported into an Excel spreadsheet; (2) the records were managed, screened and duplicates were eliminated manually by assessing the study title, authors, and abstract for inclusion; (3) only those with titles and abstracts that match the inclusion criteria were retrieved and carefully evaluated for full text review; and (4) using a separate Excel spreadsheet, a data extraction sheet was developed to independently extract the general study characteristics (author and publication year, study design, location, purpose, study population,

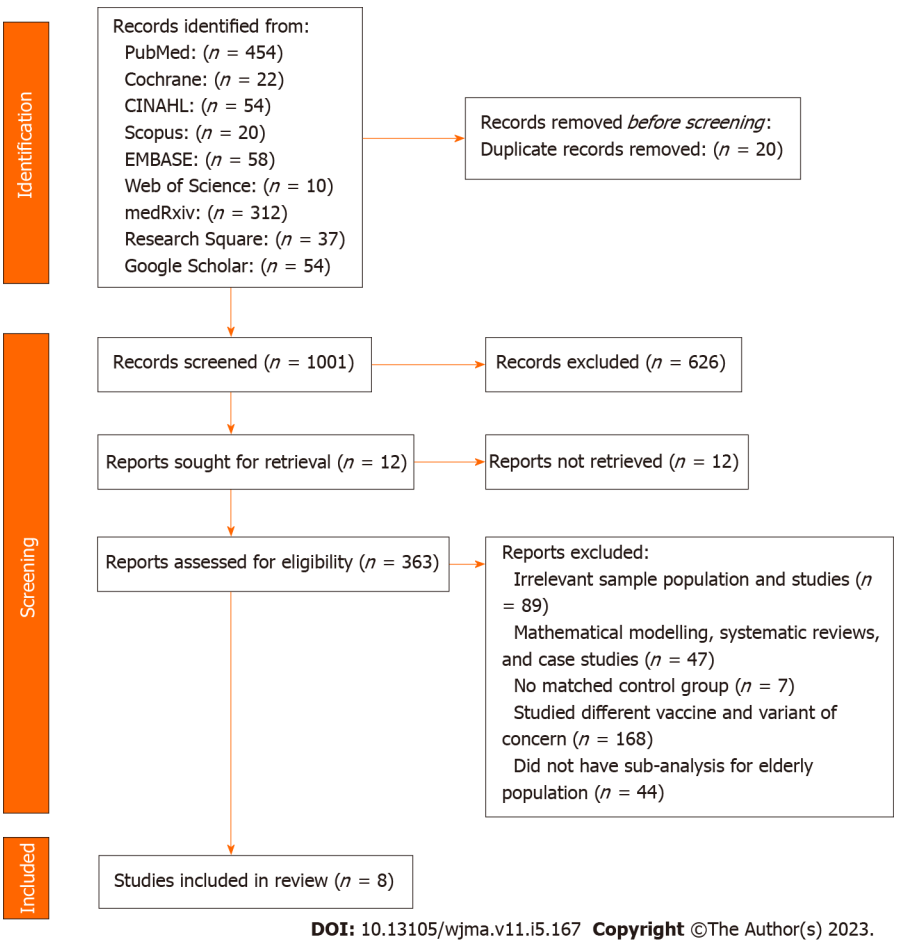

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Figure 1 Flow diagram of study identification and selection process.

including age of study population, variant of concern, vaccine type, number of doses received, outcome measures, vaccine effectiveness, and results). All qualified studies for systematic reviews were imported, stored, and managed in EndNote20.

The studies included in the review were assessed based on: (1) Age of study population; (2) variant of concern; (3) type of vaccine used; and (4) effectiveness of vaccines based on outcome measures. The effectiveness of COVID-19 mRNA vaccines in reducing morbidity and mortality were examined by comparing the following outcomes amongst the selected studies:

(1) Effectiveness of COVID-19 mRNA vaccines to reduce morbidity in terms of infections, hospitalization, admission to ICU and intubation;

And (2) effectiveness of COVID-19 mRNA vaccines to reduce mortality or deaths.

This study did not require the approval of an ethical committee or an Institutional Review Board since data collection and synthesis were gathered from already published studies in which proper consent or approvals would have been obtained by the researchers.

Quality assessment and data synthesis

The methodological quality of these observational studies was assessed through the risk of bias using ROBINS-I tool (risk of bias in non-randomized studies of interventions) and were analyzed using a narrative synthesis method which gathered the information from several sources and employed words and text to summarize and explain the findings since meta-analysis is not practical due to significant heterogeneity between the studies[31,32].

RESULTS

Study selection process and study characteristics

After searching 9 different databases, 1,021 studies were identified from PubMed (n = 454), Cochrane (n = 22), CINAHL (n = 54), Scopus (n = 20), EMBASE (n = 58), Web of Science (n = 10), medRxiv (n = 312), Research Square (n = 37), and Google Scholar (n = 54). From the preliminary review, 20 duplicates, 626 unrelated, and 12 unretrieved studies were excluded, leaving 363 studies were moved for title and

Table 1 Characteristic of studies included for vaccine effectiveness

Ref.	Study design	Location	Purpose	Age of study group	Vaccine type	Number of doses received	Variant of concern
Baum *et al*[33], 2022	Cohort study	Finland	To estimate VE against severe COVID-19 among the elderly	Adult population including ≥ 70 yr old	Pfizer-BioNTech	2 doses	Omicron
Grewal *et al* [34], 2022	Case control design	Canada	To estimate vaccine effectiveness of mRNA vaccines among aged ≥ 60 yr who were tested for SARS-CoV-2	≥ 60 yr old	Pfizer-BioNTech and Moderna	Booster	Omicron
Rosenberg *et al* [35], 2021	Cohort study	USA (NY)	To describe vaccine efficacy in NY	Adult population including ≥ 50 yr old	Pfizer-BioNTech and Moderna	2 doses	Delta
Rosero-Bixby [36], 2021	Cross-sectional study	Costa Rica	To estimate the dose-dependent effectiveness of coronavirus disease (COVID-19) vaccines to prevent severe illness in real-world conditions	Adult population including ≥ 58 yr old	Pfizer-BioNTech	2 doses	Delta
Rane *et al*[37], 2022	Case control study	USA (NY)	To monitor changes in vaccine effectiveness against COVID-19 outcomes for various vaccine products in different population subgroups	Adult population including ≥ 50 yr old	Pfizer-BioNTech	2 doses	Delta
Chemaitelly *et al*[38], 2021	Case control study	Qatar	To estimate vaccine effectiveness against any SARS-CoV-2 infection and against any severe, critical, or fatal case of COVID-19	Adult population including ≥ 50 yr old	Pfizer-BioNTech	2 doses	Delta
Lytras *et al* [39], 2022	Cohort study	Greece	To estimate COVID-19 effectiveness against disease and death	Adult population including ≥ 60 yr old	Pfizer-BioNTech and Moderna	2 doses and booster	Delta
Ranzani *et al* [40], 2022	Case control study	Brazil	To evaluate vaccine effectiveness against symptomatic COVID-19 and severe COVID-19 (hospital admission or deaths)	Adult population including ≥ 70 yr old	Pfizer-BioNTech	2 doses and booster	Omicron

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; USA (NY): United States of America (New York); VE: Vaccine effectiveness.

abstract screening. As per the inclusion and exclusion conditions in the eligibility criteria, 354 studies were excluded for the following reasons: (1) Irrelevant sample population and studies (n = 89); (2) mathematical modelling, systematic reviews, and case studies (n = 47); (3) no matched control group (n = 7); (4) studied different vaccine and variant of concern (n = 168); (4) did not have sub-analysis for elderly population (n = 43); and (5) overlap in study population (n = 1). As a result, only 8 studies were included for systematic review[33-40]. PRISMA Flow Diagram summarized the literature selection process (Figure 1).

Among these studies, 3 were published and 5 were published on the pre-print platforms[33-40]. All of the 8 studies used observational study designs such as cohort, case control, and cross-sectional studies [33-40]. These studies reported the effectiveness of Pfizer-BioNTech (n = 8) and Moderna (n = 4) vaccines, with 7 studies examining 2 doses, 2 studies examining 2nd and booster doses, and 1 study examining booster dose in reducing COVID-19 morbidity and mortality during the prevalence of Delta (B.1.617.2) and Omicron (B.1.1.529/BA) variants[33-40]. Study locations were in New York, Finland, Canada, Costa Rica, Qatar, Greece, and Brazil published between 2021 (n = 3) and 2022 (n = 5)[33-40]. The studies compared an estimated total sample size of 8740562 vaccinated elderly people and 9658245 unvaccinated elderly cohorts from an estimated total study population of 26535692 which evaluated the effectiveness of mRNA vaccines of an adult population including elderly cohorts who were 50 years old and older[33-40]. Although the goal of the study is to focus on elderly subjects who were 60 years old and older, some of the selected studies in this review, grouped the elderly subjects from 50 years old to include 60 years old and older subjects[35-38]. The largest sample size of vaccinated elderly people was 3479102 and 8138482 unvaccinated elderly cohorts while the smallest sample size of vaccinated and unvaccinated elderly people was 45345 and 1272, respectively[34,35,39]. The outcome measures used by the selected studies defined morbidity as infection (n = 5), hospitalization (n = 6), admission to ICU and intubation (n = 2) and mortality or death (n = 4) as outcome measurements[33-40]. The characteristics of included studies are shown in Tables 1 and 2.

Risk of bias

The risk of bias was evaluated by following ROBINS-I tool (risk of bias in non-randomized studies of interventions)[31]. All of the 8 observational studies were rated to have moderate risk of bias mainly

Table 2 Characteristic of participants included for vaccine effectiveness

Ref.		Age of study population	mRNA vaccinated elderly participants with 2 doses	mRNA vaccinated participants with 2 doses according to vaccine type		mRNA vaccinated elderly participants with 2 doses according to age		Unvaccinated elderly participants	Unvaccinated elderly participants according to age
				Pfizer-BioNTech	Moderna	Pfizer-BioNTech	Moderna		
Baum *et al* [33], 2022	897932	Adult population including ≥ 70 yr old	241630	-	-	70-79 yr old: 171816; 80-89 yr old: 57024; 90-115 yr old: 12790		747486	70-79 yr old: 480532; 80-89 yr old: 223267; 90-115 yr old: 43687
Grewal *et al* [34], 2022	46849	≥ 60 yr old	45345	-	-	-	-	1272	-
Rosenberg *et al*[35], 2021	8834604	Adult population including ≥ 50 yr old	3479102	-	-	50-64 yr old: 846664; ≥ 65 yr old: 984464	50-64 yr old: 624226; ≥ 65 yr old: 1023748	976536	50-64 yr old: 606411; ≥ 65 yr old: 370125
Rosero-Bixby[36], 2021	3670000	Adult population including ≥ 58 yr old	741474	-	-	741474		58887	58887
Rane *et al* [37], 2022	1058493	Adult population including ≥ 50 yr old	143104	-	-	50-59 yr old: 64806; 60-69 yr old: 48260; 70-79 yr old: 22997; ≥ 80 yr old: 7041		27362	50-59 yr old: 14936; 60-69 yr old: 8352; 70-79 yr old: 3066; ≥ 80 yr old: 1008
Chemaitelly *et al*[38], 2021	-	Adult population including ≥ 50 yr old	1402622	907763	494859	-	-	8043	50-59 yr old: 6350; 60-69 yr old: 1326; ≥ 70 yr old: 367
Lytras *et al* [39], 2022	9200000	Adult population including ≥ 60 yr old	2380402	2128913	251492	-		-	8138482
Ranzani *et al* [40], 2022	1417149	Adult population including ≥ 60 yr old	306883	-	-	60-79 yr old: 258306; ≥ 80 yr old: 48577		306588	60-79 yr old: 265073; ≥ 80 yr old: 41515

due to lack of control for confounders such as comorbidities or socioeconomic status like age and occupation, outbreak data such as location and time of test, and other risk-taking behavior modification [33-40]. Due to the dependence in surveillance data which were subject to incomplete information, 5 studies received a moderate risk of bias score because of missing data, while 3 studies due to misclassification of measurement of outcomes, were rated with moderate bias[35-40]. Table 3 shows the results of ROBINS-I risk of bias assessment of observational studies.

Synthesis of results

Vaccine effectiveness against infection: 5 of the 8 studies (36%) reported the effectiveness of vaccines using infection as an outcome measure[34,35,37,38,40]. Among these, 2 of the studies used booster dose to evaluate vaccine effectiveness against asymptomatic and symptomatic infections while 3 studies assessed the effectiveness of 2 doses of vaccines[34,35,37,38,40]. The findings from these studies revealed that 2 doses of mRNA vaccines offer 83%-89% protection against infection, while other studies revealed vaccine's protection level against infection at 40%-63%, marginally lower for 65 years old when compared to Moderna, Pfizer-BioNTech vaccine was reported to have slightly lower efficacy against infections with indications of declining protection over a period of time[34,35,37,38,40].

Vaccine effectiveness against hospitalization: 3 of the 8 studies (21%) reported the effectiveness of vaccines using hospitalization as an outcome measure which demonstrated 92% efficacy for older people[33,35,36]. Similarly, when compared to Moderna, Pfizer-BioNTech vaccine have lower marginal protection against hospitalization with indication of waning effectiveness against hospitalization, 6 months after the 2nd dose[33,35].

Vaccine effectiveness against ICU admission and intubation: 2 out of the 8 studies (14%) reported the effectiveness of vaccines using admission to ICU and intubation as outcome measures[33,39]. The study on ICU admissions revealed that Pfizer-BioNTech vaccine's protection waned from 98% down to 85%

Table 3 ROBINS-I risk of bias assessment of observational studies

Ref.	Confounding	Selection of participants	Classification of interventions	Deviations from interventions	Missing data	Measurement of outcomes	Reported result	Overall bias
Baum *et al* [33], 2022	Moderate	Low	Moderate	Moderate	Low	Low	Low	Moderate
Grewal *et al* [34], 2022	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Rosenberg *et al* [35], 2021	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Rosero-Bixby [36], 2021	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Rane *et al*[37], 2022	Low	Low	Low	Low	Moderate	Low	Low	Low
Chemaitelly *et al*[38], 2021	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Lytras *et al* [39], 2022	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Ranzani *et al* [40], 2022	Low	Low	Low	Low	Low	Moderate	Low	Moderate

Low risk: Comparable to a well-performed randomised trial; Moderate risk: Sound for a non-randomised study but cannot be compared to a well performed randomised trial; Serious risk: Study has some important problems; Critical risk: Study is too problematic to provide any useful evidence.

after 6 months among 70 years old and older[33]. Similar findings was observed when intubation was used as an outcome measure, which revealed diminished vaccine effectiveness from 96.9% down to 86%, in 6 months among 60 years old and older populations but was restored at 97.6% by booster dose [39].

Vaccine effectiveness against death: 4 out of the 8 studies (29%) reported the effectiveness of vaccines using death with hospitalization as outcome measures[34,38-40]. The findings showed that although 2 doses of mRNA vaccine can prevent death, it offers a marginally limited protection against death among 75 years old and older with indications of diminishing protection which was only restored by a booster dose[38-40]. Additionally, the finding showed that Pfizer-BioNTech has marginally higher protection level against death at 87% when compared to Moderna at 77%[34]. The outcomes of included studies for vaccine effectiveness are shown in Table 4.

DISCUSSION

While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated 94% effectiveness among the elderly, the results in this study showed that the effectiveness of mRNA vaccines in real-world settings is marginally lower against COVID-19 infection, hospitalization, ICU admission and intubation, and deaths during the predominance of Delta and Omicron variants[33-40].

The results in this systematic review further strengthen and supplement the increasing evidence on the real-world effectiveness of mRNA vaccines. While the inclusion and exclusion criteria of this review limits a variety of similar studies in the data analysis, for discussion purposes these studies echoed similar findings. A study conducted in United Kingdom revealed that vaccine effectiveness for ≥ 60 years old is 42.3%[41]. The same observed pattern is reported for ≥ 75 years old in a study conducted in Israel, in a case-control study conducted among US military personnel and in a test-negative design study conducted in Malaysia[42-44]. Using random-effects model on 15 observational studies to estimate the pooled vaccine effectiveness (VE) with 95% confidence intervals for each vaccine type against each variant, the systematic review and meta-analysis conducted by Zhang *et al*[45] revealed a limited vaccine effectiveness among ≥ 65 years old. The result in this study also align with the result in our study and with the findings of other studies focusing on vaccine effectiveness in the elderly during the predominance of Delta and Omicron variants[46-48]. Utilizing the same research model, a contrasting result was reported by Li *et al*[49] when they evaluated the effectiveness of vaccine in over 30000 participants aged 60 years and older. This systematic review and meta-analysis however, largely focused on randomized controlled trials which may have skewed the outcomes. Given that clinical trials on COVID-19 vaccines are conducted under controlled clinical conditions from volunteer subjects of targeted age groups, these studies are not able to take into account the abilities of COVID-19 to mutate

Table 4 Outcomes of studies included for vaccine effectiveness

Ref.	Outcome measurements					Vaccine effectiveness
	Infection (*n*/%)	Hospitalization (*n*/%)	ICU admission (*n*/%)	Intubation (*n*/%)	Death (*n*/%)	
Baum *et al* [33], 2022	-	2 doses of Pfizer (within 3 mo): 30/5.64%; 2 doses of Pfizer (within 6 mo): 193/36.28%; 2 doses of Pfizer (≥ 6 mo): 148/27.82%; 3 doses of Pfizer (within 3 mo): 95/17.86%; 3 doses of Pfizer (≥ 6 mo): 66/12.41%	2 doses of Pfizer (within 3 mo): 5/8.33%; 2 doses of Pfizer (within 6 mo): 24/40%; 2 doses of Pfizer (≥ 6 mo): 14/23.33%; 3 doses of Pfizer (within 3 mo): 9/15%; 3 doses of Pfizer (≥ 6 mo): 8/13.33%	-	-	Hospitalization: 2 doses of Pfizer (within 3 mo): 90%; 2 doses of Pfizer (within 6 mo): 85%; 2 doses of Pfizer (≥ 6 mo): 72%; 3 doses of Pfizer (within 3 mo): 95%; 3 doses of Pfizer (≥ 6 mo): 88%; ICU Admission: 2 doses of Pfizer (within 3 mo): 98%; 2 doses of Pfizer (within 6 mo): 95%; 2 doses of Pfizer (≥ 6 mo): 82%; 3 doses of Pfizer (within 3 mo): 98%; 3 doses of Pfizer (≥ 6 mo): 85%
Grewal *et al* [34], 2022	Infection: 3 doses of Pfizer: 2691/42.43%; 3 doses of Moderna: 3651/57.57%; Symptomatic Infection: 3 doses of Pfizer: 395/38.69%; 3 doses of Moderna: 626/61.31%	3 doses of Pfizer: 214/58.79%; 3 doses of Moderna: 150/41.21%	-	-	3 doses of Pfizer: 214/58.79%; 3 doses of Moderna: 150/41.21%	Infection: 3 doses of Pfizer: 31%; 3 doses of Moderna: 51%; Symptomatic Infection: 3 doses of Pfizer: 61%; 3 doses of Moderna: 73%; Hospitalization or Death: 3 doses of Pfizer: 87%; 3 doses of Moderna: 77%
Rosenberg *et al*[35], 2021	≥ 65 yr old (2 doses of Pfizer): 5302/61.70%; ≥ 65 yr old (2 doses of Moderna): 3291/38.30%	≥ 65 yr old (2 doses of Pfizer): 972/64.07%; ≥ 65 yr old (2 doses of Moderna): 545/35.93%	-	-	-	Infection: ≥ 65 yr old (2 doses of Pfizer): 83.0%; ≥ 65 yr old (2 doses of Moderna): 89.2%; Hospitalization: ≥ 65 yr old (2 doses of Pfizer): 91.9%; ≥ 65 yr old (2 doses of Moderna): 95.7%
Rosero-Bixby[36], 2021		40-57 yr old: 37/0.006%; ≥ 58 yr old: 65/0.009%	-	-	-	Hospitalization: 40-57 yr old: 94%; ≥ 58 yr old: 92%
Rane *et al* [37], 2022	60-69 yr old: 3232/5.8%; 70-79 yr old: 1221/2.2%; ≥ 80 yr old: 468/0.8%	-	-	-	-	Infection: 51-64 yr old: 60%; 65 80 yr old: 55%; ≥ 80 yr old: 51%
Chemaitelly *et al*[38], 2021	2 doses of Pfizer (within 1 mo): 2915/2.51%; 2 doses of Pfizer (within 2 mo): 1450/1.28%; 2 doses of Pfizer (within 3 mo): 800/0.71%; 2 doses of Pfizer (within 4 mo): 492/0.44%; 2 doses of Pfizer (within 5 mo): 548/0.49%; 2 doses of Pfizer (within 6 mo): 460/0.41%; 2 doses of Pfizer (≥ 7 mo): 135/0.12%	2 doses of Pfizer (within 1 mo): 32/0.78%; 2 doses of Pfizer (within 2 mo): 23/0.56%; 2 doses of Pfizer (within 3 mo): 17/0.42%; 2 doses of Pfizer (within 4 mo): 10/0.25%; 2 doses of Pfizer (within 5 mo): 0/0; 2 doses of Pfizer (within 6 mo): 8/0.20%; 2 doses of Pfizer (≥ 7 mo): 6/0.15%			2 doses of Pfizer (within 1 mo): 32/0.78%; 2 doses of Pfizer (within 2 mo): 23/0.56%; 2 doses of Pfizer (within 3 mo): 17/0.42%; 2 doses of Pfizer (within 4 mo): 10/0.25%; 2 doses of Pfizer (within 5 mo): 0/0; 2 doses of Pfizer (within 6 mo): 8/0.20%; 2 doses of Pfizer (≥ 7 mo): 6/0.15%	Infection: 2 doses of Pfizer (within 1 mo): 75.8%; 2 doses of Pfizer (within 2 mo): 69.7%; 2 doses of Pfizer (within 3 mo): 63.7%; 2 doses of Pfizer (within 4 mo): 39.1%; 2 doses of Pfizer (within 5 mo): 11.4%; 2 doses of Pfizer (within 6 mo): 9.2%; 2 doses of Pfizer (≥ 7 mo): -4.4%; Hospitalization and Death: 2 doses of Pfizer (within 1 mo): 95.9%; 2 doses of Pfizer (within 2 mo): 96.3%; 2 doses of Pfizer (within 3 mo): 93.4%; 2 doses of Pfizer (within 4 mo): 80.8%; 2 doses of Pfizer (within 5 mo): 100%; 2 doses of Pfizer (within 6 mo): 81.8%; 2 doses of Pfizer (≥ 7 mo): 44.1%
Lytras *et al* [39], 2022				2 doses of Pfizer: 548/90.28%; 2 doses of Moderna: 35/5.77%; 3 doses of Pfizer: 24/0.04%	2 doses of Pfizer: 1629/64.60%; 2 doses of Moderna: 42/2.44%; 3 doses of Pfizer: 51/5.96%	Intubation: 60-79 yr old (2 doses): 96.9%; ≥ 80 yr old (2 doses): 94.4%; ≥ 80 yr old (2 doses, within 6 mo): 86.0%; ≥ 80 yr old (3 doses): 97.6%; Death: 60-79 yr old (2 doses): 94.6%; ≥ 80 yr old (2 doses): 91.0%; ≥ 80 yr old (2 doses, within 6 mo): 84.1%; ≥ 80 yr old (3 doses): 98.4%
Ranzani *et al*[40], 2022	Symptomatic Infection: 60-74 yr old (2 doses): 34077/86.93%; ≥ 75 yr				60-74 yr old (2 doses): 2035/63.3%; ≥ 75 yr old (2 doses):	Infection: 60-74 yr old (2 doses): 63.4%; ≥ 75 yr old (2 doses): 40.7%; 60-74 yr old (3

	old (2 doses): 15539/79.84%; 60-74 yr old (3 doses, within 2 mo): 15053/64%; 60-74 yr old (3 doses, after 2 mo): 3273/66.36%; ≥ 75 yr old (3 doses, within 2 mo): 116955/89.86%; ≥ 75 yr old (3 doses, after 2 mo): 64495/99.36%	2750/52.81%; 60-74 yr old (3 doses, within 2 mo): 50/68.50%; 60-74 yr old (3 doses, after 2 mo): 51/96.01%; ≥ 75 yr old (3 doses, within 2 mo): 511/90.41%; ≥ 75 yr old (3 doses, after 2 mo): 2964/72.40%	doses, within 2 mo): 88.4%; 60-74 yr old (3 doses, after 2 mo): 90.4%; ≥ 75 yr old (3 doses, within 2 mo): 77.3%; ≥ 75 yr old (3 doses, after 2 mo): 78.5%; Hospitalization or death: 60-74 yr old (2 doses): 63.4%; ≥ 75 yr old (2 doses): 40.7%; 60-74 yr old (3 doses, within 2 mo): 88.4%; 60-74 yr old (3 doses, after 2 mo): 90.4%; ≥ 75 yr old (3 doses, within 2 mo): 77.3%; ≥ 75 yr old (3 doses, after 2 mo): 78.5%

and evade the vaccine[46,47,50-53]. Therefore, the tangible effect of vaccines can be substantially different from the real-world which may not necessarily illustrate the authentic effectiveness of vaccines. Furthermore, although interventional studies such as clinical trials are more methodologically sound, observational studies are more reliable since they produce practical and realistic results that are grounded from real-world experiences.

By focusing on Delta and Omicron variants, we hypothesize that much of the previous research on vaccine effectiveness only included earlier variants which may have skewed the results for newer and more dominant variants like Delta and Omicron. We also aim to provide value in understanding the effectiveness of mRNA vaccines by comparing their effectiveness in real-world settings. While the results in this study reported a marginal difference in effectiveness between Moderna and Pfizer-BioNTech vaccines, the minor difference on an absolute scale can be significant when considering world-wide population for vaccination[54].

Furthermore, the observed waning effectiveness of vaccine in this study supports the findings of other studies which suggested that the diminishing effectiveness of vaccine is due to the extensive abilities of COVID-19 virus to evolve and generate new variants which allow them to avoid the effects of the vaccines[51-53]. The ability of Delta and Omicron variants to elude sensitivity to antibody neutralization was observed to decline over time making the vaccine less effective[41,55-58]. Consistent to the findings of this study, this imply that 2 doses of mRNA vaccines is inadequate and only provides interim protection against COVID-19 infection, hospitalization, ICU admission and intubation, and deaths[58-61]. Because of the vaccine's natural diminishing effectiveness, the importance of booster dose to restore its efficacy is vital in providing additional protection against emerging variants[33,34,39,40,49,62-64]. This position is in line with the study conducted in an elderly long-term care facility where the effectiveness of vaccine was observed to only have improved after the second dose, along with other studies pointing out that booster dose can provide significant protection and is the most effective approach to COVID-19 prevention[59,63,65].

Strengths and limitations

This study provides useful information on the effectiveness of mRNA vaccines in the real-world settings which are not under a regulated condition of clinical trials. Specifically, the strengths of this study made use of an inexpensive design that is reproducible since it rests on an organized search strategy, strong procedure with the inclusion of literature from pre-print servers. It also included a broad range of possible outcome measures to include as many studies as possible that can provide relevant information on the topic. Furthermore, this systematic review included research studies from different parts of the world that have relatively large representatives of elderly population with longer follow up which is useful in minimizing selection bias.

The findings of this study should be cautiously interpreted due to certain limitations. First, the included literature were observational studies which have restrictions in statistical power. Second, since there is limitation to access the data used by the research studies, this study has a risk in information bias. Third, due to the missing data and estimation of some studies, a degree of misclassification further delimits this study. Fourth, in exchange of large sample sizes, this study sits on a potential bias of unmeasured confounder such as comorbidities or socioeconomic status like age and occupation, outbreak data such as location and time of test, and other risk-taking behavior modification. Finally, the use of heterogenous outcome measures creates limitation due to potential classification errors.

CONCLUSION

As a response to the rapidly evolving COVID-19 outbreak, many research studies were organized and carried out resulting in highly heterogeneous outcome measurements. From a research perspective, this heterogeneity inhibits the comparison, contrast, and integration of the results which makes data pooling across different studies problematic. Therefore, this systematic review suggests that, while pharma-

ceutical intervention like vaccination is important to fight an epidemic, utilizing common outcome measurements or carrying out studies with minimal heterogeneity in outcome measurements, is equally crucial to better understand and respond to an international health crisis. Notwithstanding these limitations, the consistent findings of this review indicated waning of vaccine effectiveness over time, implying that a large proportion of the vaccinated population, particularly the elderly, may lose protection unless booster doses are rolled out to restore the effectiveness of the vaccine (Supplementary Table 1).

ARTICLE HIGHLIGHTS

Research background

Although there has been a rise in the administration of vaccinations and booster shots, coronavirus disease 2019 (COVID-19) infections and fatalities continue to persist at a significant level. The effectiveness of these vaccines has been confirmed by multiple manufacturers and were rapidly developed for emergency use with testing conducted in controlled clinical conditions and on voluntary participants, whose characteristics may differ from those of the broader population.

Research motivation

The COVID-19 pandemic has caused an unprecedented global health crisis resulting in millions of deaths and infections worldwide. Despite the availability of COVID-19 vaccines and the administration of booster shots, the number of cases and deaths remains high. The development and clinical trials of these vaccines were conducted in controlled environments with volunteers which may not fully represent the general population. Therefore, there is a need to determine the real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the predominance of Delta and Omicron variants in preventing COVID-19-related infections, hospitalizations, intensive care unit (ICU) admission and intubation, and death.

Research objectives

This study aimed to conduct a systematic review of available research articles to evaluate the effectiveness of Pfizer-BioNTech and Moderna vaccines on the elderly using infection, hospitalization, ICU admission and intubation, and death as outcome measures.

Research methods

The study utilized a combination of Medical Subject Headings (MeSH) and non-MeSH to identify relevant research articles from various databases and pre-print servers.

Research results

While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated high vaccine effectiveness in the elderly, the results of this study showed that vaccine effectiveness in real-world settings is marginally lower against infection, hospitalization, ICU admission and intubation, and death, with an indication of diminished effectiveness of the vaccine over time. Furthermore, 2 doses of mRNA vaccines are inadequate and only provide interim protection, emphasizing the need for booster doses to restore its efficacy.

Research conclusions

Continued monitoring and research to improve the effectiveness of vaccines and combat the virus effectively is important to evaluate vaccine efficacy in real-world settings, especially as new variants emerge. In addition, the use of highly heterogeneous outcome measures poses a challenge in comparing and integrating the results, and standardized outcome measures or minimal heterogeneity in outcome measurements are essential to better understand and respond to a global health crisis.

Research perspectives

Future research should continue to evaluate the real-world effectiveness of COVID-19 vaccines, including the efficacy of booster shots and the effectiveness of vaccines against new variants. Additionally, efforts should be made to standardize outcome measures to enable better comparisons across studies and facilitate the integration of findings. Ultimately, such research will be crucial in guiding public health policies and interventions aimed at controlling the spread of COVID-19 and in mitigating its impact on public health.

FOOTNOTES

Author contributions: Palalay H conceived the manuscript from study design, literature search, study selection process, data extraction, analysis, and synthesis; Tafuto B reviewed the draft, added critical comment and intellectual content, and participated in most of the study steps; Vyas R provided additional input and guidance; All authors read and approved the final manuscript for submission and take full responsibility for the content.

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SYSTEMATIC REVIEWS

Haploidentical hematopoietic stem cell transplantation as promising therapy in the improved survival of pediatric patients with leukemias and myelodysplasias

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Abstract

BACKGROUND

Haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) is often performed in children with hematologic malignancies. Faced with the gap in the literature regarding the approach to experiences related to Haplo-HSCT with pediatric patients with leukemias and myelodysplasias aged up to 18 years, there was an interest in exploring the clinical outcomes of patients undergoing this treatment.

AIM

To identify and summarize the scientific contributions available on Haplo-HSCT performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

METHODS

This is a descriptive systematic review. We extracted data including characteristics of participants, health condition, characteristics of the donation, conditioning regimen, recurrent clinical complications and clinical outcomes. The Virtual Health Library Brazil, PubMed, EMBASE, and SciELO platforms were used, finding a total of 1052 studies. After the eligibility criteria and complete reading of the texts, 18 articles were included for analysis.

RESULTS

The total sample of all study cohorts was 1825 patients, mostly male, the highest reported median age was 15.0 years and the lowest was 1.2 years. Acute graft-versus-host disease and chronic graft-versus-host disease were observed in almost all studies. Relapse, graft rejection and delayed immune recovery were identified as major clinical challenges. Pre-transplant minimal positive residual disease was identified in 288 patients. Infections are also among the main clinical complic-

ations, viral, bacterial and fungal infections being reported. It is observed that in the 5-year interval, the lowest rates of EFS and overall survival (OS) were 29.5% and 68.0%, respectively. While, the highest rates of EFS and OS, in the same interval, were 80.1% and 81.0%.

CONCLUSION

Haplo-HSCT represents a promising therapy, considering the potential number of possible donors and the conditioning and treatment platforms that can be offered. The results obtained show that this type of transplant has a strong antileukemic effect, with generally favorable OS rates. Overcoming relapse as the first cause of transplant failure is the great clinical challenge.

Key Words: Haploidentical; Stem cell transplantation; Children; Cancer; Treatment outcome; Prognosis

Core Tip: In recent years, the number of children under 18 years of age with leukemias and myelodysplasias undergoing haploidentical hematopoietic stem cell transplantation has increased. This type of transplant has been shown to be a promising therapy due to the availability of potential donors. The main objective is to identify the scientific contributions available on haploidentical hematopoietic stem cell transplantation performed with this audience. It has been observed that prognostic factors such as treatment platforms, cytogenetic abnormalities and disease status exert a strong influence on the clinical outcomes of transplant patients. Other variables can be obtained to collaborate with risk stratification and donor selection approaches.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) has been shown to be a curative option for children with malignant and non-malignant diseases[1,2]. In this type of transplant, the progenitor cells come from genetically distinct donors, who may be related or unrelated and with human leukocyte antigen (HLA) matching or HLA partially matching. The ideal donors for hematopoietic stem cell transplantation are HLA-matched siblings or matched unrelated donors (MUD-HSCTs), but only approximately 30% of patients will have a matched sibling donor and 33% of patients will have a MUD-HSCT[1].

Haploidentical HSCT (Haplo-HSCT), a type of allogeneic transplant, represents a promising therapy in this prospect, as this type of transplant is performed with a partially HLA-matched related donor, which is available in 95% of the cases[3]. Related donors can be a father, mother, sibling or son. This transplant has a strong antileukemic effect, the graft-versus leukemia (GVL), which contributes to a lower tendency to relapse. However, due to its nature, the occurrence of clinical complications is common, such as complete rejection of the graft, the development of graft-versus-host disease (GvHD) and relapses[2,4].

The main platforms of Haplo-HSCT are *ex vivo* grafts of depleted T cells (TCD) and T- cell-filled grafts followed by post-transplantation cyclophosphamide (PT-Cy). The first is associated with a great limitation of the development of GvHD, but with slow immune reconstitution and infectious complications. While PT-Cy is associated with excellent immune reconstitution, a low incidence of serious opportunistic infections[3] and it has a more attractive cost-benefit ratio, as it does not require specific technical knowledge. There is also the infusion of unmanipulated grafts with administration of antithymocyte globulin (ATG). This platform consists of activating the donor with granulocyte colony-stimulating factor; intensified post-transplant immunosuppression with cyclosporine, methotrexate and mycophenolate mofetil; inclusion of ATG in a combined graft of bone marrow and peripheral blood[5].

Haplo-HSCT has been frequently performed in children with hematological malignancies[6]. When considering the highest incidences of childhood malignancies, it is observed that acute lymphocytic leukemia (ALL) is responsible for approximately 70% to 80% of childhood leukemia cases and acute myelogenous leukemia (AML) is responsible for approximately 15% to 20%[7-9]. In addition, among other malignancies, myelodysplastic syndrome (MDS) has a very strong interface with the neoplasms mentioned and that, although its incidence is more common in adults, the chance of myelodysplasia

evolving to more advanced forms and AML is greater in children. Therefore, many pediatric patients with MDS also are submitted to Haplo-HSCT[2,3].

Regarding the state of the art on allogeneic transplants, it should be noted that there are few publications involving the pediatric public aged up to 18 years[10]. In this perspective, we had the interest in exploring the clinical outcomes of pediatric patients with leukemias and myelodysplasias undergoing the Haplo-HSCT. For this, we carried out a systematic review, whose general objective is to identify and summarize the scientific contributions available on haploidentical hematopoietic stem cell transplants performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

MATERIALS AND METHODS

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which consists of a 27-item checklist and a flow chart for the conduction and reporting of this systematic review[11].

Search strategy

This is a descriptive systematic review, which sought to analyze the scientific contributions available on Haplo-HSCT performed in the last 10 years with selected pediatric audience. To elaborate the guiding question, the strategy PICO-acronym to Patientes, Interventation, Comparation and Outcomes-was used [12]. Therefore, the research question that was used to guide the review was: "What is the efficacy and safety of haploidentical hematopoietic stem cell transplantation performed with the pediatric public with leukemias or myelodysplasias?".

The electronic search for articles was carried out on November 20, 2022 in the Virtual Health Library Brazil (VHL) and on the PubMed website, using the keywords selected according to the classification of Health Sciences Descriptors (DeCS): Cancer, children, transplant, and haploidentical. The Boolean operator "AND" was used. Inclusion criteria were applied, the first being the filter "language-English", "language-Spanish", and "language- Portuguese"; and the second, selection of the 10-year period (2012-2022). Forty-one results were found in VHL and 549 in PubMed, totaling 590 articles, all in English. After crossing the bases, 31 repeated articles were discarded (Figure 1).

For the analysis of the 559 articles, the abstracts were read based on the exclusion criteria: Other languages, review studies, case reports, experimental studies, paid articles, other health conditions and age over 18 years old. This step was performed by a pair of reviewers, independently, and all disagreements were resolved by consensus.

It is important to emphasize that articles that included a mixed audience with children and adults over 18 years of age were also discarded, due to the central objective of analyzing the clinical results separately. In addition, paid studies that did not allow the reading of articles through access by the Federated Academic Community of institutional link of the authors of the work were excluded. Finally, it remains to inform that the experimental studies included: Randomized clinical trials, prospective clinical trials, controlled tests and control cases, all with clinical intervention.

The order of exclusion criteria was followed: Types of study, paid articles, health condition and age. The following were discarded at this stage: 59 review articles and meta-analyses, 64 case reports, 112 experimental studies, 117 paid articles without institutional access, 55 articles on other clinical conditions and other hematological neoplastic conditions, 15 studies with mixed age and 19 with age outside the established age range. Qualitative studies, editorials, annals, reports and comments were also excluded. These other types of study, together, totaled 18 articles.

In this perspective, 100 articles were included for full text reading. However, 10 articles were excluded for not providing the full text for free and 02 unavailable studies were also discarded. After the complete reading, 72 articles were excluded for deviating from the eligibility criteria (Figure 1). The final sample included 16 articles.

A new search was performed in other databases, on April 4, 2023. For this, the same descriptors were used, as well as the same Boolean operator, the language inclusion criteria and the 10-year interval used in the previous research. The new search was carried out in the EMBASE and SciELO databases. In the last base, no results were found. At EMBASE, the platform filter "Articles" and "Erratum" was also used to select materials. There were 462 results found. However, with data crossing, 265 articles were excluded due to repetition.

After completing the reading of titles and abstracts, 174 articles were excluded due to the type of study criteria, mixed age, other clinical conditions involved and availability of the article (Figure 1). As a result, 23 articles were read in full, but only 2 studies metal eligibility criteria. In this context, with the results already obtained from the first search, 18 articles were included for analysis in this review. Among them, the types of observational studies involved were: Retrospective, retrospective comparative, and prospective cohort studies.

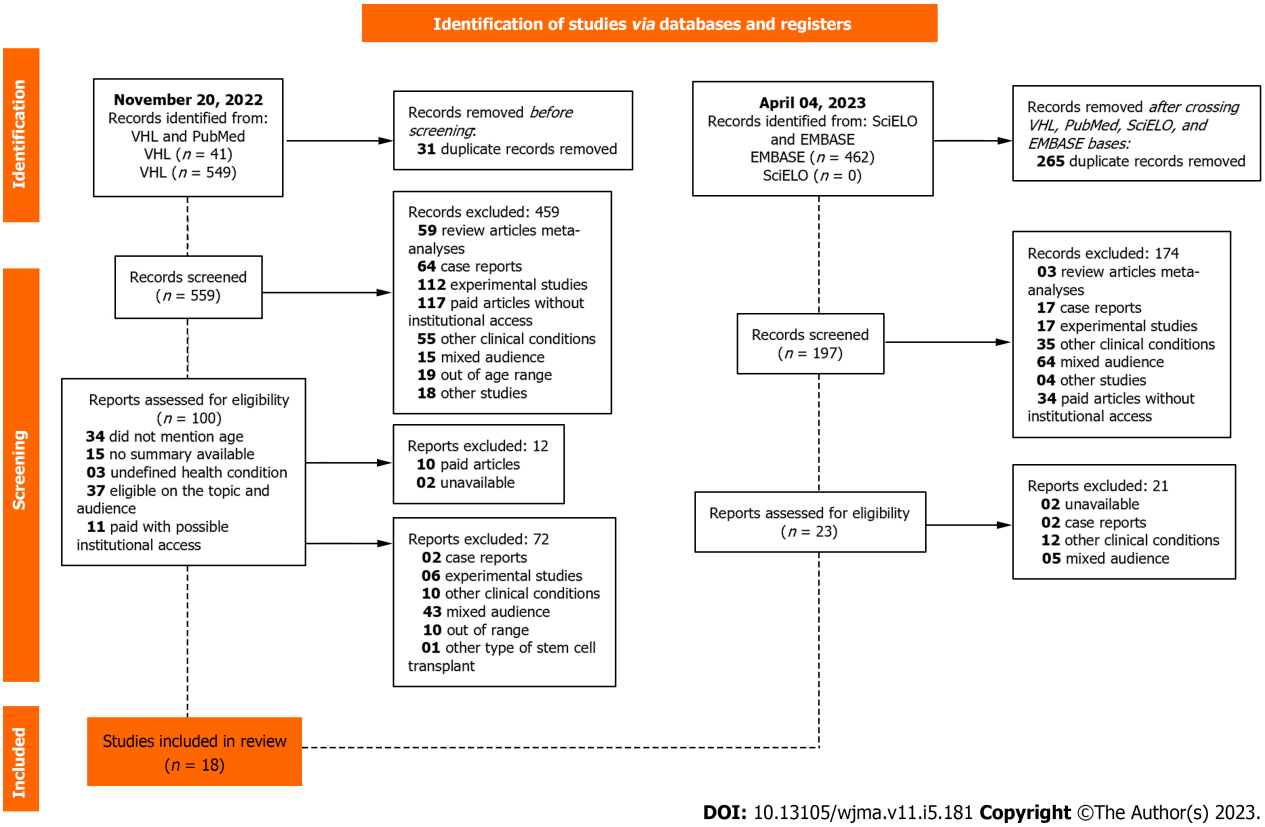

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Figure 1 Flowchart of studies selected for inclusion in the review following Preferred Reporting Items for Systematic Reviews.

Data extraction

For data extraction, a spread sheet was prepared in advance for analysis of patients and treatment, which included: (1) Participants: Number of patients, age group, gender; (2) health condition: The type of hematological malignancy; (3) characteristics of the donation: source of cells; (4) intervention: Conditioning regimen; (5) recurrent clinical complications: Types of complications; and (6) clinical outcomes: The overall survival (OS) and event-free survival (EFS) and the main reasons for death of patients.

In all articles, data on the age of the patients were obtained through the available tables, verifying the age range surveyed. In comparative studies, when possible, data were extracted from the public that received the Haplo-HSCT separately. The presentation of the statistical results of OS and EFS will also be directed to the Haplo-HSCT data of the included studies. Thus, OS and EFS rates, which have Haplo-HSCT results separately, will be presented according to their analysis intervals.

Evaluation of the quality of studies

For analysis of the studies, a survey of methodological aspects was carried out, with the authors' names, journal, year of publication, country where the study was carried out, study design, time of analysis and purpose of the study. The risk of bias of the selected studies was assessed using the Cochrane tool: Risk of Bias In Non-randomized Studies-of Interventions (ROBINS-I)[13].

The ROBINS-I presents seven domains that provide theoretical support for detecting factors that can lead to confounding when analyzing a patient's outcome, as well as enabling the analysis of possible biases in the selection of participants, performance of interventions, deviations from usual practice, availability of data, assessment of measures and reporting of studies. In this step, two reviewers, independently, assessed each domain and managed to classify each study as low, moderate, serious or critical risk, based on the platform's guidelines, as can be seen Figure 2.

In order to analyze the clinical results, the factors that influence the prognosis of patients submitted to allogeneic transplants were considered for the detection of the confounding domain[14]. These factors were divided into: Pre-transplant, peri-transplant and post-transplant. In pre-transplantation, the disease status, age and sex of the patient, information about donors and source of cells were considered. In the peri-transplantation, it was verified if there was information on the conditioning regimen, prevention of GvHD, the number of cells infused. In the post-transplant period, information on the development of acute and chronic GvHD was considered.

For all factors, the existence of variables that could statistically assess this domain was verified, including: The *P* value for gender and age of patients, source of cells and donors; the immunopheno-

Figure 2 Assessment of the risk of bias of studies in each domain of the tools Revised Cochrane Risk of Bias In Non-randomized Studies-of Interventions (ROBINS-I).

typing, white blood cell counting, platelet counting, percentage of blasts, hemoglobin levels, chimerism, cytogenetic techniques and molecular genetics were also observed, the last two when it was necessary. Thus, the indication of the factor and the establishment of the variable for its evaluation were classified as low-risk bias, while the absence of both was considered as critical condition.

RESULTS

Characteristics of the studies

The studies were published between 2014 and 2022, with retrospective and prospective analyses. Thus, in retrospective analyses, the interval between articles was from 1988 to 2021; while in prospective analyses, the public was analyzed between 2011 and 2019. The research was concentrated in seven countries: Korea, China, Italy, Colombia, Spain, Germany and Japan. It is noteworthy that China was responsible for 8 publications (Table 1).

Table 1 Methodological aspects: General characteristics on the studies included

Ref.	Journal	Country	Study designs	Study analysis time	Objective
Kim *et al*[15], 2021	*British Journal of Haematology*	Korea	Retrospective	2009-2020	To analyze genetic abnormalities in JMML to evaluate the genetic profile of this rare paediatric leukaemia in a single Korean institution
Hong *et al* [16], 2022	*Transplan tation and Cellular Therapy*	Korea	Retrospective comparative	2013-2020	To compare outcomes in children and adolescents with high-risk acute leukemia after a busulfan-based myeloablative conditioning regimen along with HRD HSCT with PT-Cy or MUD HSCT
Bertaina *et al* [17], 2018	*Blood*	Italy	Retrospective	2010-2015	To report the outcome of children with acute leukemia who received either UD-HSCT or αβhaplo-HSCT
Bai *et al*[18], 2020	*Leukemia Research*	China	Retrospective	2008-2018	To investigate the clinical characteristics, outcomes, and effects of HSCT (especially haplo-HSCT) among non- infant children with t(v;11q23)/MLL-r B-ALL
Ruggeri *et al* [19], 2021	*Transplan tation and Cellular Therapy*	Italy	Prospective cohort	2011-2019	To analyze the outcomes of unmanipulated haploidentical Transplantation using PT-Cy in pediatric patients with acute lympho-blastic leukemia
Sun *et al*[20], 2015	*European Review for Medi cal Pharmaco logical Sciences*	China	Retrospective	2002-2012	To discuss the effect of transplantation and the difference in treatment effect among children having different donor patterns, aiming to identify the prognostic factors
Sano *et al*[21], 2021	*Frontiers in pediatrics*	Japan	Retrospective	2009-2019	To aimed to evaluate the efficacy of T-cell replete HLA-HSCT for pediatric RR-BCP-ALL
Paina *et al* [22], 2018	*Cellular Therapy and Transplantation*	Germany	Prospective cohort	2006-2016	To assess efficiency of haplo-HSCT performed with non-manipulated grafts of children and adolescents with high-risk acute leukemias. In this respect an efficiency study of haploidentical GVHD was performed at our clinic in children and adolescents with high-risk ALL and AML, at maximal observation terms of 10 years
Mo *et al*[23], 2016	*Internatio nal Journal of Cancer*	China	Retrospective comparative	2011-2015	To compare the therapeutic effects of single UCBT and unmanipulated haplo-HSCT in high-risk ALL children
Wang *et al* [24], 2020	*Journal of Internatio nal Clinical Cytometr y Society*	China	Prospective cohort	2011-2016	To determine the impact of pre- and post-MRD status as well as peri-transplant MRD kinetics on clinical outcomes focused on children with ALL who received haploidentical allografts
Zhang *et al* [25], 2022	*Chinese Medical Journal*	China	Retrospective comparative	2012-2018	To explore the effect of allo- HSCT (especially haploidentical HSCT) on improving survival and reducing relapse for high-risk childhood T-ALL in CR1 and the prognostic factors of childhood T-ALL in order to identify who could benefit from HSCT
Zheng *et al* [26], 2020	*Cancer Communi cations*	China	Retrospective comparative	2013-2017	To compare the survival outcomes between high-risk AML children who underwent either unmanipulated HID-SCT or ISD-SCT at three large Chinese SCT centers
Trujillo *et al* [27], 2021	*American Society For Transplan tation and Celular Therapy*	Colombia	Retrospective	2012-2017	To decrease the toxicity associated with the addition of 100 mg/kg of cyclophosphamide to a myeloablative regimen while maintaining a good antileukemic effect and a good engraftment rate, using an intermediate-intensity regimen
Yang *et al*[28], 2022	*Hematology*	China	Retrospective	2015-2021	To investigate the outcomes and prognostic factors of pediatric AML patients with *KMT2A* rearrangements who were treated at our institution over a 5-year period
Bai *et al*[29], 2022	*BMC cancer*	China	Retrospective	2014-2019	To explore the role of allo- HSCT (especially haploidentical-HSCT) in the treatment of paediatric patients with MLL-r AML in CR1 and investigated the prognostic factors of these patients
Miyamura *et al*[30], 2019	*Leukemia Research*	Japan	Retrospective	1988-2011	To investigate the outcomes and prognostic factors of AML with KMT2A rearrangement treated with allogeneic HSCT
Oevermann *et al*[32], 2014	*Blood*	Germany	Retrospective comparative	1996-2013	To analyze the influence of KIR haplotypes on the outcome of children with ALL given haploidentical HSCT
Pérez-Martí nez *et al*[33], 2020	*American Journal of Hematolo gy*	Spain	Retrospective	1999-2016	To compare and analyze the feasibility and outcome of a Spanish cohort of 2 haplo-HSCT platforms in children and adolescents with high-risk hematological malignancies: PT-Cy and *ex vivo* TCD grafts

JMML: Juvenile myelomonocytic leukemia; HSCT: Hematopoietic stem cell transplantation; PT-Cy: Post-transplantation cyclophosphamide; MUD: Matched unrelated donors; RR-BCP: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia; KIR: Killer cell immunoglobulin-like receptor; TCD: T cells; ALL: Acute lymphocytic leukemia.

Regarding the risk of bias in the studies, the serious-risk in the analysis of selection bias is due to the fact that some of the aspects of the attributions of the status of the intervention were determined in a way that could have been affected by the knowledge of the previous result combined with the fact that the beginning of the follow-up and the beginning of the intervention did not coincide, so that the interpretation could not be adjusted in the final analysis of the outcomes. While, in the deviations, those studies were indicated that had to switch regimens and co-interventions due to the initial responses of the patients. The changes were not balanced across intervention groups. In addition, the data and reports concern the availability of all information from participants in the interventions and demonstration of multiple analyzes and different subgroups.

Characteristics of the patients

The total sample of all cohorts of the analyzed studies was 1825 patients, considering the entire audience in the comparative studies and information on patient removal due to death before treatment (Table 2). The majority of the sample was composed of males, the highest median age reported was 15 years and the lowest, 1.2 years. The ethnicity of the participants was not a topic well explored by the authors.

Among the reported clinical conditions, the following were observed: Juvenile myelomonocytic leukemia (JMML), ALL, acute myeloid leukemia, chronic myelogenous leukemia, mixed lineage leukemia, mixed-phenotype acute leukemia and NK cell leukemia. In addition, it is verified that 1295 patients underwent Haplo-HSCT, considering the information on the withdrawal of patients from the original cohorts due to another type of donation, such as a MUD-HSCT and matched sibling donor (MSDT) (Table 2).

Regarding the type of conditioning, different types of regimens were observed, with the adoption of the Myeloablative Conditioning Regimen, some with total body irradiation, and also the Reduced Intensity Regimen. In studies that detailed the types of chemotherapy, it was observed that the main drugs used were: Busulfan, Fludarabine, Cytarabine, Cyclophosphamide, Melphalan, and Semustine (Table 3).

In addition, for the prevention of graft disease and mobilization of the BM and peripheral blood stem cells (PBSC), the interventionists of the analyzed studies used different combinations of drugs, therefore, the same study used one or more compounds. As a result, ATG was administered by 12 studies; post-transplant cyclophosphamide, 5; Cyclosporine A, 13; Methotrexate (MTX), 11; Mycophenolate mofetil (MMF), 10; Tacrolimus, 6; granulocyte colony stimulating factor, 6; and Sirolimus, 1. Two studies did not present the names of the drugs used for this purpose.

Outcomes

Recurrence, graft rejection and delayed immune recovery are the major clinical challenges that have been identified. The occurrence of hematological recurrences was observed in most of the studies, with the exception of Kim *et al*[15], in which this type of clinical complication was not explicitly mentioned. Among the authors who reported, seven studies pointed to extramedullary recurrences (EMR). Hong *et al*[16] identified extramedullary recurrence in the central nervous system, the others did not report the location of the EMR.

Acute graft-versus-host disease (aGvHD) and chronic graft-versus-host disease (cGvHD) were also observed in most of the analyses, with the exception of the study by Bertaina *et al*[17], in which there were no cases of grade III-IV or visceral aGvHD in the haploidentical transplant cohort, and two other studies that did not discuss this type of complication.

In the total sample of all cohorts of the analyzed studies, the pre-transplant minimal positive residual disease (pre-MRD+) was identified in 288 patients; while 337 patients were MRD negative (pre-MRD-). After transplants, 90 patients were identified with positive MRD (post-MRD+), 19 with reemerging MRD. However, these data are limited, considering the fact that some authors did not present the pre-transplant and post-transplant MRD status together, and also not all comparative studies that separated the results of the analyzed cohorts. In addition, eight other articles did not have either status.

It is known that immunosuppression makes the patient susceptible to infections. Therefore, infections are also among the main clinical complications, with viral, bacterial and fungal infections being reported. Among viral infections, cytomegalovirus and adenovirus were the most common. In addition, due to treatment-related toxicity, multiple organ failure, hemorrhagic cystitis, and cerebral and alveolar hemorrhages have been reported. Among organ failure, liver impairment was reported in 05 studies and 02 studies also pointed to the involvement of the gastrointestinal tract and skin. Other causes of complications include sepsis, pneumonia, and cases refractory to treatment. Other types of complications occurred in smaller numbers.

The main causes of death were relapses, graft-versus-host disease, infections and transplant-related complications. Furthermore, non-recurring mortality (NRM) was also presented in most of the studies. However, in the study by Hong *et al*[16], the group that received Haplo-HSCT did not present any cases of NRM.

The OS and EFS rates are indicated in Table 3. It is observed that in the 5-year interval, the lowest EFS and OS rates were 29.5% and 68.0%, respectively. The EFS result of 29.5% was reported in patients with transplants from a KIR A haplotype donor. In this same interval, the highest rates of EFS and OS were 80.1% and 81.0%, respectively. At the 10-year interval, OS rates were 64.7% for patients in a first

Table 2 Characteristics of haploidentical transplants identified in the studies included

Ref.	All patients, *n*	Age, yr, median	Sex, male, *n*	Condition clinic	Haplo transplant cohort, *n*	Age, yr, median	Sex, male, *n*	Source of stem cells
Kim *et al*[15], 2021	24	1.20[1]	15	JMML	14	NR	NR	PBSC
Hong *et al*[16], 2022	80	NR	51	ALL, AML, MPAL, and NK cell leukemia	35	7.00	22	PBSC
Bertaina *et al*[17], 2018	343	3.30	210	ALL, AML	98	6.60	65	PBSC[5] BM
Bai *et al*[18], 2020	38[3]	4.00	25	MLL-r B-ALL	19[4]	4.00	13	NR
Ruggeri *et al*[19], 2021	180	9.25	114	ALL	180	9.25	114	PBSC BM
Sun *et al*[20], 2015	111	10.00	73	AML, ALL, CML, and MLL	111	10.00	73	PBSC BM
Sano *et al*[21], 2021	19	10.00	12	RR-BCP-ALL	19	10.00	12	PBSC, PB + BM
Paina *et al*[22], 2018	106	7.00	65	ALL, AML	106	7.00	65	BM + PBSC BM
Mo *et al*[23], 2016	129	NR	42	HR, ALL	65	10.00	33	G-BM, G-PB
Wang *et al*[24], 2020	166	15.00	114	B-ALL and T-ALL	166	15.00	114	NR
Zhang *et al*[25], 2022	74	11.00	52	HR T-ALL	27[2]	12.00	21	BM
Zheng *et al*[26], 2020	82	NR	56	HR AML	69	12.00	42	PBSC, BM
Trujillo *et al*[27], 2021	42	11.00	24	ALL, AML, JMML, and CML	42	11.00	24	PBSC
Yang *et al*[28], 2022	21	NR	15	AML, *KMT2A* rearrangents	17	6.06	12	NR
Bai *et al*[29], 2022	44	9.00	25	MLL-r AML	37	NR	NR	NR
Miyamura *et al* [30], 2019	90	3.00	49	AML *KMT2A* rearrangents	10	NR	NR	NR
Oevermann *et al* [32], 2014	85	10.00	NR	ALL	85	10.00	NR	PBSC
Pérez-Martínez *et al*[33], 2020	192	8.60	118	ALL, AML, MDS, JMML, CML, and biphenotyipic	192	8.60	118	PBSC BM

[1]In the study, this information was given in months.
[2]Four patients had a matched sibling donor. So, only 23 patients received haplo-hematopoietic stem cell transplantation. However, Zhang *et al*[25] didn't give the age and numbers by sex separately.
[3]One patient was excluded from the analysis owing to death from pulmonary infection during induction. So, only 37 patients were analyzed.
[4]One patient received human leukocyte antigen-MUDT. So, only 18 received the haplo-transplant CR1. However, Bai *et al*[18] didn't give the age and numbers by sex separately.
[5]All patients in the haplo cohort received stem cells from peripheral blood stem cells.
JMML: Juvenile myelomonocytic leukemia; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myelogenous leukemia; MLL: Mixed lineage leukemia; MPAL: Mixed-phenotype acute leukemia; NK: Natural Killer; RR-BCP: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia; NR: Not related; PBSC: Peripheral blood stem cells; BM: Bone marrow; PB: Peripheral blood.

complete remission (CR1) and second CR (CR2); and 18.1% for patients transplanted beyond remission (Table 3).

It is emphasized that, in the study by Bai *et al*[18], patients in the chemotherapy regimen cohort who relapsed and opted for haploidentical transplantation had an OS rate of 57.1%. Thus, in CR2, the results were less satisfactory in relation to the results of transplants performed in CR1 in that same study. At the same time, it was observed in the study by Ruggeri *et al*[19] that patients in CR1, CR2, and CR3 had a 2-year EFS of 65.0%, 44.0%, and 18.8%, respectively. Finally, it is noted that three other studies showed an EFS rate below 50%, with an interval of 2 years in two studies and 3 years in two studies (Table 3).

Table 3 Conditioning, event-free survival and overall survival of the analyzed patients

Ref.	Haplo transplant cohort, *n*	Conditioning regimens (all cohorts)				Haplo cohort	
		I	II	III	IV	EFS (%)	OS (%)
Kim *et al*[15], 2021	14	MAC: Bu-Flu	MAC: Bu-Flu-TBI	RIC: Bu-Flu-TBI	-	NRS	NRS
Hong *et al*[16], 2022	35	MAC, Bu, Flu	MAC, Bu, Flu, and Cy	TBI after blinatumomab	-	74.4% (3 years)	88.6% (3 years)
Bertaina *et al*[17], 2018	98	MAC: Bu	MAC/TBI: TBI-based	Treosulfan based	-	62.0% (5 years)	68.0% (5 years)
Bai *et al*[18], 2020	18[1], 08[7]	MAC/chemo: Cytarabine, Cy, Bu, and semustine	-	-	-	89.5% (4 years), NRS	87.4% (4 years); 57.1% (4 years)
Ruggeri *et al*[19], 2021	180	MAC/chemo	MAC/TBI	RIC	-	38.5%[2] (2 years); 65%[3]; 44%[4], and 18.8%[5]	50.8% (2 years); 76.5%[7]; 61.2%[7]; (NRS)
Sun *et al*[20], 2015	111	MAC: Bu, cycytarabine, and Me-CCNU	MAC/TBI Cy, cytarabine	-	-	79.2% (5 years)	NR
R	19	MAC: Bu, Flu, and melphalan, TBI-based	MAC: Bu-based	RIC	-	42.1% (3 years)	57.4% (3 years)
Paina *et al*[22], 2018	106	MAC: Bu, Cy, and Lomustin	MAC, Bu-flu	MAC: Treosulfan	RIC: Melphalan; RIC: Bu	NR	33.3% (10 years); 64.7%; 18.1%, (10 years)[6]
Mo *et al*[23], 2016	65	Cytarabine, Bu, Cy, and semustine	TBI	MAC: Bu-Flu Carmustine	MAC: CyFlu-TBI	71% (2 years)	82.0% (2 years)
Wang *et al*[24], 2020	166	RIC: Cy, MTX, MMF	-	-	-	60.2% (100 d)	60.8% (100 d)
Zhang *et al*[25], 2022	23	MAC: Bu-Cy, hydroxyurea cytarabine, and methy	-	-	-	80.1% (5 years)	81.0% (5 years)
Zheng *et al*[26], 2020	69	Bu-Cy, cytarabine, semustine	Bu-Cy-Hu, cytarabine, semustine	-	-	72.9% (3 years)	73.0% (3 years)
Trujillo *et al*[27], 2021	42	RIC: Bu-Flu-TBI	RIC: Flu-Mel-TBI	-	-	46% (3 years)	56% (3 years)
Yang *et al*[28], 2022	17	Cytarabine, Bu, and Cy Me-CCNU	Cytarabine, Bu-Cy	-	-	NRS	NRS
Bai *et al*[29], 2022	37	Cytarabine, Bu-Cy, and semustine	-	-	-	65.6% (3 years)	73.0% (3 years)
Miyamura *et al*[30], 2019	10	MAC, Bu-TBI	RIC, NR	-	-	NRS	NRS
Oevermann *et al*[32], 2014	85	TBI	Non TBI	-	-	50.6%[7] (5 years); 29.5%[7] (5 years)	NR
Pérez-Martínez *et al*[33]	192	Flu-Thiotepa-Mel or Bu	TLI or TBI	-	-	49.2% (2 years)	55.1% (2 years)

[1]In the study, 18 patients in the complete remission 1 (CR1) e 8 other patients from the other cohort experiencing relapse opted for allogeneic hematopoietic stem cell transplantation (HSCT, CR2, *n* = 13, but just 8 patients opted for allogeneic HSCT).
[2]General.
[3]CR1.
[4]CR2.
[5]CR3.
[6]CR1 and CR2; patients transplanted beyond the remission.
[7]KIR B haplotype; KIR A haplotype.
NRS: Not reported separately; NR: Not reported; TLI: Traumatic lung injury; TBI: Total body irradiation; MAC: Myeloablative conditioning regimen; RIC: Reduced intensity regimen.

DISCUSSION

Based on the analysis of selected studies, this review presented the clinical results indicated of pediatric

patients with leukemias and myelodysplasias younger than 18 years old who underwent Haplo-HSCT. Until the moment, there are few published reports on the use of Haplo-HSCT in selected pediatric populations. In our review, the total sample in the analyzed studies of patients undergoing Haplo-HSCT was 1295 patients, in which both favorable outcomes and poor prognostic factors were observed. Haploidentical transplantation is often indicated in more severe cases and for patients in second remission according to the time and place of disease recurrence[19], however, studies have indicated efficient results for patients treated in first complete remission and with early referral[19,20-22].

Ruggeri *et al*[19] indicate the importance of disease status as one of the most important prognostic factors influencing the risk of disease recurrence and the probability of EFS and OS. In that study, patients in CR1, CR2, and CR3 had 2-year EFS of 65.0%, 44.0%, and 18.8% and 2- year OS of CR1 and CR2, 76.5% and 61.2%, respectively. These results are consistent with the study by Bai *et al*[18], in which patients in CR1 had a 4-year OS of 87.4% and patients in CR2 had an OS at the same interval of 57.1%. Thus, both studies indicate the worsening of the patient's prognosis as the disease progresses and indicate that the results show the feasibility of Haplo-HSCT for patients in CR1 and CR2. In contrast, Mo *et al*[23] found no relationship between pre-transplant disease and EFS, however, the authors point to the low number of patients in non-remission or relapse at the time of transplantation, which limits their analyses.

Pre-transplant MRD status is also indicated as a poor prognostic factor, often related to an increased probability of recurrence[19,23,24]. In our review, 288 patients were identified with pre-MRD+ in the analyzed studies. These patients had higher recurrence rates than the pre-MRD- group. However, in the analysis by Zhang *et al*[25] and Bai *et al*[18], there was no clear impact predictor at the level of MRD after induction. That is, despite a trend towards lower OS/EFS and higher cumulative incidence of relapse in patients with MRD+ after induction, the results were not statistically significant[18]. The authors presented as justifications the limited number of patients in the analysis and the effectiveness of allo-HSCT in the impact of the MRD level after induction[18].

However, in our series, the data extracted on MRD was limited, as not all studies explored this prognostic factor and few authors provided the comparison and follow-up of cohorts with pre-MRD+/pre-MRD- and post-MRD+/post-MRD-. Thus, there is little information on the effects of MRD on outcomes in Haplo-HSCT, although MRD can be configured as a transformative approach in risk stratification[18].

The graft *vs* leukemia (GVL) effect is related to chronic GvHD[23]. Studies indicate that the GVL effect is stronger in patients who receive haploidentical transplantation[23,26]. In a multivariate analysis in the study by Mo *et al*[23], mild and moderate cGvHD was associated with a significant improvement in the survival of patients who presented with transplantation, possibly due to the GVL effect, and that, despite the high incidence of cGvHD, there was no significant increase in the risk of NRM in the Haplo-HSCT group. However, the same authors alert to the fact that intense immunosuppressive therapy, which has been correlated with severe cGvHD, can revoke the effector cells of the GVL effect and impair the quality of life of these patients.

When analyzing aGvHD, the study by Bertaina *et al*[17] was noteworthy. There were no cases of grade III-IV or visceral aGvHD in the haploidentical transplant cohort[17]. In this study, the authors performed a multicenter scaled analysis to compare the efficacy of αβhaplo- HSCT and MUD-HSCT in a cohort where the TBI-based conditioning regimen was frequently used. Furthermore, in that study, there was a lower risk of NRM in αβhaplo-HSCT recipients compared to HLA misMUD-HSCTs, the authors attributed to the fact that chronic GvHD was also limited.

Other variables such as age have been identified as prognostic factors in some studies. In the study by Zhang *et al*[25], children with ALL aged ≥ 10 years was an independent risk factor that affected 5-year OS and EFS rates. Advanced age was also associated with a poor prognosis with a higher risk of extramedullary recurrence, according to Ruggeri *et al*[19]. However, compared to all the data, it is noted that few studies have identified the statistical significance of advanced recipient age. No statistical significance was found for the recipient's gender either.

The studies Indicate the association between high initial leukocyte count and risk of recurrence[25] and, in Ruggeri *et al*[19], the use of PBSC was associated with a significantly lower OS, with a higher risk of NRM. While, Trujillo *et al*[27] indicate that PBSC is associated with a lower number of relapses. In this regard, as the source of graft cells is a modifiable factor, it would be interesting if the source was better researched, considering the characteristics of patients and diseases.

Genetic abnormalities and rearrangements

Cytogenetic abnormalities are important prognostic factors in cases of hematologic malignancies. Thus, understanding these manifestations can contribute to decisions regarding treatment strategies[15,25]. In this regard, our study brought, based on retrospective analyses, the presentation of the effects of cytogenetic alterations in high-risk myeloid and lymphoid leukemias, such as rearrangements of mixed-lineage leukemia genes, and in myelodysplastic syndromes with rare genetic profiles.

Therapeutic considerations range from observation to allogeneic stem cell transplantation, depending on the genetic subtype. In the case of JMML, a very aggressive form of MDS, Kim *et al*[15] showed, in their analyses, that allo-HSCT is still presented as the only curative treatment option for most patients and that patients frequently have poor EFS rates. In that study[15], patients with mutations involving

RAS pathway genes and somatic mutations in non-receptor protein tyrosine phosphatase type 11 were the most common mutations identified, and had a 5-year EFS of 72.9% and 41.7%, respectively. Among these patients, 14 patients received Haplo-HSCT. The authors drew attention to the fact that cytogenetic changes influence disease progression, rather than the onset of leukemia, which makes it valuable for predicting disease outcomes.

In the same perspective, the presence of cytogenetic abnormalities in 11q23 involving lysine-specific methyltransferase 2A (KMT2A) has been associated with adverse outcomes and higher rates of early death and relapse even after allogeneic hematopoietic stem cell transplantation[28,29]. Its occurrence is more common in children than in adults, and the prognostic value influencing outcomes in pediatric AML is associated with the fusion partner gene. The KMT2A/MLLT3 fusion resulting from t(9;11)(p22;q23) KMT2A is the most common rearrangement in children. However, it is the t(6,11) and AF10 translocation partners in t(10,11) that are often associated with poor prognosis[25].

In the study by Miyamura *et al*[30], no patient with t(6,11) remained alive in CR and only 1 patient with t(10,11) remained alive in CR, which corroborates the findings in the literature. However, the authors note that the t(9,11) translocation partner was found more frequently in their patients and that their results did not differ significantly from other 11q23 abnormalities. Although the lack of difference in transplant results was justified based on the retrospective analysis and the possible biases generated, this is something that deserves to be further studied.

In this regard, Yang *et al*[28] noted the high occurrence of KMT2A rearrangements in childhood AML and how the prognosis of children with t(9;11)(p22;q23) remains controversial. Thus, when they performed a retrospective investigation on the outcomes and prognostic factors of pediatric AML patients with KMT2A rearrangements, it was identified that approximately 31.3% of the investigated children had the KMT2A/MLLT3 fusion gene. Some of these children underwent hematopoietic stem cell transplantation, where four received donations from compatible sibling donors and another seventeen received haploidentical transplants. As a result, presented, they had EFS between the two groups of $P = 0.303$. Therefore, EFS rates were not statistically significant among patients who received haplo-HSCT and full-matched HSCT, which indicates that, in the absence of a suitable fully matched donor, children with high-risk AML who carry mutations in the KMT2A gene, may accept haploidentical hematopoietic stem cell transplantation.

KIR haplotypes impacts

It has been observed that the presence of donor-derived alloreactive NK cells influences the outcome of haploidentical hematopoietic stem cell transplantation, given that among HLA non-identical donors and recipients, donor NK cells that encounter recipient target cells without an HLA class I allele present in the donor's HLA genotype can exert antileukemic effects[31]. Among these effects are lower rates of relapses, graft failure and GvHD, which contributes to patient survival[31]. In this context, it was discussed about the response of patients to treatment considering the influence of killer cell immunoglobulin-like receptors (KIRs) present on NK cells.

The expression of inhibitory KIR receptors is responsible for the alloreactivity of NK cells in allogeneic hematopoietic stem cell transplantation[31,32]. Oevermann and other collaborators[32] presented a series of 85 patients with high-risk ALL confirmed by Haplo- HSCT, where 74% of donors had KIR B haplotype and 26.0% of the donors had KIR A haplotype. Patients transplanted from the B haplotype donor had a 5-year EFS of 50.6%, while patients transplanted from the A haplotype donor had 29.5%.

This was also observed in the study by Pérez-Martínez *et al*[33], where early reconstitution of NK cells was reported on the *ex vivo* TCD platform and related prognoses with the donor KIR B haplotype, while the KIR A haplotype increased the probability of relapse on the PT-Cy and *ex vivo* TCD platforms. In this regard, the authors drew attention to the inclusion of genotyping when choosing donors, with preferential selection of KIR B haplotype donors due to the results observed.

Therapeutic and regimens effects

Discussions about the main platforms of Haplo-HSCT and the type of conditioning regimen that patients are submitted during treatment are points of evaluation between the authors. In the records of Pérez-Martínez *et al*[33], in an analysis of morbidity and mortality associated with GvHD, considerations were found regarding *ex vivo* grafts of depleted TCD and grafts filled with T cells followed by PT-Cy. Thus, although a higher incidence of aGvHD grades I-II was noted in patients treated with the PT-Cy platform, the results that include OS, EFS and recurrence demonstrated that there are no statistical differences between both grafts in the outcomes analyzed by the authors. The great challenge that remains, on both platforms, is overcoming relapse as the main cause of transplant failure[33].

Treatment platforms have been widely studied. Studies point to the impact of high doses of purification of CD34 cells on GvHD, with a reduction and decrease in cases. However, this technique has a high transplant-related mortality due to the delay in immune reconstitution, which promotes a high risk of infection during the first months after transplantation. In this perspective, another type of purification, which has been widely used, is the partial depletion of T cells, such as αβ, which has shown optimistic results, since this technique maintains some subsets of T cells, such as γδ T cells, NK cells and memory T cells without increasing GvHD. Regarding the PT-Cy approach, which has been shown to be

effective in reducing GvHD, there is the advantage of not requiring *ex vivo* manipulation of the graft. However, PT-Cy requires prolonged immunosuppression treatment[19,27,33].

With regard to conditioning, discussions of myeloablative (MAC) and low-intensity (RIC) regimens have been contrasting. Bertaina and other authors[17] pointed to a low incidence of graft failure (2%) in the αβhaplo-HSCT group with the use of a fully MAC conditioning regimen and associated the regimen as a possible explanation for the lower incidences of relapse in the analyzed patients. As in the studies by Ruggeri *et al*[19], the MAC regimen was associated with significantly longer GvHD/relapse-free survival. While Trujillo *et al*[27] point out that the MAC regimen is often associated with acute and long-term toxicities, such as secondary malignancies and increased acute mortality, and that the combination of a RIC with haploidentical cells using the PT-Cy platform has a very strong antileukemic effect. From this perspective, studies that analyze MAC and RIC regimens and their contribution to patients' quality of life are needed.

CONCLUSION

Haplo-HSCT has been shown to be a promising therapeutic option. In recent years, the number of Haplo-HSCT has increased with the pediatric public under the age of 18, however, publications do not keep up with this pace. This review was performed based on retrospective and prospective data; thus, the methodological aspects of the studies may have influenced the analysis. Therefore, randomized clinical trials and meta-analyses should be encouraged in order to confirm the reported findings.

When exploring the published studies, it was observed that prognostic factors such as treatment platforms, cytogenetic abnormalities and disease state exert a strong influence on the clinical outcomes of transplanted patients and other variables can be obtained in order to collaborate with risk stratification and selection approaches of donors. Nevertheless, the information extracted about age and source of stem cells as prognostic factors is insufficient to provide a conclusion, considering the counterpoint of information across the studies presented.

The indication of Haplo-HSCT for patients in first complete remission is evident. Studies have indicated efficient results for patients treated at this stage and with early referral, with significantly important and different survival rates. Thus, it is noted that disease status as one of the most important prognostic factors influencing the risk of disease recurrence and the probability of EFS and OS.

One of the clinical challenges is the delay in immune recovery. This delay depends on the chosen treatment platform, since in grafts with highly purified CD34 cells there is a limitation of cell reconstitution. While on the PT-Cy, reconstitution has greater speed and lower financial cost, but with prolonged immunosuppression treatment, and, in partial T-cell depletion, some T-cell subsets are received without increasing GvHD. In this perspective, there are pros and cons between the treatment platforms, and, therefore, the characteristics of the disease and the patients to be transplanted must be considered.

Relapse, identified as a primary transplant failure, was the most recurrent clinical complication, with many factors contributing to relapse. Among these factors, a limitation of this review was the analysis of MRD status, with pre-MRD+/pre-MRD- and post-MRD+/post- MRD- cohorts. Here, although pre-MRD+ was pointed out as a poor prognostic factor, the numbers were too few for a complete analysis. Thus, studies that seek to identify the effectiveness of Haplo-HSCT in the impact of the MRD level after induction should be encouraged.

In summary, Haplo-HSCT represents a promising therapy, considering the potential number of possible donors and the accommodation and treatment platforms that can be offered. The results obtained show that this type of transplant has a strong antileukemic effect, with generally accepted rates of survival. Overcoming relapse as the first cause of transplant failure is the great clinical challenge.

ARTICLE HIGHLIGHTS

Research background

Haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) has been performed in patients with different hematological malignancies. This type of transplant is performed with a related donor with partially HLA matching; therefore, it has a high availability. In recent years, the number of children with leukemia and myelodysplasia submitted to Haplo-HSCT has increased. However, there are few evaluations on the efficacy and safety of this treatment, considering only the pediatric public under 18 years of age.

Research motivation

The availability of donors in the Haplo-HSCT has been listed as one of the main reasons for carrying it out with the pediatric public, arousing the interest of researchers in evaluating the benefits of this treatment. In this sense, we sought to assess the factors that influence the prognosis of patients, complic-

ations and clinical outcomes.

Research objectives
To identify and summarize the scientific contributions available on haploidentical hematopoietic stem cell transplants performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

Research methods
This is a descriptive systematic review. The VHL, PubMed, EMBASE and SciELO databases were consulted, but the results were only obtained in the first three. Based on the eligibility criteria, 18 articles were included in this review. For data extraction, the characteristics of the patients and treatment were sought, which included the number of patients, age group, gender, health condition, characteristics of the donation, conditioning regimen and recurrent clinical complications.

Research results
The studies included 1825 patients, most of whom were men, although gender was not an independent factor for the patients' prognosis. Regarding age, the data are inconclusive, as well as for the source of stem cells. Pre-transplant DRM status and intense immunosuppressive therapy are also factors that impact patient prognosis. The main complications observed were acute graft-versus-host disease, chronic graft-versus-host disease and infections. Clinical challenges are relapse, graft rejection and delayed immune recovery. In general, the studies indicated good results for patients treated in first complete remission and with early referral.

Research conclusions
The indication of Haplo-HSCT for patients in first complete remission is evident. Studies have shown efficient results for patients treated in this phase and with early referral, with significantly important and differentiated survival. In this perspective, considering the potential number of potential donors and the treatment platforms that can be offered, Haplo-HSCT appears to be a promising therapy. Randomized clinical trials and meta-analyses should be performed to confirm the reported findings.

Research perspectives
The pre-MRD+ was pointed out as a poor prognostic factor, as well as age and cell source, but the numbers were too few for a complete analysis. Thus, it is suggested that researchers consider these aspects and include the MRD status, with pre-MRD+/pre-MRD- and post-MRD+/post-MRD- cohorts. The analysis of the influence of the ethnicity of the patients must be done, this will contribute even more to the evaluation of the Haplo-HSCT.

FOOTNOTES

Author contributions: Cardoso Brito ACC, Oliveira Carneiro Ribeiro E, and Freire de Melo F equally contributed to this paper with the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; and all authors agree to be accountable for all aspects of the work in ensuring that questions that are related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SYSTEMATIC REVIEWS

Exploratory systematic review and meta-analysis on period poverty

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Abstract

BACKGROUND

Period poverty is a global health and social issue that needs to be addressed. It has been reported that many females compromise their education, employment, and social commitments during their menstruation days due to a number of reasons, including lack of access to toilets or menstrual products.

AIM

To provide a comprehensive understanding on period poverty, including outcomes associated with menstruation.

METHODS

All observational and randomised clinical trials reporting menstruation challenges, menstrual poverty and menstrual products were included. Our search strategy included multiple electronic databases of PubMed, Web of Science, ScienceDirect, ProQuest and EMBASE. Studies published in a peer review journal in English between the 30th of April 1980 and the 30th of April 2022 were included. The Newcastle-Ottawa Scale was used to assess the risk of bias of the systematic included studies. Pooled odds ratios (ORs) together with 95% confidence intervals (CIs) are reported overall and for sub-groups.

RESULTS

A total of 80 studies were systematically selected, where 38 were included in the meta-analysis. Of the 38 studies, 28 focused on children and young girls (*i.e.*, 10-24 years old) and 10 included participants with a wider age range of 15-49 years. The prevalence of using disposable sanitary pads was 45% (95%CI: 0.35-0.58). The prevalence of menstrual education pre-menarche was 68% (95%CI: 0.56-0.82). The prevalence of good menstrual hygiene management (MHM) was 39% (95%CI: 0.25-0.61). Women in rural areas (OR = 0.30, 95%CI: 0.13-0.69) were 0.70 times less likely to have good MHM practices than those living in urban areas.

CONCLUSION

There was a lack of evidence, especially from low- and middle- income countries. Further research to better understand the scope and prevalence of period poverty should be considered. This will enable the development of improved policies to increase access to menstrual products and medical support where necessary.

Key Words: Period poverty; Menstruation; Mental health; Menstrual education; Menstrual hygiene

Core Tip: Period poverty is an important health issue, impacting social and psychological wellbeing. Issues are predominantly seen in low- and middle- income countries, affected by conflicts, disasters, and economic struggles. Evidence showed a link between menstruation and prevalence of stress, anxiety, and depression. Whilst menstruation is a physical health issue, there are clear associations with mental health. Despite the global scale of period poverty, it is under-researched and is not well understood. Further research in this area will help to form healthcare policies and support for women and girls.

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INTRODUCTION

The World Health Organization (WHO) defines health as complete mental, physical, and social well-being, thus not a mere absence of a disease or infirmity[1]. For women, menstrual health is integral to maintain their overall health as menstruation occurs between menarche and menopause, which may have a significant impact on their mental, physical, and social wellbeing. Menstruation, or periods, is a biological process that is part of nearly every biological female's life and is defined as cyclical bleeding that occurs as a result of the regeneration of the uterine endometrium corpus. Clinically, the normal menstrual process is of 4 phases across a cycle of 28-35 days[2,3]. The regularity of these cycles, duration

of each of the bleeding episodes within a cycle, and the volume or heaviness of the bleed varies across women and can change throughout an individual's lifespan[2,3]. All women do not experience normal menstrual bleeding, with approximately 30% experiencing alterations to their pattern or volume of menstrual flow due to multiple aetiologies[2,4]. Many women also report symptoms such as pain, anxiety, fatigue, dysmenorrhea, and depression associated with their menstrual cycle that may require clinical involvement to diagnose potential reproductive health issues such as premenstrual dysphoric disorder, premenstrual syndrome, or endometriosis[2-4]. To promote positive health and wellbeing outcomes to all genders and clinicians, it is important to understand menstrual cycles and menstrual health that can be promoted in the first instance by way of menstrual health literacy and various public interventions such as maintaining good hygiene practices and access to menstrual products.

Access to menstrual products is as vital as access to other hygiene products. The WHO and United Nations International Children's Emergency Fund has reported that many girls miss school and put their lives on hold to remain at home during their menstruation days due to a number of reasons, including access to toilets or menstrual products[5,6]. This is commonly reported as period or menstruation poverty[7]. Period poverty is a global health issue impacting people who do not have access to hygienic and safe menstrual products. This is particularly important for regions with conflicts and disasters, which leave menstruating people with minimal or no access to safe menstrual products or clean toilets. This could lead to the use of unconventional methods to manage the bleeding such as the use of clothing, rags or sitting on old tin cans[8-10]. Ancient traditions such as Chhaupadi practices could further risk girls and women from securely managing their menstruation[11]. Chhaupadi is practiced in some far western rural regions in Nepal where young girls are banished into sheds or mud huts during menstruation or even longer as they believe this brings ill health or bad luck to the families [11]. Often these people have little or no access to washing facilities or supplies leading to health issues, including physical and psychological hardship[11,12]. Despite Chhaupadi being illegal in Nepal since 2005, Action Aid reports that it is practiced in some communities to date[12]. Whilst poverty and stigma impact the right for a girl child's education, especially in low-middle-income countries, The United Nations Educational, Scientific and Cultural Organization reports that 1 in 10 girls in Africa alone misses school during their menstruation[13]. Missing school could lead to dropping out, risking child marriage and pregnancy at a younger age, as reported by Action Aid[14].

It has been reported for many decades that menstrual poverty is associated with stigma and shame and impacts the dignity and overall wellbeing. Despite being a developed country, over 37% of women in the United Kingdom (UK) have experienced period shaming by way of isolation, bullying and jokes, based on an Action Aid survey report[15]. Approximately 40% of women reported being humiliated by their partners, while over half of UK women said they were embarrassed when they got their periods for the first time. In addition, over 52% reported they hide sanitary products when taking these to the toilet to prevent anyone else from being embarrassed, whilst 43% reported they felt people would make inappropriate remarks. The New York Post reported similar findings from a study commissioned by THINX, which indicated 58% of women felt embarrassed during the menstruation period whilst 42% experienced period-shaming, where 1 in 5 of those women reported these feelings were due to comments made by male friends[16].

It is evident that period poverty appears to be a global phenomenon, and key sociological as well as clinical features may differ due to varying risk factors in diverse geographical regions. To identify the impact of period poverty in diverse populations and common denominators observed between low-middle-income countries (LMICs) and high-income countries, it is vital to better understand current gaps in knowledge, policies and practice. Prior to this study, a comprehensive evidence synthesis had not been conducted to demonstrate the impact of period poverty. To achieve this, we developed the PLatform for the Analysis, Translation, and Organization of large-scale data project (PLATO) with the first component focusing on an evidence synthesis of the existing peer reviewed literature.

MATERIALS AND METHODS

A systematic methodology was developed and published as a protocol in PROSPERO (CRD-42022339536) to explore period poverty. A meta-analysis was conducted in addition to two key thematic variables identified through the systematic review of homelessness, infections, lived experiences and mental health impact due to menstruation.

Within the context of this study, rural and urban areas of the study were defined by natural administrative division of the location as reported within the peer review publications. The division of LMIC, middle-low-income countries (MICs) and high-income countries were defined based on the dividing standards of the World Banking Group.

The primary aim of this study was to provide a comprehensive understanding on period poverty, including outcomes associated menstruation such as affordability of menstrual products, disposable sanitary pads, accessibility to menstruation education tools, adequate menstrual hygiene management (MHM) practice and urinary tract infections. The difference in MHM practices in a variety of contexts such as age groups, religious beliefs, parents' educational status, and school absenteeism due to

dysmenorrhea were also explored.

Inclusion/exclusion

All observational and randomised clinical trials reporting menstruation challenges, menstrual poverty and menstrual products were included. Studies published in a peer review journal in English between the 30th of April 1980 and the 30th of April 2022 were included. All editorials, letters to editors and commentaries, and papers published in languages other than English were excluded.

Patient and public involvement

All the data used in this systematic review is publicly available. No further patient or public involvement was implemented for this paper.

Search strategy

Our search strategy included multiple electronic databases of PubMed, Web of Science, ScienceDirect, ProQuest and EMBASE. Subject index terms used were: Menstrual education, anthropology, period poverty, pads, sanitary pads, sanitary facilities, menstrual hygiene, urinary tract infections, menstrual health, and women's periods. The title and abstract of each publication were screened independently by two investigators. A consensus was reached for studies that were unsuitable for inclusion. Articles that were included were reviewed in in full independently by two investigators. These were re-reviewed independently prior to the data extraction. Difference of opinions and queries were resolved by the by the Principal Investigator and Chief Investigator.

Data extraction

We developed an extraction template specific to the objectives of the study although the aim was to gather a wider dataset to ensure vital data was not missed to answer the research aims comprehensively. Participants included in the study populations were those who live and/or are at risk of menstrual poverty. All studies reporting a menstrual product and/or an educational intervention associated with menstruation were extracted by way of the instruments, measures of tool and questionnaires. The final dataset was independently reviewed before the analysis commenced.

Participants included in the study populations were those who have experienced or are at risk of menstrual poverty. All studies reporting a menstrual product and/or an educational intervention associated with menstruation were extracted by way of the instruments, measures of tool and questionnaires. The final dataset was independently reviewed before the analysis commenced.

Risk of bias

The Newcastle-Ottawa Scale was used to assess the risk of bias (RoB) of the systematic included studies. A risk of bias table has been made available as a Supplementary material. The RoB table reflects a fixed set of biases linked to the study design, conduct and reporting (Table 1).

Meta-analyses

Out of the 1432 studies screened, 1182 were excluded. Of the 250 studies assessed for eligibility, 170 were excluded. Hence, 80 studies were systematically included, and 38 were included in the meta-analysis (Figure 1). The 38 studies were explored to obtain several indicators of period poverty, such as access to menstrual education tools, use of menstrual pads and MHM practice, as well as their related issues such as urinary tract infections, religious status, educational level of parents, geographical location including urban and rural areas, and the presence of a financial allowance.

To calculate the summary effect size across studies, meta-analysis of single proportions was applied to (a)-(c), and meta-analysis for comparison of two interventions was applied to (d)-(k)[17,18]. Since almost all outcomes of interest in the current analysis were dichotomous, meta-analysis with binary data was performed, and accordingly the pooled odds ratio (OR) with a 95% confidence interval (CI) was used to access the effect of two interventions[19,20]. Statistical heterogeneity was evaluated by the commonly used measure I^2 with P value, and further I^2 larger than 50% with a much small P value indicates strong heterogeneity. In comparison, I^2 less than 50% with a large P value indicates fairly weak heterogeneity[20]. In the presence of high heterogeneity, the random effects model was employed; instead, the fixed effects model was used if there was weak or no heterogeneity[21]. In some cases, subgroup analysis was carried out to identify the sources of heterogeneity, and sensitivity analysis was conducted for mainly assessing robustness of the synthesized results. Finally, publication bias was addressed seriously in the discussion part. All statistical outputs were reported using R[22,23].

A systematic analysis was used for studies that were excluded from the meta-analysis including those reporting lived experiences and the mental health impact associated with menstruation.

Table 1 Quality assessment of studies using a modified Newcastle-Ottowa scale

	Ref.	Selection				Comparability (**)	Outcome		Total (10*)
		Representativeness of the sample (*)	Sample size (*)	Non-respondents (*)	Ascertainment of exposure (**)		Assessment of outcome (**)	Statistical test (*)	
1	Garg *et al*[9], 2001	*	-	-	*	**	*	*	6*
2	Hennegan *et al* [44], 2016	*	-	-	*	**	*	*	6*
3	Sychareun *et al* [45], 2020	*	*	-	*	**	*	*	7*
4	Ha *et al*[46], 2020	*	*	-	*	**	*	*	7*
5	Fialkov *et al* [47], 2021	*	-	-	**	*	*	*	6*
6	Torondel *et al* [48], 2022	*	*	-	*	**	*	*	7*
7	Al-Jefout *et al* [49], 2015	-	-	-	*	**	*	*	5*
8	Birhane *et al* [50], 2019	*	*	-	*	**	*	*	7*
9	Alemayehu *et al*[51], 2020	*	*	-	*	**	*	*	7*
10	Kitesa *et al*[52], 2016	*	*	-	*	**	*	*	7*
11	Serbesa *et al* [53], 2018	*	*	*	*	**	*	*	8*
12	Shah *et al*[54], 2019	*	*	*	*	**	*	*	8*
13	Austrian *et al* [55], 2021	*	*	*	*	**	**	*	9*
14	Ocaktan *et al* [56], 2010	*	*	-	*	**	*	*	7*
15	Dhingra *et al* [57], 2009	*	*	-	*	**	**	*	7*
16	Boosey *et al* [58], 2014	*	-	-	*	*	**	*	6*
17	Amatya *et al* [59], 2018	*	*	-	*	*	**	*	7*
18	Caruso *et al* [60], 2020	*	*	*	*	**	*	*	8*
19	Sveinsdóttir *et al*[61], 2018	*	-	-	**	**	*	*	7*
20	Sveinsdóttir *et al*[62], 2017	*	*	-	**	**	*	*	8*
21	Mukherjee *et al* [63], 2020	*	*	-	*	**	*	*	7*
22	Hennegan *et al* [64], 2018	*	-	-	*	**	*	*	6*
23	Gharacheh *et al* [65], 2021	*	*	-	*	**	*	*	7*
24	Lee *et al*[66], 2017	*	-	-	*	**	*	*	6*
25	Hennegan *et al* [67], 2021	*	*	-	*	**	*	*	7*

26	Mao *et al*[68], 2021	*	*	-	*	**	*	*	7*
27	Roy *et al*[69], 2021	*	*	-	*	**	*	*	7*
28	Komada *et al* [70], 2019	-	-	-	**	**	*	*	6*
29	Crankshaw *et al*[71], 2020	*	*	-	*	**	*	*	7*
30	Afiaz *et al*[72], 2021	*	*	-	*	**	**	*	8*
31	Smith *et al*[73], 2020	*	-	-	*	**	*	*	6*
32	Toffol *et al*[74], 2014	*	*	*	**	**	**	*	10*
33	McMaster *et al* [75], 1997	*	-	-	*	*	*	*	5*
34	Janoowalla *et al*[26], 2020	*	-	-	*	**	**	*	7*
35	Ademas *et al* [76], 2020	*	*	-	*	**	*	*	7*
36	Bromberger *et al*[77], 2012	*	*	*	*	**	**	*	9*
37	Strine *et al*[78], 2005	*	*	-	*	**	*	*	7*
38	Mansoor *et al* [79], 2020	*	*	-	*	**	*	*	7*
39	Cardoso *et al* [80], 2019	*	-	-	*	**	*	*	6*
40	Choi *et al*[81], 2021	*	*	-	*	**	*	*	7*
41	Shimamoto *et al*[82], 2021	-	-	-	*	**	*	*	5*
42	Nohara *et al* [83], 2011	*	*	-	*	**	*	*	7*
43	Ahamed *et al* [84], 2015	*	*	-	-	**	*	*	6*
44	Mokhtari *et al* [85], 2020	*	*	-	*	**	*	*	7*
45	Warner *et al* [86], 2001	*	-	*	*	**	**	*	8*
46	Nishikitani *et al*[87], 2017	*	*	-	*	**	*	*	7*
47	Tanaka *et al* [88], 2013	*	*	-	*	**	*	*	7*
48	Zhou *et al*[89], 2010	*	-	-	*	**	**	*	7*
49	Chang *et al* [90], 2009	*	-	-	*	**	*	*	6*
50	Yirsaw *et al* [91], 2021	*	*	-	*	**	*	*	7*
51	Gokyildiz *et al* [92], 2013	*	-	-	*	**	*	*	6*
52	Jiang *et al*[93], 2019	*	*	-	*	**	*	*	7*
53	Parent *et al* [94], 2022	*	-	-	*	**	*	*	6*

54	Schoep *et al* [95], 2019	*	-	-	*	**	*	*	6*
55	Fernández-Martínez *et al* [96], 2020	*	*	-	*	**	**	*	8*
56	Abedian *et al* [97], 2011	-	*	-	**	**	*	*	7*
57	Beksinska *et al* [98], 2015	*	*	-	*	**	*	*	7*
58	Blake *et al*[99], 2018	*	*	-	*	**	*	*	7*
59	Djalalinia *et al* [100], 2012	*	*	-	*	**	*	*	7*
60	El-Mowafy *et al*[101], 2014	*	*	-	*	**	*	*	7*
61	Fakhri *et al* [102], 2012	*	-	-	*	**	*	*	6*
62	Montgomery *et al*[103], 2012	*	-	-	*	**	*	*	6*
63	Montgomery *et al*[44], 2016	*	*	*	*	**	*	*	8*
64	Hennegan *et al* [104], 2016	*	-	-	*	**	*	*	6*
65	Deshpande *et al*[105], 2018	*	*	-	*	**	*	*	7*
66	Cardoso *et al* [25], 2021	*	-	-	*	**	*	*	6*
67	Nyothach *et al* [106], 2015	*	-	-	*	**	**	*	7*
68	Kuhlmann *et al* [107], 2020	-	-	-	*	**	*	*	5*
69	Miiro *et al*[48], 2018	*	-	-	*	**	**	*	7*
70	Hensen *et al* [108], 2022	*	*	-	*	**	**	*	8*
71	Kuhlmann *et al* [109], 2019	*	-	-	*	**	**	*	7*
72	Shibeshi *et al* [110], 2021	*	*	-	*	**	**	*	8*
73	Kumbeni *et al* [111], 2020	*	*	-	*	**	**	*	8*
74	Adinma *et al* [112], 2014	*	*	-	*	*	*	*	6*
75	Eswi *et al*[113], 2012	*	-	-	*	**	*	*	6*
76	El-Hameed *et al*[114], 2011	*	-	-	*	**	*	*	6*
77	Abed *et al* [115], 2015	-	-	-	*	**	*	*	5*
78	Mohamed [116], 2012	*	-	-	*	**	*	*	6*
79	El-Mawgod *et al*[117], 2016	*	*	-	*	**	*	*	7*
80	Zegeye *et al* [118], 2009	*	*	-	*	**	*	*	7*

RESULTS

Studies with limited discussion about menstrual products, menstruation knowledge and MHM practice were excluded, resulting in a final dataset of 80 studies (Table 2). Of the 80 studies, 38 studies were selected for meta-analysis. Of 38 the studies, 34 were from LMICs and 4 from developed countries (non-LMICs).

Meta-analysis

Prevalence of using disposable sanitary pads: We explored the link of disposable sanitary pads as an indicator of period poverty. A meta-analysis of single proportions was applied to 32 studies with a sample of 212459 women, that indicated a prevalence of 45% (95%CI: 0.35-0.58). Figure 2A shows the forest plot for 32 studies. The value of 100% of I^2 (P value = 0) indicates a significant statistical heterogeneity.

To explore the sources of heterogeneity, a subgroup analysis was conducted using the geographical locations of the studies and demonstrated in a forest plot (Figure 2B). A statistically significant difference (P value < 0.01) was identified between LMICs and non-LMICs using sanitary pads where the pooled prevalence was 43% (95%CI: 0.33-0.56) and 76% (95%CI: 0.60-0.96), respectively. Figure 2B also showed that heterogeneity remained unchanged in LMICs (I^2 = 100%, P value = 0) and non-LMICs (I^2 = 98%, P value < 0.01), indicating that the identified heterogeneity was not geographical location influenced.

Prevalence of having knowledge/awareness on menstruation before menarche

Several surveys were meta-analysed to better understand adolescent girls' menstrual education and pre-menarche awareness. Common survey questions notably included, "*were you familiar with menstruation before you got your first period* [(Study 3)]", "*Information availability before reaching menarche* [(Study 4)]", "*heard about menstruation before menarche* [(Study 9)]", *and* "*prior knowledge about menstruation before menarche* [(Study 11)]" and "*awareness about menarche before its onset* [(Study 79)]". This information was used to conduct a meta-analysis of 11 studies with a sample size of 4944 young women. A high heterogeneity was detected with I^2 = 98% and P value < 0.01) (Figure 3A). The random effects model reported the overall prevalence to be 68% (95%CI: 0.56-0.82).

Prevalence of good MHM practice

Good MHM practice during menstruation is essential to prevent various other health issues such as urinary tract infections (UTIs)[24]. MHM practice lacks a standardised definition although a consensus is that it is expected that throughout the bleeding phase, people require clean absorbents, adequate frequency of absorbent change, washing the body with soap and water, adequate disposal, and privacy for managing menstruation. All involved studies predesigned some practice-related questions in research studies to determine the level of MHM practice, defined simply as good or bad. Figure 3B demonstrates a forest plot of the prevalence of good MHM practice across ten studies with a total of 5432 women. The random effects model was used due to strong heterogeneity indicated by I^2 = 99% and P value < 0.01. The overall prevalence of good MHM practice was 39% (95%CI: 0.25-0.61).

Rural-urban difference in MHM practice level (good/bad)

A total of 5 studies with a sample size of 2705 women reported differences of MHM practice levels within rural and urban settings. The pooled OR of good MHM practice between rural and urban areas was 0.30 (95%CI: 0.13-0.69), indicating that women living in rural area were 0.70 times less likely to have good MHM practices in comparison to those living in an urban area. A high heterogeneity of 91% of I^2 (P value < 0.01) was identified (Figure 3C), possibly due to the differences in covariates, assessment tools and other factors.

Difference of MHM practice level (good/bad) between two age groups

Based on available data from 3 studies with a total of 1637 adolescent girls, special attention is paid to two groups aged at less than or equal to 15 years and 16 to 19 years. The random effects model yielded a I^2 of 82% with a pooled OR of good MHM practices between two age groups of 0.77 (95%CI: 0.44-1.34), which is not statistically significant (Figure 4A).

Difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated father/mother

Parents' educational background showed an impact on MHM practices among adolescent girls. In some studies father's or mother's educational status was divided into illiterate and literate, while in other studies categorised as uneducated, primary education, secondary or high school education, and college or above. To simplify the data, father's or mother's educational status was defined as uneducated, where either parent lacked primary education whilst, educated was anyone that had any above secondary. Figure 4B showed a forest plot for difference of MHM practice level (good/bad) among

Table 2 Characteristics of the studies included in the systematic review

Study ID	Ref.	Year	Study type	Sample size	Country	Mean age	Meta-analysis inclusion Y/N
1	Garg *et al*[9]	2001	Epidemiological and sociological study	380	India		Y
2	Hennegan *et al*[44]	2016	Cross-sectional study	201	Uganda	14.2	Y
3	Sychareun *et al*[45]	2020	Cross-sectional study	343	LAO	15.6	Y
4	Ha *et al*[46]	2020	Cross-sectional study design with systematic random sampling	589	Bangladesh	15.5	Y
5	Fialkov *et al*[47]	2021	Pre- and post-test design that compared six cohort groups	311	Kenya		N
6	Torondel *et al*[48]	2022	Nested within a pair-matched cohort study	1045	India	27	Y
7	Al-Jefout *et al*[49]	2015	Cross-sectional study	272	Jordanian	22	Y
8	Birhane *et al*[50]	2019	Cross-sectional study	466	Ethiopia	15.5	Y
9	Alemayehu *et al*[51]	2020	Cross-sectional study	301	Ethiopia	15.87	Y
10	Kitesa *et al*[52]	2016	Cross-sectional study	430	Ethiopia	16	Y
11	Serbesa *et al*[53]	2018	Cross-sectional study	310	Ethiopia	15.72	Y
12	Shah *et al*[54]	2019	Cross-sectional study	331	Gambia	15.3	Y
13	Austrian *et al*[55]	2021	Cluster RCT	3489	Kenya	14.8	N
14	Ocaktan *et al*[56]	2010	Cross-sectional study	400	Turkey	32.19	Y
15	Dhingra *et al*[57]	2009	Cross-sectional study	200	India	13.97	Y
16	Boosey *et al*[58]	2014	Cross-sectional study	140	Uganda	14.45	N
17	Amatya *et al*[59]	2018	Cross-sectional mixed-methods study	104	Nepal	15	N
18	Caruso *et al*[60]	2020	Cross-sectional study	878	India	26.8	Y
19	Sveinsdóttir *et al*[61]	2018	Cross-sectional study	319	Iceland	30	Y
20	Sveinsdóttir *et al*[62]	2017	Cross-sectional study	319	Iceland	30	N
21	Mukherjee *et al*[63]	2020	Cross-sectional study	1342	Nepal		N
22	Hennegan *et al*[64]	2018	Cross-sectional study	2934	Nigeria	26.66	Y
23	Gharacheh *et al*[65]	2021	Cross-sectional study	515	Iran	29.61	N
24	Lee *et al*[66]	2017	Prospective observational cohort study	1495	USA	46.8	N
25	Hennegan *et al*[67]	2021	Secondary data analysis	11806	Burkina Faso, Niger, Nigeria		N
26	Mao *et al*[68]	2021	Cross-sectional study	156055	China	26.32	N
27	Roy *et al*[69]	2021	Secondary data analysis	94034	India		Y
28	Komada *et al*[70]	2019	Cross-sectional study	150	Japan	18.8	N
29	Crankshaw *et al*[71]	2020	Mixed-method study	472	South Africa	17.5	Y
30	Afiaz *et al*[72]	2021	Cross-sectional study	54242	Bangladesh	29	Y
31	Smith *et al*[73]	2020	Secondary data analysis	38257	Uganda, Kenya, Ethiopia *etc.*		Y
32	Toffol *et al*[74]	2014	Cross-sectional study	4391	Finland	56.2	N
33	McMaster *et al*[75]	1997	exploratory phase of the study	50	Zimbabwe		N
34	Janoowalla *et al*[26]	2020	Prospective cohort study	240	Rwanda	19.1	Y
35	Ademas *et al*[76]	2020	Cross-sectional study	602	Ethiopia		Y
36	Bromberger *et al*[77]	2012	Multisite study	934	USA		N
37	Strine *et al*[78]	2005	Cross-sectional study	11648	USA		N

38	Mansoor *et al*[79]	2020	Cross-sectional study	1777	Pakistan	20.38	Y
39	Cardoso *et al*[80]	2019	Baseline data from a larger RCT	1800	Nepal	34.5	N
40	Choi *et al*[81]	2021	Cross-sectional study	8658	Korea	35.1	Y
41	Shimamoto *et al*[82]	2021	Self-reporting questionnaire survey	6048	Japan		N
42	Nohara *et al*[83]	2011	Cross-sectional study	2166	Japan		N
43	Ahamed *et al*[84]	2015	Cross-sectional study	344	India	28	Y
44	Mokhtari *et al*[85]	2020	Cross-sectional study	164	Iran	27.78	N
45	Warner *et al*[86]	2001	Cross-sectional study	952	Scotland		N
46	Nishikitani *et al*[87]	2017	Cross-sectional study	505	Japan		N
47	Tanaka *et al*[88]	2013	Online survey	19254	Japan	33.6	N
48	Zhou *et al*[89]	2010	Cross-sectional study	1642	China	37	N
49	Chang *et al*[90]	2009	Cross-sectional survey	1095	Taiwan		N
50	Yirsaw *et al*[91]	2021	Cross-sectional study	713	Ethiopia	21.13	N
51	Gokyildiz *et al*[92]	2013	Case-control study	295	Turkey		N
52	Jiang *et al*[93]	2019	Cross-sectional study	12881	China		N
53	Parent *et al*[94]	2022	Cross-sectional study	1153	France	31.7	Y
54	Schoep *et al*[95]	2019	Cross-sectional study	42879	Netherlands	28.7	N
55	Fernández-Martínez *et al*[96]	2020	Cross-sectional study	7208	Spain	19.51	N
56	Abedian *et al*[97]	2011	RCT	165	Iran		N
57	Beksinska *et al*[98]	2015	Randomized two-period Cross-over trial	124	South Africa	29	N
58	Blake *et al*[99]	2018	Mixed-methods evaluation	636	Ethiopia	13.45	Y
59	Djalalinia *et al*[100]	2012	Community-based participatory research	1823	Iran		N
60	El-Mowafy *et al*[101]	2014	Quasi-experimental study	234	Egypt		N
61	Fakhri *et al*[102]	2012	Quasi-experimental study	698	Iran	15.7	N
62	Montgomery *et al*[103]	2012	Non-randomized trial	120	Ghana	15.7	N
63	Montgomery *et al*[44]	2016	Cluster quasi-randomised controlled trial	1124	Uganda		N
64	Hennegan *et al*[104]	2016	Secondary data analysis	205	Uganda	14.2	Y
65	Deshpande *et al*[105]	2018	Cross-sectional study	100	India		Y
66	Cardoso *et al*[25]	2021	Online survey	471	United States	20.6	N
67	Nyothach *et al*[106]	2015	Retrospective study		Kenya		N
68	Kuhlmann *et al*[107]	2020	Cross-sectional study	58	USA	15.21	N
69	Miiro *et al*[48]	2018	Cross-sectional study	352	Uganda	15.6	Y
70	Hensen *et al*[108]	2022	Mixed-methods analysis	7546	Zambia		N
71	Kuhlmann *et al*[109]	2019	Cross-sectional study	183	USA	35.8	Y
72	Shibeshi *et al*[110]	2021	Cross-sectional study	1078	Ethiopia	17.35	Y
73	Kumbeni *et al*[111]	2020	Cross-sectional study	705	Ghana		Y
74	Adinma *et al*[112]	2014	Cross-sectional study	550	Nigeria		Y
75	Eswi *et al*[113]	2012	Cross-sectional study	200	Egypt	15.45	N
76	El-Hameed *et al*[114]	2011	Cross-sectional study	160	Egypt	17.2	N
77	Abed *et al*[115]	2015	Cross-sectional study	100	Egypt	14.25	Y
78	Mohamed[116]	2012	Cross-sectional study	885	Egypt	16	Y
79	El-Mawgod *et al*[117]	2016	Cross-sectional study	344	Saudi Arabia	16.2	Y

80	Zegeye *et al*[118]	2009	Cross-sectional study	612	Ethiopia	16.9	Y

RCT: Randomized control trial.

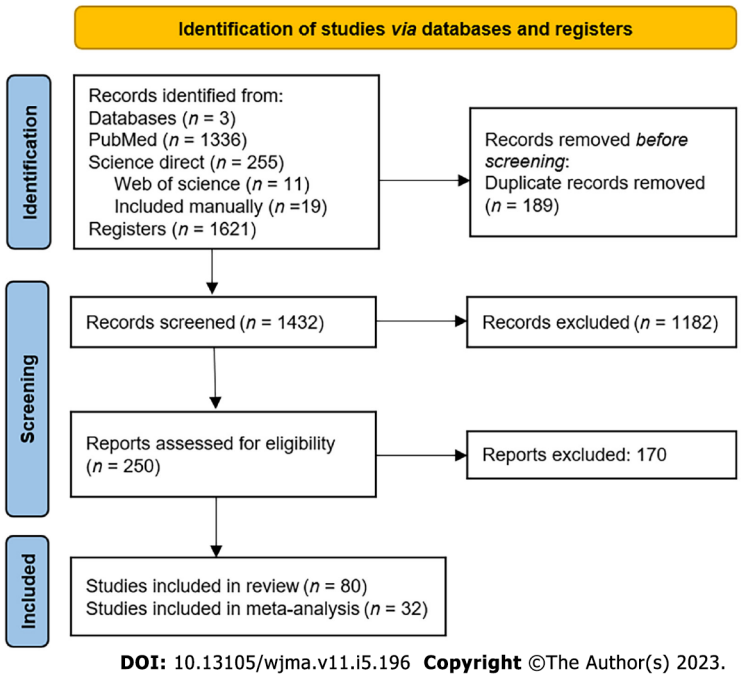

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Figure 1 PRISMA 2020 flow diagram showing study selection.

adolescent girls with uneducated and educated fathers, and the pooled OR was 0.55 (95%CI: 0.36-0.83). This provides significant evidence of the lower prevalence of good MHM practice among adolescent girls with uneducated fathers. Similarly, Figure 4C demonstrated that adolescent girls with uneducated mothers were 0.48 times less likely to have good MHM practices than those with educated mothers.

Difference of MHM practice level (good/bad) among adolescent girls without and with pocket money

To some extent, the possibility of getting a financial allowance, also referred to as a pocket money indicated the socioeconomic status of the family which would indicate their affordability to disposable sanitary pads. Thus, two studies that reported on the use of disposable sanitary pads with a total of 731 adolescent girls were analysed. The forest plot (Figure 5A) demonstrates the difference of MHM practice levels among adolescent girls with and without pocket money. The I^2 = 0 (P value = 0.41) means that there was very weak statistical heterogeneity. The pooled OR was 0.45 (95%CI: 0.32-0.64), indicating that adolescent girls who have no pocket money were 0.55 times less likely to have good MHM practices than those who have pocket money.

Difference of MHM practice level (good/bad) among adolescent girls of having no and having discussion about menstruation with parents

Discussion points between a parent and a young girl were explored where the paradigm indicated open discussions around menstruation issues. Responses to these questions reflects the parent-child relationship. The forest plot indicates (Figure 5B) a difference between MHM practices among adolescent girls who did not have a discussion with their parents *vs* those who had a discussion was 0.46 (95%CI: 0.28-0.75).

Difference of MHM practice level (good/bad) among female followers of different religions

Literature indicated the presence of a correlation between religious views and MHM practices, as demonstrated within 3 studies conducted in Ethiopia, with a combined sample size of 1128 adolescent girls. Thus, a pairwise meta-analysis was employed to compare the MHM practice levels among women of Orthodox, Protestant and Islamic beliefs. Figures 5C-E demonstrated forest plots comparing Orthodox *vs* Protestant, Protestant *vs* Islam, and Orthodox *vs* Islam, respectively. The corresponding pooled ORs were 1.81 (95%CI: 0.47-6.99), 0.66 (95%CI: 0.23-1.92), and 0.66 (95%CI: 0.87-1.72). Based on the CIs, there is no statistically significant difference in MHM practice levels among women from Orthodox, Protestant and Islamic beliefs.

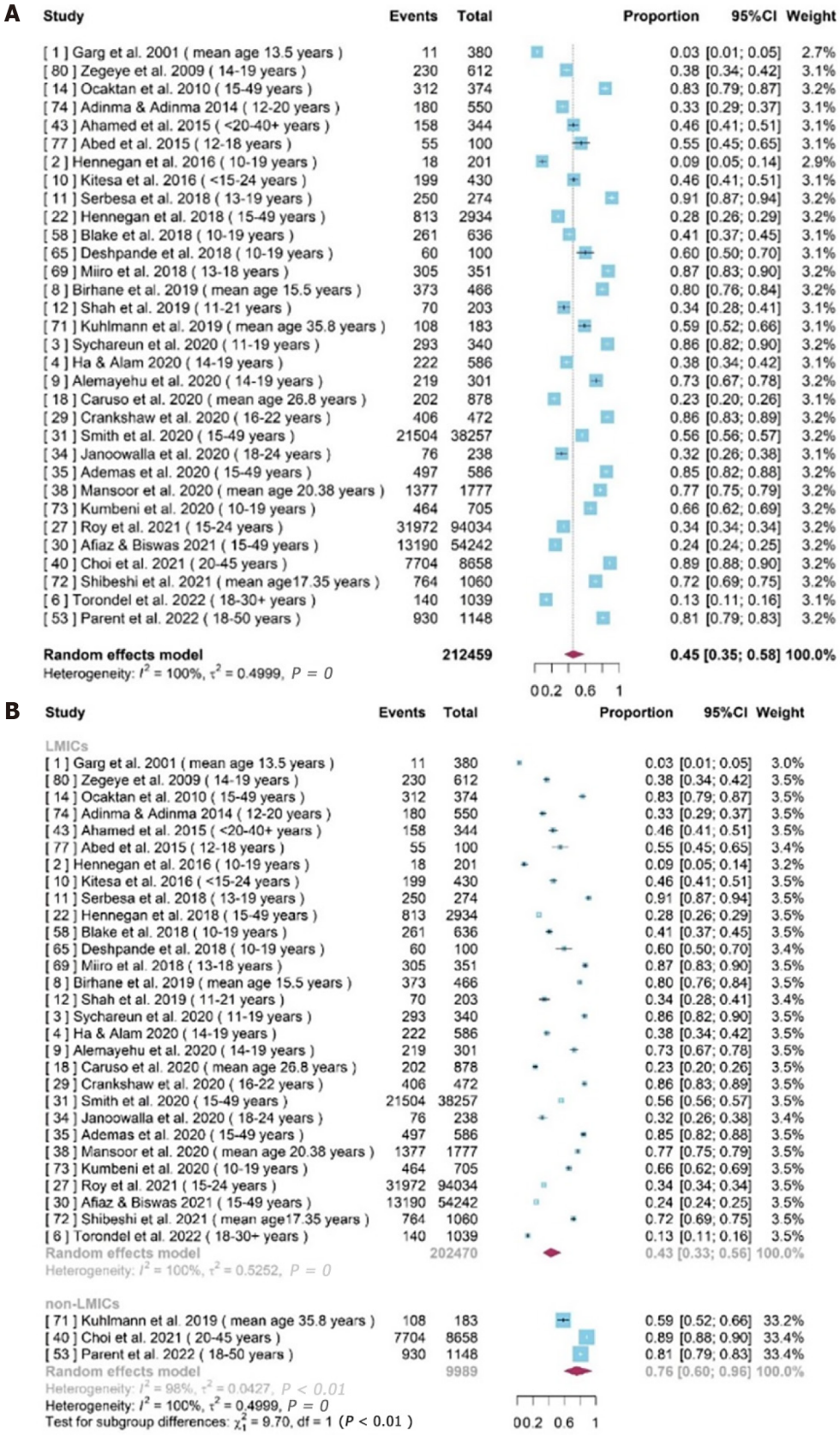

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Figure 2 Forest plots showing the prevalence of using disposable sanitary pads. A: Forest plot shows the prevalence of using disposable sanitary pads across 32 studies; B: Forest plot shows the prevalence of using disposable sanitary pads in low-middle-income countries (LMICs) and non-LMICs, respectively.

School absenteeism due to dysmenorrhea

Dysmenorrhea is another key feature of menstruation indicating an important reason for school absenteeism among adolescent girls. Two studies reported mild and moderate menstrual pain among

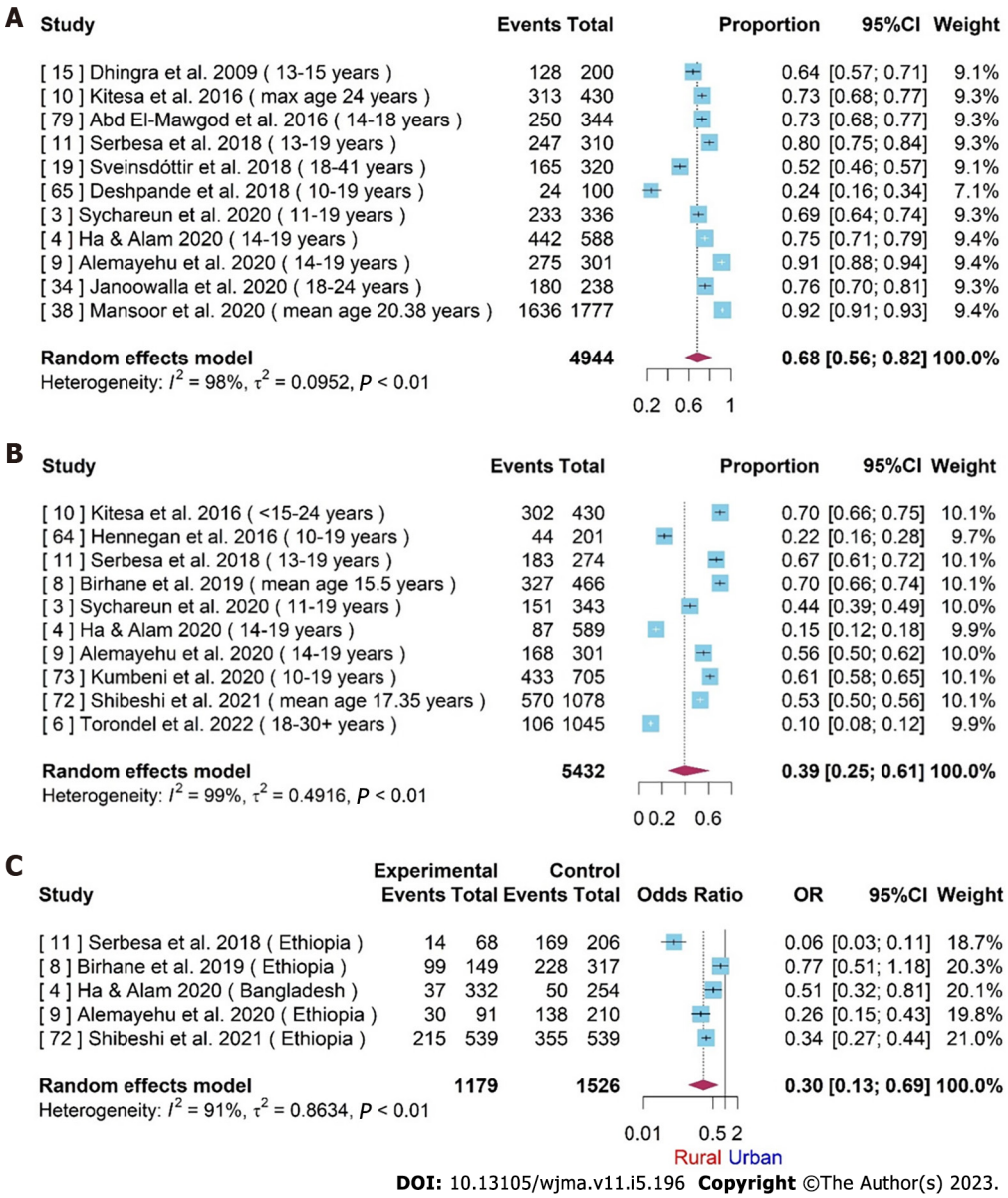

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Figure 3 Forest plots exploring menstrual education and hygiene management practices. A: Forest plot for the prevalence of having knowledge/awareness on menstruation before menarche across 11 studies; B: Forest plot for the prevalence of good menstrual hygiene management (MHM) practice across ten studies; C: Forest plot for the rural-urban difference of MHM practice level (good/bad).

their participants. We combined mild to moderate pain and defined as not severe menstrual pain for the analyses. This was combined with four studies. The total sample size was 1582 (Supplementary Figure 1). The pooled OR of school absenteeism between adolescent girls with severe and not severe menstrual pain was 4.26 (95%CI: 2.27-7.99), indicating those with severe menstrual pain were 4.26 times more likely to miss school than those without menstrual pain.

Participants in study 7 were aged between 19 to 25 years of age, whilst others were less than 19 years old. There appears to be high heterogeneity (I^2 =83%, P value < 0.01) in the sample. Thus, it was excluded, and the heterogeneity was re-evaluated where the pooled OR is 2.98 (95%CI: 2.29-3.87). Supplementary Figure 2 indicates I^2 to be 0 with a P value of < 0.01. The heterogeneity, therefore, was specific to Study 7. The participant group of 19 to 25 years old, or, more precisely, age group may be one of the main sources of heterogeneity.

To explore the association between school absenteeism and whether or not using disposable sanitary pads have any impact, a meta-analysis was applied to 3 studies with a total sample size of 1280 adolescent girls. Supplementary Figure 3 indicated significant evidence of statistical heterogeneity (I^2 =83%, P value < 0.01). The pooled OR of 2.08 (95%CI: 1.10-3.91) indicates that adolescent schoolgirls who did not use disposable sanitary pads were 1.08 times more likely to be absent from school than those using sanitary pads.

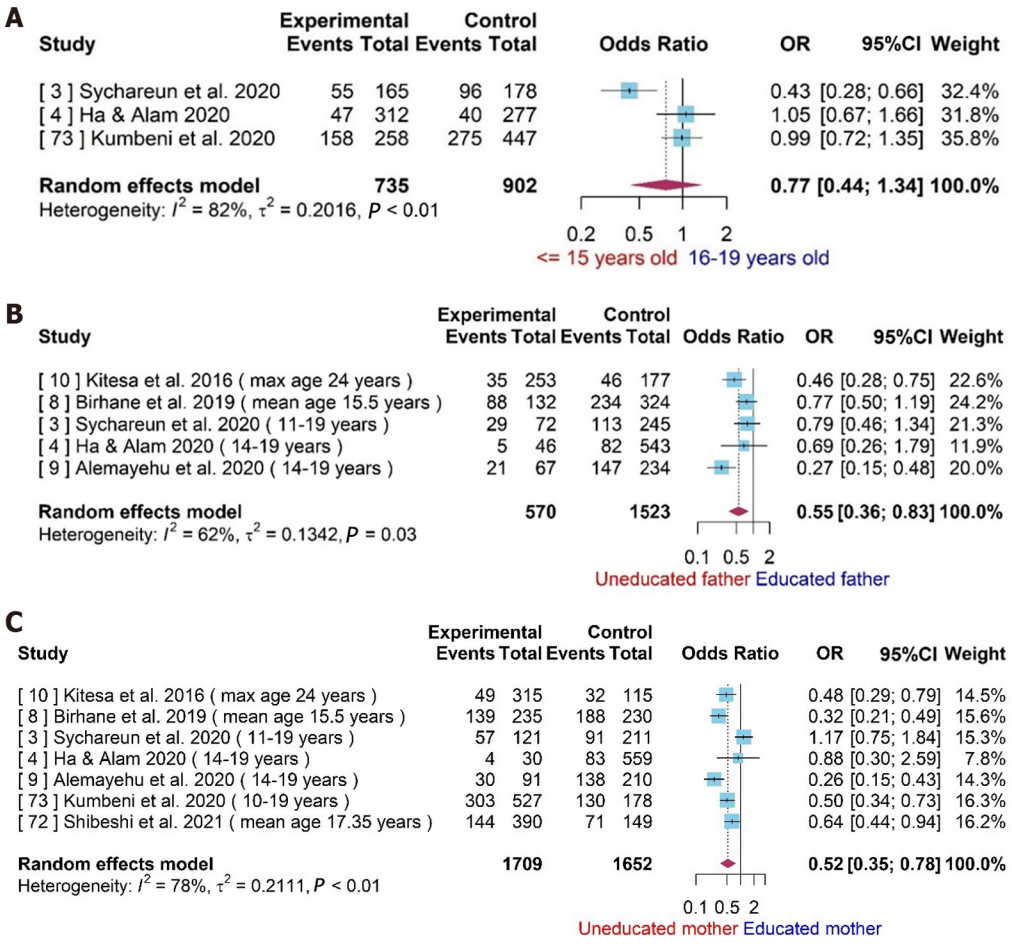

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Figure 4 Forest plot for the difference of menstrual hygiene management. A: Forest plot for the difference of menstrual hygiene management (MHM) practice level (good/bad) between two age groups; B: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated father; C: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated mother. Available in Supplemental material.

Association between dysmenorrhea and regularity of menstrual cycle

As presented in the former part, there is a statistically significant association between the severity of dysmenorrhea and school absenteeism. To further identify the possible causes of dysmenorrhea, two studies were meta-analysed with a total sample size of 1285 with confirmed experience of regular or irregular menstrual cycles. Supplementary Figure 4 indicated a lack of statistical heterogeneity (I^2 = 0, P value = 0.89) and thus the fixed effects model was used. The pooled OR was 2.31 (95%CI: 1.76-3.02), indicating the prevalence of dysmenorrhea among adolescent girls with irregular menstrual cycles is 2.31 times as high as those with a regular cycle.

Another key area of period poverty is the associated mental health impact, which can differ between those who suffer from mental illness and those who do not. Whilst there was insufficient data for a meta-analysis, there was evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression[3]. In addition, socioeconomic status can impact the prevalence of stress, anxiety and depression experienced by different populations.

DISCUSSION

Period poverty is a global health issue, more prominent in low-middle-income countries. There are varying risk factors dependent on geographical location and this reflects in the differing sociological and clinical features, as explored in this paper.

This study demonstrates correlations between severity of dysmenorrhea and school absenteeism among girls between 14-19 years of age with and without regular menstruation. Another key area of period poverty is the associated mental health impact, which can differ between those who suffer from mental illness and those who do not. Whilst there was insufficient data for a meta-analysis, there was evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression[3]. In

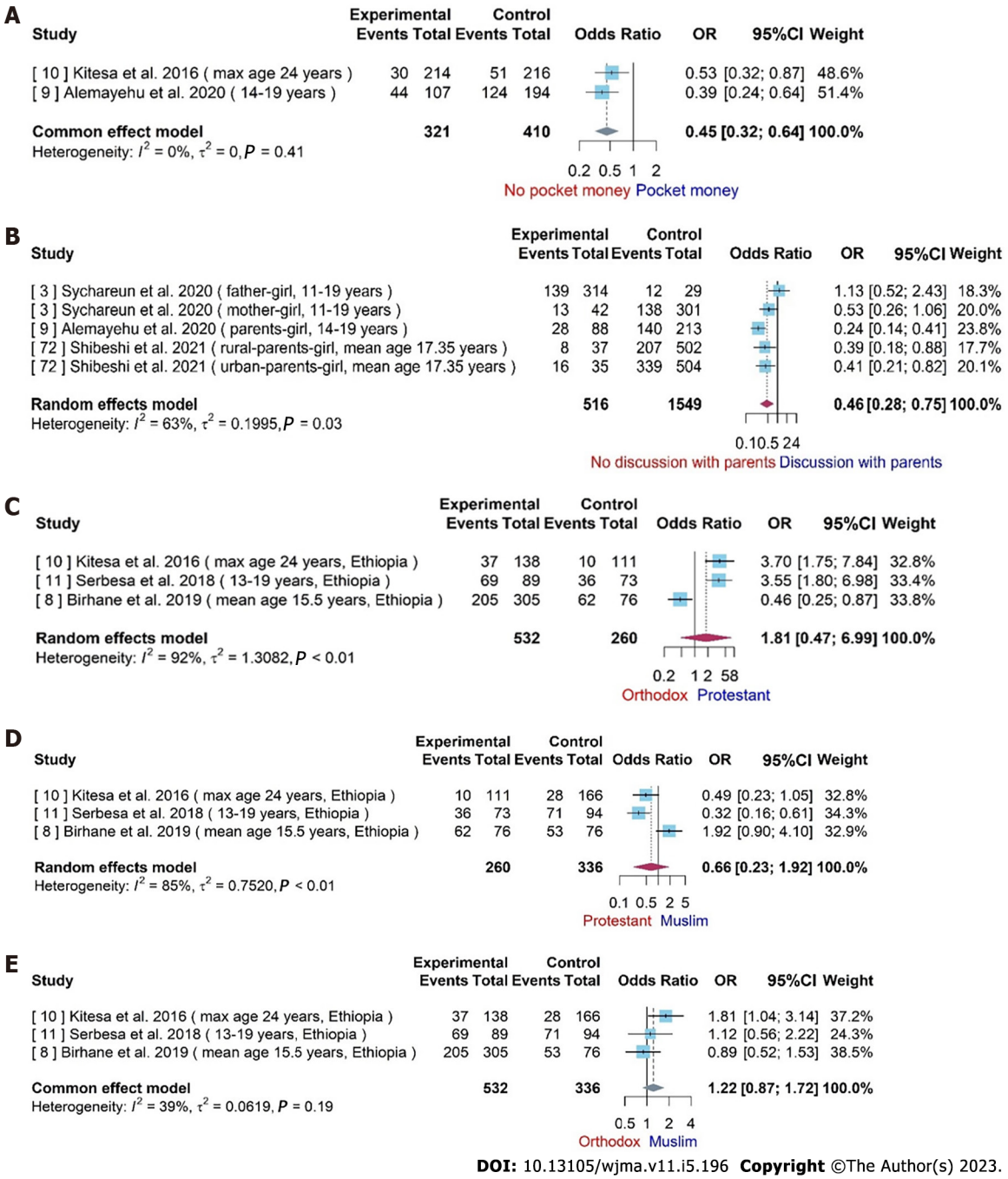

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Figure 5 Forest plots showing the differences in menstrual hygiene management across various factors. A: Forest plot for difference of menstrual hygiene management (MHM) practice level (good/bad) among adolescent girls without and with pocket money; B: Forest plot for difference of MHM practice level (good/bad) among adolescent girls of having no and having discussion about menstruation with parents. Available in Supplementary material; C: Forest plot for the difference of MHM practice level (good/bad) among adolescent girls with orthodox and protestant; D: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with protestant and Muslim. Available in Supplementary material; E: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with orthodox and Muslim. Available in Supplemental material.

addition, socioeconomic status can impact the prevalence of stress, anxiety and depression experienced by different populations. This could be exacerbated among those acquiring UTIs[24,25].

UTIs have been reported by Das and colleagues to be a common problem among those without pad use. Janoowalla and colleagues demonstrated no change in the prevalence of urinary tract infections between those using and not-using pads in the Kibogora region in Rwanda[26]. Das and colleagues indicated a higher risk of urogenital infections among women using reusable absorbent pads within the Odisha region in India[24]. Bacterial vaginosis (BV) is another issue impacting women with poorer menstrual practices. Das and colleagues reported that menstrual hygiene practices were associated with a symptomatic BV or UTI[24].

MHM practices were another key endpoint in this study which demonstrated to differ among women of Islamic, Protestant and Orthodox religious beliefs in Ethiopia. Representativeness of these findings to other ethnicities requires further research.

Homelessness is another facet that is vital to explore to identify the impact of period poverty. For example, in the United States, 553000 experience homelessness in a night compared to 32000 in the UK [27,28]. It is reported that 25% of homeless service users in the UK are single women and 28% in the United States. These could be underestimated as hidden homeless is another facet where people do not access services but stay in temporary accommodation settings, including friends and relatives. Many official reports lack information regarding experiences of menstruation among the homeless. Padgett and colleagues demonstrate that this multifaceted concern or as a feature of reproductive health is now being explored, although comprehensive evidence is required[29]. Phenomenology demonstrates homeless menstrual lived experiences, which is an important aspect of understanding period poverty by exploring the interrelatedness between the consciousness, body, and the flesh of a woman[30]. Homeless people are a marginalised community; thus, menstruation could emphasize their vulnerability. Historically, social sciences research has focused on commodification, medicalisation and stigma associated with menstruation. Anglo-American publications have also failed to discuss intersectionality and focus primarily on white, middle-class, cisgender women or in a developmental context where women are in poverty[31-34]. The sociopsychological and socioeconomic aspects associated with women living in poverty *vs* those not can sometimes be polarised from a period poverty perspective. Health outcomes among disenfranchised groups of women due to lack of or minimal access to menstrual products can have significant effects where clinical interventions would be required to manage the symptoms, including systemic issues. Another facet is that the supply of menstrual products to homeless services such as shelters, and day centers should be more effective. This should include the availability of staff that could be approached to talk about menstruation or any associated problems[35].

Another facet of period poverty is the composition of menstrual pads which is not the same in terms of their textile and polymer composition. Varying viscosity of menstrual flow could also impact the suitability of the differing pads, given that these are worn for different periods. Another aspect to consider as an external factor for menstrual products would be to produce material that can be disposed of in a biodegradable manner. Velasco Perez *et al*[36] and Hait *et al*[37] indicated that sanitary pads have a higher negative environmental footprint due to eutrophication and climate change. Limited evidence is available about menstrual underwear and menstrual cups associated with environmental impact. This further complicates menstrual hygiene issues, equitable availability, and acceptability, especially among LMIC populations.

Whilst this study has indicated the majority of the evidence on period poverty is within LMIC and MICs, there appears to be a lack of studies available within developed countries despite the definition of "period poverty", including the inability to afford menstrual products. Given the risk of living costs, many media publications and social media posts indicate that period poverty is a concern within developed countries. For example, Cardoso and colleagues indicated that women in the United States reported 14.2% experienced period poverty in 2020, with an additional 10% experiencing it monthly [25]. Whilst knowledge, attitude and practices associated with menstruation among poorer and vulnerable communities are likely to be lower regardless of the geographical location. As a result, the psychosocial dynamics may have a negative impact. The findings of these studies may have been exacerbated due to the coronavirus disease 2019 pandemic with substantial increases in unemployment and cost of living. Basic goods and service cost increase includes those of menstrual products. Thus, the pandemic has had gendered implications impacting the vulnerability of women. Caretaker roles of women have significantly grown as a result of lockdowns, and such requirements have been inadequately explored[38].

In addition, limited evidence is demonstrated around mental health implications due to the period of poverty. Cardoso and colleagues demonstrated an association between period poverty and depression among women within the United States who were previously depression naïve[25]. This is similar to the findings reported between food insecurity associated with depression in adults and anxiety, depression and suicidal ideation among adolescents[25,39-41]. Similarly, depression and anxiety were reported among people experiencing housing insecurities compared to those with stable houses[42,43].

The data identified is limited to either smaller sample sizes and/or geographical locations that could limit the generalisability of the findings to introduce impactful and meaningful changes to policy and clinical practice

CONCLUSION

Period poverty is an international issue, varying based on geographical locations, social implications, and economical factors. Better understandings of this problem will highlight current gaps in knowledge, policies, and practice. Undoubtedly, many issues affect the experiences of managing menstruation and access to menstrual products. To address the current gaps and ensure period poverty can be minimised,

comprehensive research would be required. Policymakers and independent authorities should consider improved healthcare legislation, equitable access to menstrual products, information, and healthcare providers.

ARTICLE HIGHLIGHTS

Research background

Period poverty is an international health concern, impacting thousands of women and girls, especially those in underdeveloped regions or those struck with conflict and disaster. Due to issues with menstrual education and access to menstrual hygiene products, many females compromise their daily routines (*e.g.*, not attending school or going to work). There is a lack of a comprehensive evidence synthesis in relation to period poverty hence the PLatform for the Analysis, Translation, and Organization of large-scale data project (PLATO) was developed with this systematic review and meta-analysis as the first stage.

Research motivation

Period poverty influences various health and social factors to varying degrees, dependent on the geographic location and other risk factors – this effect is amplified in low- and middle- income countries. To better understand the impact of period poverty, research exploring and highlighting current gaps in knowledge in key. Following this, improved legislation and policies for women and girls will enable better access to menstrual hygiene products and accurate menstrual education.

Research objectives

Due to the sheer lack in period poverty research, especially in low- and middle- income countries, this systematic review and meta-analysis aimed to explore current understandings and highlight any areas for future research. The primary outcomes included factors associated to menstrual hygiene products, such as accessibility and affordability, but also menstrual hygiene management and education. Variations in relation to age, location, religion, and parental and individual education was also explored.

Research methods

A systematic review and meta-analysis were conducted to explore period poverty with all related observational and randomised clinical trials included in this report. Studies published in English, between the 30th of April 1980 and the 30th of April 2022 were included. An extraction template was specifically developed in line with the objectives of the study to ensure that research aims were addressed comprehensively.

Research results

Overall, 80 studies were included in the systematic review and 38 in the meta-analysis and various statistically significant findings were uncovered. Sanitary pads were used a lot more in non-Low- and Middle-income countries, with women in rural areas being 0.7 times less likely to have good menstrual hygiene and management practices. School girls who reported irregular menstrual cycles experienced severe menstrual pain and those with severe pain were almost 5 times more like to miss out on school.

Research conclusions

This study demonstrates correlations between severity of dysmenorrhea and school absenteeism among girls with and without regular menstruation. It also explored how period poverty is the associated mental health impact, with evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression. This study has indicated that the majority of the evidence on period poverty is within low-middle-income countries and middle-low-income countries. It is possible that the findings of this study could have been exacerbated due to the coronavirus disease 2019 pandemic.

Research perspectives

Period poverty is an under-researched area despite is being a global social and health issue. This research has outlined current understandings of period poverty but also where the gaps lie. Following on from this, policies and practices can be introduced and developed to ensure women and girls are supported across the globe in relation to menstrual products, information, and healthcare providers.

FOOTNOTES

Author contributions: Delanerolle G conceptualised the PLATO project as part of the ELEMI program which includes

three work-packages; Delanerolle G, Cavalini H, Shi JQ and Phiri P developed the systematic review protocol and embedded this within the PLATO project's work package 1; Delanerolle G and Shi JQ designed the statistical analysis plan; Yang XJ, Delanerolle G, and Shi JQ completed the analysis; Sajid S and Phiri P completed the risk of bias and Newcastle-Ottawa Scale; All authors critically appraised and commented on previous versions of the manuscript; All authors read and approved the final manuscript.

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META-ANALYSIS

Vitamin D deficiency among outpatients and hospitalized patients with diabetic foot ulcers: A systematic review and meta-analysis

Hyder Osman Mirghani

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Abstract

BACKGROUND

The definition of diabetic foot syndrome (DFS) varies depending on the location and resources. Few classifications are available according to the indication. DF ulcers and vitamin D deficiency are common diseases among patients with diabetes. Previous literature has shown an association between DF ulcer (DFU) and vitamin D deficiency. However, the available meta-0analysis was limited by substantial bias.

AIM

To investigate the association between DFUs and vitamin D levels.

METHODS

We searched PubMed, MEDLINE, and Cochrane Library, EBSCO, and Google Scholar for studies comparing vitamin D levels and DF. The keywords DFU, DFS, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D deficiency were used. The search engine was set for articles published during the period from inception to October 2022. A predetermined table was used to collect the study information.

RESULTS

Vitamin D level was lower among patients with DFU compared to their counterparts [odds ratio (OR): -5.77; 95% confidence interval (CI): -7.87 to -3.66; χ^2 was 84.62, mean difference, 9; I^2 for heterogeneity, 89%; $P < 0.001$ and P for overall effect < 0.001]. The results remained robust for hospitalized patients (OR: -6.32 95%CI: -11.66 to -0.97; χ^2 was 19.39; mean difference, 2; I^2 for heterogeneity, 90%; $P = 0.02$).

CONCLUSION

Vitamin D was lower among outpatients and hospitalized patients with DFUs. Further larger randomized controlled trials are needed.

Key Words: Vitamin D deficiency; Diabetic foot ulcer; Outpatient; Hospitalized patients; Diabetic foot syndrome

Core Tip: This is the first study to assess the relationship between diabetic foot ulcer and vitamin D deficiency, avoiding the bias of the two published meta-analyses.

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INTRODUCTION

Diabetes mellitus (DM) is an epidemic globally. DM is a morbid disease with many complications including microvascular and microvascular disease. Diabetic foot syndrome (DFS) is defined as peripheral neuropathy, limited joint mobility, peripheral arterial disease, immunopathy, ulceration, and Charcot arthropathy[1]. The combination of FS elements provides an environment for unrecognized injury, foot infection, and possible amputation[2]. DFS is characterized by peripheral arterial disease, but the symptoms are masked by the accompanying peripheral neuropathy. The pathology varies from pre-ulcerative callouses, ulceration, and necrosis developing at the site of high pressure (deformities of the toes and feet). Patient education and feet inspection are mandatory because repetitive trauma might pass unnoticed due to the loss of pain sensation[3]. DFS is a common complication of diabetes with a great economic burden; DTS substantially affects the patient's quality of life and leads to premature death. In addition, patients with DFS are prone to psychiatric disease[4].

There are nearly 40 classifications for DFS, with wide variation depending on the availability of resources and geographical variations. It is recommended to use classification in light of specific indications. Few classifications have been validated for use; the site, ischemia, neuropathy, bacterial infection, area, and depth (SINBAD) is six questions with yes or no answers with a maximum of six points. SINBAD score is better for communication between clinicians[5]. While, the Infectious Diseases Society of America/International Working Group on Diabetic Foot, and wound depth, ischemia, and foot infection scoring are better for infection and perfusion respectively[6,7]. The spectrum of DFS varies from minor erythema to tissue necrosis and lower limb deformity and amputation [8]. The mortality of DFS is comparable to breast and lung cancer. Five-year mortality for minor and major amputations, Charcot, and DF ulcer (DFU) were 56.6%, 46.2%, 30.5%, 29%, respectively. The pooled mortality from breast, all cancer, and lung cancer were 9%, 30%, and 80% respectively[9].

The lifetime of developing FUs among patients with diabetes varies between 19% and 34% with nearly two-thirds of recurrence in 5 years, and 1 in 5 patients with moderate to severe FUs resulting in amputation. The majority of lower extremities amputations are preceded by FUs and three amputations occur every minute due to diabetes. Patients with FUs had a 2.5 times mortality rate compared to their counterparts[10,11].

25-hydroxyvitamin D (25(OH)D) is present in almost all immune cells and is a major immunomodulatory hormone. In addition, the vitamin is a potent endothelial membrane stabilizer[12]. Due to its anti-inflammatory effects, the active form of vitamin D plays an important role in inflammatory diseases including rheumatic disorders, and a growing piece of evidence is present regarding its effects on infectious diseases[13]. Vitamin D deficiency is common; larger studies suggest that in Europe, 40% and 13% of the population are vitamin D-deficient and severely deficient, respectively[14]. Vitamin D deficiency is associated with vascular diseases including DM, hypertension, and dyslipidemias[15].

The small number of included studies, including studies published by the same authors and including poster presentations[16,17], limits the previous meta-analysis on vitamin D deficiency and diabetic septic foot. Therefore, this meta-analysis investigated vitamin D levels among patients with the diabetic septic foot.

MATERIALS AND METHODS

Eligibility criteria

The studies were eligible if they compared the level of vitamin D among patients with DFU and their counterparts without DFUs and they are randomized controlled trials or case-control studies, prospective and retrospective cohorts, and cross-sectional studies. Case reports, case series, and animal and experimental studies were excluded.

Outcomes measures

The primary outcome was the level of vitamin D among patients with DFUs.

Vitamin D assessment methods

Vitamin D measurement varied between the included studies. References 18, 19, 21, and 23 used the enzyme-linked immunosorbent assay; references 20, 22, and 25 used radioimmunoassays; references 24, 26, and 28 used the electrochemiluminescence immunoassay; reference 27 used liquid chromatography-tandem mass spectrometry; and reference 29 used the chemiluminescence assay.

Setting and DFU definition

All of the studies used outpatients except 18, 24, 28, and 29, in which hospitalized patients were included.

Information sources and search

The researcher searched PubMed, MEDLINE, and Cochrane Library, EBSCO, and Google Scholar using the keywords DFU, DFS, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D deficiency. The search engine was set for articles published during the period from inception to October 2022. A predetermined table was used to collect study information including author name, year of publication, country, age, sex, patient's number in the control and interventional groups, duration of diabetes, hemoglobin A1c (HbA1c) in the intervention and control groups, vitamin D level among patients with FUs and control groups (Figure 1 and Tables 1-3).

Data analysis

The RevMan (version 5.4) system for meta-analysis was used, and the data were all continuous. We pooled data from 12 studies to compare vitamin D levels among patients with and without diabetic septic foot; a subanalysis was done to compare vitamin D among hospitalized patients. Random effect was used because significant heterogeneity was observed. Funnel plots were used to assess lateralization. $P < 0.05$ was considered statistically significant.

RESULTS

The current meta-analysis included 12 studies including 7619 patients. The included studies were seven cross-sectional, three prospective, and two retrospective studies; nine were published in Asia and three were from Europe[18-29]. The included studies were of good quality as assessed by the Newcastle Ottawa Scale[30]. Vitamin D was lower among patients with DFUs [odds ratio (OR): -5.77, 95% confidence interval (CI): -7.87 to -3.66; χ^2 was 84.62; mean difference, 9; I^2 for heterogeneity, 89%; $P <$ 0.001, and P for overall effect < 0.001] (Figure 2). Vitamin D level was low when a subanalysis was conducted including only hospitalized patients with diabetes septic foot (OR: -6.32; 95%CI: -11.66 to -0.97; χ^2 was 19.39; mean difference, 2; I^2 for heterogeneity, 90%; $P = 0.02$) (Figure 3). Vitamin D level was lower among patients with DFUs after including studies that controlled for age, sex, duration of diabetes, and HbA1c (OR: -6.32; 95%CI: -923 to -3.42; χ^2 was 18.72; mean difference, 4; I^2 for heterogeneity, 79%; $P < 0.001$) (Figure 4).

DISCUSSION

In the present meta-analysis, vitamin D levels were lower among patients with DFUs compared to their counterparts without FUs (OR: -5.77; 95%CI: -7.87 to -3.66). There were no differences between hospitalized patients and outpatients. The results remained robust when including studies that controlled for age, sex, duration of diabetes, and HbA1c. The quality of the included studies was good[30]. The current findings were in line with a narrative review including three studies[31]. The present findings were similar to the first meta-analysis published by Dai and colleagues in 2019. Dai *et al*[16] found an association between vitamin D levels and DFUs. However, Kota *et al*[32] included studies published by the same authors and some were poster presentations. Yammine *et al*[33] found similar results.

Table 1 Basic characteristics of patients with and without diabetic foot ulcers

Ref.	Study type	Country	Duration	Diabetes	Control	Results
Afarideh *et al*[18], 2016	Cross-sectional, 30, and 30	Iran	-	41.93 ± 45.48	39.94 ± 26.07	Non-significant, 0.487
Çağlar *et al*[19], 2018	Prospective, 58 interventions and 47 controls	Turkey	12 mo	7.9 ± 6.3	11.6 ± 6.5	Lower among diabetes, < 0.001
Dai *et al*[20], 2020	Prospective, 21, and 30	China	9 mo	11.21 ± 5.20	17.73 ± 3.20	Lower among diabetes, < 0.001
Danny Darlington *et al*[21], 2019	Cross-sectional, 67, and 66	India	-	19.38 ± 5.32	21.91 ± 5.16	No significant difference, 0.306
Feldkamp *et al*[22], 2018	Cross-sectional, 104, and 103	Germany	-	11.8 ± 11.3	19 ± 14.4	Lower among diabetes, < 0.001
Gupta *et al*[23], 2016	Retrospective, 50, and 50	India	-	14.25 ± 8.46	21.28 ± 10.98	Lower among diabetes, < 0.001
Tang *et al*[24], 2021	Prospective, 547, and 1174	China	8 yr	35.8 ± 10.98	45.48 ± 12.91	Lower among diabetes, < 0.001
Tiwari *et al*[25], 2014	Cross-sectional, 112 cases, 107 controls	India	-	40.2 ± 3.7	49.4 ± 3.2	Lower among diabetes, 0.06
Todorova *et al*[26], 2020	Cross-sectional, 73, and 169	Bulgaria	-	11.6	13.5	Lower among diabetes, 0.001
Tsitsou *et al*[27], 2021	Cross-sectional, 33, and 35	Greece	-	17.9 ± 6.7	19.8 ± 8.7	Non-significant, 0.329
Wang *et al*[28], 2022	Retrospective, 242, 187	China	34 mo	26.89	35.64	Lower among diabetes, < 0.001
Xiao *et al*[29], 2020	Cross-sectional, 245, and 4039	China	-	36.96 ± 18.03	40.97 ± 17.82	Lower among diabetes, 0.001

Table 2 Age, sex, duration of diabetes, and hemoglobin of patients with and without diabetic foot ulcers

Ref.	Study type	Country	Age	Sex	DM duration	HbA1c
Afarideh *et al*[18], 2016	Cross-sectional, 30, and 30	Iran	Matched	Matched	Matched	Matched
Çağlar *et al*[19], 2018	Prospective, 58 interventions and 47 controls	Turkey	Controls younger	Matched	Controls newly diagnosed	Matched
Dai *et al*[20], 2020	Prospective, 21, and 30	China	Matched	Matched	Matched	Matched
Danny Darlington *et al*[21], 2019	Cross-sectional, 67, and 66	India	Matched	Matched	Matched	Poor glycemic among foot ulcer
Feldkamp *et al*[22], 2018	Cross-sectional, 104, and 103	Germany	Matched	Matched	Matched	Matched
Gupta *et al*[23], 2016	Retrospective, 50, and 50	India	Control was younger	Males high among DM	Lon among diabetes	Poor glycemic among foot ulcer
Tang *et al*[24], 2021	Prospective, 547, and 1174	China	Control was younger	Higher females in control	Lon among diabetes	Matched
Tiwari *et al*[25], 2014	Cross-sectional, 112 cases, 107 controls	India	Matched	Matched	Matched	Matched
Todorova *et al*[26], 2020	Cross-sectional, 73, and 169	Bulgaria	Control was younger	Matched	Matched	NA
Tsitsou *et al*[27], 2021	Cross-sectional, 33, and 35	Greece	Matched	Matched	Matched	Matched
Wang *et al*[28], 2022	Retrospective, 242, 187	China	Control was younger	Males higher among DM	Lon among diabetes	NA
Xiao *et al*[29], 2020	Cross-sectional, 245, and 4039	China	Matched	Females more	Matched	Poor glycemic among foot ulcer

DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; NA: Not available.

Table 3 Newcastle Ottawa scale risk of bias of the included studies

Ref.	Country	Selection bias	Comparability bias	Outcome	Total score
Afarideh *et al*[18], 2016	Iran	4	2	2	8
Çağlar *et al*[19], 2018	Turkey	4	2	2	8
Dai *et al*[20], 2020	China	4	2	2	8
Danny Darlington *et al*[21], 2019		4	1	2	7
Feldkamp *et al*[22], 2018	India	4	2	2	8
Gupta *et al*[23], 2016	Germany	4	2	2	8
Tang *et al*[24], 2021	India	4	2	2	8
Tiwari *et al*[25], 2014	China	4	1	2	7
Todorova *et al*[26], 2020	India	4	2	2	8
Tsitsou *et al*[27], 2021	Bulgaria	4	1	2	7
Wang *et al*[28], 2022	Greece	4	2	2	8
Xiao *et al*[29], 2020	China	4	1	2	7

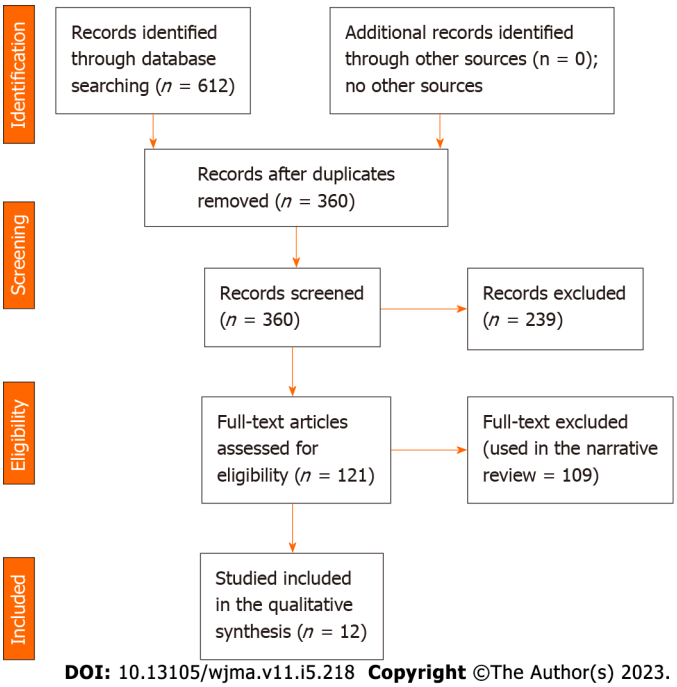

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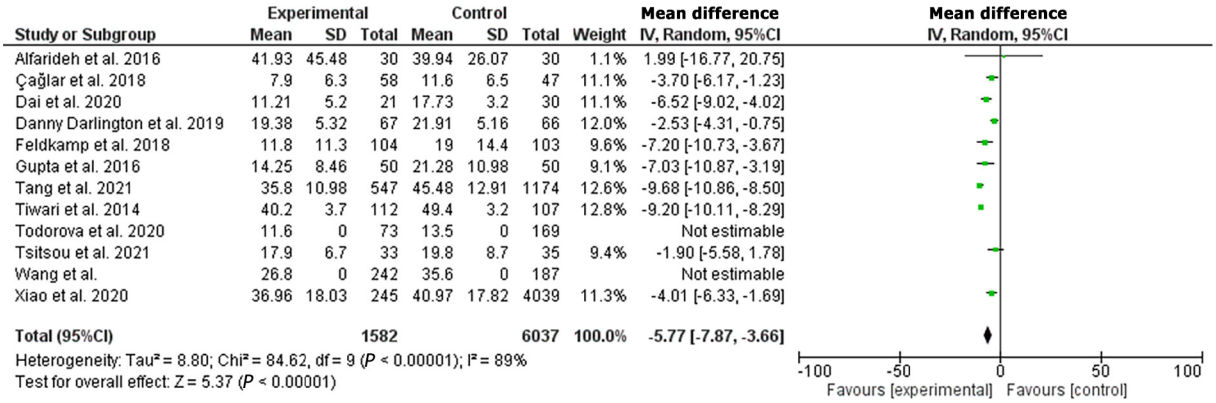
Figure 1 Vitamin D levels among diabetic patients with and without diabetic foot ulcer.

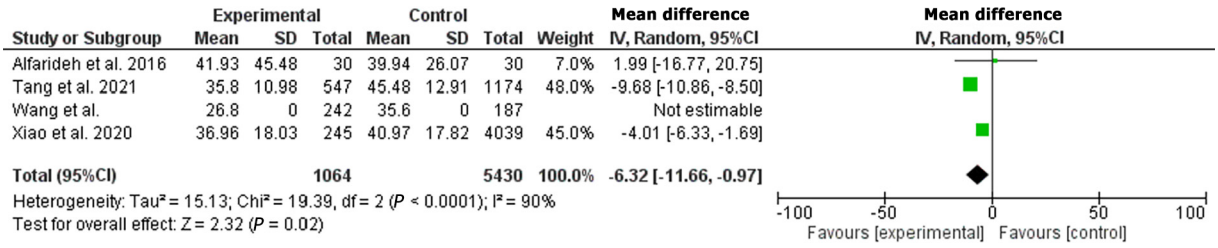
Importantly, Yammine and colleagues included poster presentations, studies published by the same authors, and studies that assessed Charcot's joints[34]. In addition, the previous meta-analysis included Zubair *et al*[35] study in which vitamin D median was reported and not the mean ± standard deviation. A recently published meta-analysis reported similar findings to our results. However, the substantial heterogeneity including posters, research by the same authors, and different primary outcomes limited their results[17]. The main strength of this meta-analysis is the subanalysis on vitamin D among hospitalized patients. Although a single measurement is not enough during stress, the results remain robust even among admitted patients[36].

Vitamin D has been considered a magic bullet and cures many chronic disorders. However, the results were obtained from observational studies. The findings of lower FUs among patients with higher vitamin D may not prove causality. Other confounders might explain the lower vitamin D levels among patients with DFUs including a healthier diet, good exposure to sunlight, and physical activity[37,38]. In addition, vitamin D improves glycemic control among patients with diabetes[39,40]. Thus, high vitamin D may indirectly protect against DFUs by improving glycemic control.



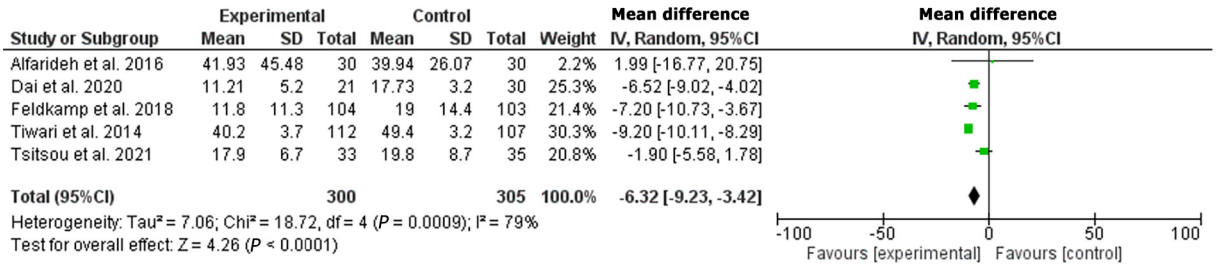
DOI: 10.13105/wjma.v11.i5.218

Figure 2 Vitamin D level among diabetic patients with and without septic foot.



DOI: 10.13105/wjma.v11.i5.218

Figure 3 Vitamin D level among diabetic patients with and without septic foot (hepatized).



DOI: 10.13105/wjma.v11.i5.218

Figure 4 Vitamin D level among diabetic patients with and without septic foot (controlling for age, sex, duration of diabetes, and hemoglobin).

Osteoblasts (bone formation) and osteoclasts (bone resorption) orchestrate bone remodeling. Osteoclasts genesis activation is through receptor activator of tumor necrosis factor (RANK-osteoprotegerin), ultimately leading to osteolysis and destruction of bone tissue. This pathway is of great therapeutic and clinical implications. Medications that influence different levels of RANK-osteoprotegerin are bisphosphonates, calcitonin, and denosumab. Denosumab is encouraging for the treatment of Charcot diabetic foot. However, bisphosphonates have been evaluated recently due to the adverse events. Calcitonin efficacy is limited[41,42].

In this review, some of the included studies were not matched for age, duration of diabetes, duration of diabetes, or HbA1c. The young age of control subjects, their good glycemic control, and the short duration of diabetes might increase their risk of DFUs.

Vitamin D supplementation and diabetic septic foot

Although, the association between low vitamin D levels and diabetic septic foot was documented. However, the effect of vitamin D therapy on DFUs is unclear. In addition, it is not clear if the relationship is correlated or causal[43]. A double-blinded randomized controlled trial showed that high-dose vitamin D supplementation (170 μg/d) was superior to low doses (20 μg/d) on diabetic ulcer healing[44]. A recent review showed that vitamin D improved diabetic septic foot healing, an effect mediated by the remodeling and proliferation of cells involved. In addition, vitamin D suppresses

proinflammatory responses, enhances antimicrobial peptides, and enhances anti-inflammatory effects [45]. The review by Papaioannou and colleagues, which included 34 studies[46], supported the above findings. A randomized controlled trial published in Asia showed that vitamin D supplementation reduced ulcer length, width, and depth[47]. A recent review of the literature concluded that vitamin D supplementation might slow the progression of neural damage. In addition to the adjuvant role in neuropathic pain and cardiovascular autonomic neuropathy among patients with type 2 diabetes[48].

The current meta-analysis strength is that we included observational studies excluding poster presentations, studies published by the same authors, and studies that used the median of vitamin D. The limitation of this study was the substantial heterogeneity.

CONCLUSION

Vitamin D levels were lower among patients with DFUs compared to their counterparts without ulcers. A low level was observed among hospitalized patients. Randomized control trials investigating the association of vitamin D and DFs and assessing the role of vitamin D supplementation are needed.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is associated with various disorders ranging from glycemic control to cancer and suicide. Diabetic foot syndrome (DFS) is a common disorder with high morbidity and mortality. The association of DF ulcers (DFUs) with vitamin D deficiency was documented. However, the available meta-analyses were limited by bias and few included studies.

Research motivation

Diabetes mellitus (DM) is approaching an epidemic, the disease is associated with vascular and neuropathic complications. Most people with diabetes are not approaching the recommended targets for cardiovascular risk factors with increasing FUs. DFUs are a preventable disease and vitamin D deficiency is promising. Despite the association of vitamin D deficiency and DM and its complications. However, a cause and effect were not confirmed. In addition, vitamin D supplementation is not without complications and vitamin D is readily synthesized by sun exposure. We included vitamin D supplementation to address this issue.

Research objectives

To assess vitamin D levels among patients with diabetic septic foot and the role of vitamin D supplementation in the treatment of DFS.

Research methods

We searched four databases and included studies other than case reports, perspectives, opinions, and editorials. The studies were included if they assessed the relationship between diabetic foot ulcers and vitamin D levels. The most recent RevMan system was used for data analysis.

Research results

Evidence from observational studies confirmed the association between vitamin D deficiency and diabetic foot ulcers, both among outpatients and hospitalized patients, the associations remained robot after controlling for demographic factors, the duration since the diagnosis of type 2 diabetes, and glycated hemoglobin (odds ratio: -6.32, 95% confidence interval: -923 to -3.42).

Research conclusions

Vitamin D deficiency was associated with DFUs, and vitamin D supplementation was effective in slowing the progress. Various therapies along the RANK-osteoprotegerin pathway are promising.

Research perspectives

The question of vitamin D and the optimal effective dose is elucidated. In addition, future therapies along the RANK-osteoprotegerin might address this dangerous diabetes complication.

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FOOTNOTES

Author contributions: Mirghani HO contributed to the concept and design, literature search, data analysis and interpretation, and manuscript drafting.

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META-ANALYSIS

Evidence relating cigarette, cigar and pipe smoking to lung cancer and chronic obstructive pulmonary disease: Meta-analysis of recent data from three regions

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Abstract

BACKGROUND

There is a need to have up-to-date information for various diseases on the risk related to the use of different smoked products and the use of other nicotine-containing products. Here, we contribute to the information pool by presenting up-to-date quantitative evidence for North America, Europe and Japan and for both lung cancer and chronic obstructive pulmonary disease (COPD) on the relative risk (RR) relating to current *vs* never product use for each of the three smoked tobacco products, cigarettes, cigars and pipes.

AIM

To estimate lung cancer and COPD current smoking RRs for the three products using recent data for the three regions.

METHODS

Publications in English from 2010 to 2020 were considered that, based on epidemiological studies in the three regions, estimated the current smoking RR of lung cancer and/or COPD for one or more of the three products. The studies should involve at least 100 cases of the disease considered, not be restricted to specific lung cancer types or populations with specific medical conditions, and should be of cohort or nested case-control study design or randomized controlled trials. Literature searches were conducted on MEDLINE separately for lung cancer and for COPD, examining titles and abstracts initially, and then full texts. Additional papers were sought from reference lists of selected papers, reviews and meta-analyses. For each study identified, the most recent available data on each product

were entered on current smoking, as well as on characteristics of the study and the RR estimates. Combined RR estimates were derived using random-effects meta-analysis. For cigarette smoking, where far more data were available, heterogeneity was studied by a wide range of factors. For cigar and pipe smoking, a more limited heterogeneity analysis was carried out. Results were compared with those from previous meta-analyses published since 2000.

RESULTS

Current cigarette smoking: For lung cancer, 44 studies (26 North American, 14 European, three Japanese, and one in multiple continents), gave an overall estimate of 12.14 [95% confidence interval (CI) 10.30-14.30]. The estimates were higher (heterogeneity $P < 0.001$) for North American (15.15, CI 12.77-17.96) and European studies (12.30, CI 9.77-15.49) than for Japanese studies (3.61, CI 2.87-4.55), consistent with previous evidence of lower RRs for Asia. RRs were higher ($P < 0.05$) for death (14.85, CI 11.99-18.38) than diagnosis (10.82, CI 8.61-13.60). There was some variation ($P < 0.05$) by study population, with higher RRs for international and regional studies than for national studies and studies of specific populations. RRs were higher in males, as previously reported, the within-study male/female ratio of RRs being 1.52 (CI 1.20-1.92). RRs did not vary significantly ($P \geq 0.05$) by other factors. For COPD, RR estimates were provided by 18 studies (10 North American, seven European, and one Japanese). The overall estimate of 9.19 (CI 6.97-12.13), was based on heterogeneous data ($P < 0.001$), and higher than reported earlier. There was no ($P > 0.1$) variation by sex, region or exclusive use, but limited evidence ($0.05 < P < 0.1$) that RR estimates were greater where cases occurring shortly after baseline were ignored; where bronchiectasis was excluded from the COPD definition; and with greater confounder adjustment. Within-study comparisons showed adjusted RRs exceeded unadjusted RRs. Current cigar smoking: Three studies gave an overall lung cancer RR of 2.73 (CI 2.36-3.15), with no heterogeneity, lower than the 4.67 (CI 3.49-6.25) reported in an earlier review. Only one study gave COPD results, the RR (2.44, CI 0.98-6.05) being imprecise. Current pipe smoking: Four studies gave an overall lung cancer RR of 4.93 (CI 1.97-12.32), close to the 5.20 (CI 3.50-7.73) given earlier. However, the estimates were heterogeneous, with two above 10, and two below 3. Only one study gave COPD results, the RR (1.12, CI 0.29-4.40), being imprecise. For both diseases, the lower RR estimates for cigars and for pipes than for current smoking of cigarettes aligns with earlier published evidence.

CONCLUSION

Current cigarette smoking substantially increases lung cancer and COPD risk, more so in North America and Europe than Japan. Limited evidence confirms lower risks for cigars and pipes than cigarettes.

Key Words: Cigarettes; Cigars; Pipes; Lung cancer; Meta-analysis; Review

Core Tip: For lung cancer, recent North American and European studies indicate current cigarette smoking increases risk > 10-fold in each sex. Limited evidence suggests cigars increase risk about 3-fold, but is variable for pipes. For Japanese studies the risk increase from cigarettes is much less than in Western regions. For chronic obstructive pulmonary disease, cigarettes increase risk about 9-fold, with little sex or regional variation. One North American study reports a lower increase for cigars and pipes. Smoking markedly increases risk of both diseases. While quitting reduces risk most effectively, available evidence suggests switching to nicotine products that are not smoked could potentially reduce these risks.

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INTRODUCTION

It is well-known[1,2] that smoking cigarettes markedly increases the risk of various diseases, particularly lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease and acute

myocardial infarction, and stroke. However, the increase in risk associated with smoking of cigars and pipes, and with the use of other nicotine-containing products is less well characterized. As part of a project comparing relative risks (RRs) of these diseases for current *vs* never use of various products, we have previously published in this journal a review with meta-analysis of the epidemiological evidence relating to the use of snus (Swedish snuff) and of smokeless tobacco[3]. Here we present a systematic review with meta-analysis of the evidence relating both lung cancer and chronic obstructive pulmonary disease (COPD) to current smoking of cigarettes, cigars and pipes based on publications in 2010 to 2020, and a planned further publication will review recent evidence relating current smoking of the same three products to ischaemic heart disease, acute myocardial infarction and stroke. More recently introduced products, such as electronic cigarettes and heat-not-burn products, are not considered in our project at this time, as large long-term epidemiological studies relating their use to the main smoking-related diseases have not so far been conducted. It should be noted that our objective is only to conduct meta-analyses relating to current use of the products considered, and to investigate how the resultant RR estimates vary by other factors, such as sex and region. We do not consider how RRs vary by amount smoked, duration of smoking, or time quit.

The work described in this publication represents a partial update of two earlier meta-analyses we were involved in. One related lung cancer risk to smoking of cigarettes, cigars and pipes, based on publications in the 1900s[4], reporting overall random-effects RR estimates of 8.43 (95%CI 7.63-9.31) for cigarettes, 4.67 (CI 3.49-6.25) for cigars and 5.20 (CI 3.50-7.73) for pipes. The other related COPD risk to cigarette smoking only based on publications up to 2006[5], giving an RR estimate of 3.51 (CI 3.08-3.99). We compare the RR estimates we derive from the more recent publications with these earlier results, and with the findings of various other meta-analyses published in 2000 to 2020[6-18].

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 2010 to 2020 which provided RR estimates for lung cancer or COPD comparing current and never smokers of cigarettes, of cigars, or of pipes. These had to be based on epidemiological cohort or nested case-control studies or randomized controlled trials which were conducted in North America, Europe or Japan, and which involved at least 100 cases of the disease of interest. The studies were excluded if they were restricted to specific types of lung cancer or COPD, or to patients with specific medical conditions, or if the results were superseded by corresponding later results from the same study.

Literature searches

Initially, at stage 0, literature searches were conducted on MEDLINE using simple text searches for publications in 2010 to 2020. For lung cancer the search, carried out on November 7, 2021, used the terms "smoking" and "lung cancer". For COPD the search, carried out on 9th November 2021, linked "smoking" to the term "COPD" or the following terms associated with it – "Pulmonary Disease, Chronic Obstructive", "Lung Disease, Obstructive", "Bronchitis" and "Emphysema".

Then, at stage 1, titles and abstracts were screened to select publications that appeared to describe studies satisfying the inclusion criteria, and both meta-analyses and reviews that may cite other relevant publications. The initial screening was usually carried out by Katharine J Coombs (KJC), with acceptances checked by Peter N Lee (PNL), though in some cases PNL did the initial screening and KJC checked. Disagreements were resolved *via* discussion.

Then, at stage 2, the full texts of the selected publications (and of relevant Supplementary material and other publications linked to them in the MEDLINE search) were obtained, and examined by PNL, who classified the publication as being an acceptance (*i.e.* it appeared to include relevant data), a reject (giving reason), a relevant review or a relevant meta-analysis. The rejections were then checked by KJC, with any disagreements resolved.

At stage 3, additional accepted publications not detected by the MEDLINE searches were sought by examination of reference lists of the accepted papers and of the relevant reviews and meta-analyses and, when obtained, dealt with as in stage 2.

Finally, at stage 4, copies of all the accepted publications (not the meta-analyses) were organized, first by country, and then by study within country, with studies conducted in multiple countries considered as a separate group. The aim was to eliminate from consideration those publications giving results for a study that were superseded by a later publication, and those publications which, on more detailed examination, did not fully satisfy the inclusion criteria.

Data entry

Data were entered into a study database and into an associated RR database. The study-specific information recorded was: Study name; country; region (North America, Europe, Japan or multiple); study design (cohort, nested case-control, or randomized controlled), study population (international, national, regional or specific, *e.g.* workers in a particular industry); study size (number of cases of the

disease); year of start; length of follow-up; sexes considered (males only, females only, or both); and age range considered.

The information recorded relating to each RR was: The RR itself and its 95% confidence interval (CI), the RR and CI being estimated from the data provided if necessary; the study to which it related; an identifier for the paper providing the estimate; the year of publication of the paper; for COPD only the definition of COPD used; the product considered (cigarettes, cigars or pipe); whether the RR related to exclusive use of the product; the sex to which it related (males, females or combined - combined RRs only being entered if sex-specific RRs were not available); the age range considered; the years of follow-up considered; the endpoint (from death certification only, or involving in-life diagnosis); whether a latency rule was applied (*i.e.* whether cases identified in the first few years of follow-up were ignored), and the number of adjustment factors applied to the risk estimate.

Meta-analyses

Meta-analyses could not be conducted relating risk of COPD to current cigar or current pipe smoking as the available data originated from a single study.

Otherwise, individual study RR estimates were combined using fixed- and random-effects meta-analyses[19], with the significance of between-study heterogeneity also estimated.

For current cigar and for current pipe smoking and the risk of lung cancer, where the extent of available data was rather limited, meta-analyses were based on the most adjusted RR estimate per study, with heterogeneity studied by sex and by region.

For current cigarette smoking, where data were much more extensive, more detailed meta-analyses were conducted, as described below.

Initially, meta-analyses were conducted based on either two RR estimates from each study, if separate RRs were available for each sex, or on a single estimate if the study reported only combined sex results or results for only one sex. Where there was a choice of RRs available for a study, those selected were based on a sequence of preferences applied in turn.

For lung cancer the sequence was as follows: (1) Exclusive rather than non-exclusive cigarette smoking; (2) a latency rule had been applied rather than not; (3) the longest follow-up period available; 4) adjustment for the most possible confounders; (5) lung cancer identified by diagnosis rather than death; and (6) separate sex RRs selected rather than the combined sex RR. For COPD the sequence only involved preferences 1, 2 and 6 in turn, due to the more limited data.

For lung cancer the RRs were estimated overall, with heterogeneity studied by the following factors: Sex; region; study population; year of start; study size; exclusive use; latency rule used; study type; lowest age considered; years of follow-up; endpoint; and number of adjustment factors. Grouped levels of the variables were used as appropriate. For COPD, the same factors were studied, except that study type was omitted (all the COPD studies proving to be cohort studies), and that heterogeneity was also studied by definition of COPD (excluding bronchiectasis, including bronchiectasis, or other).

For lung cancer it became clear that RRs were much lower in Japan than in North America or Europe, so these analyses were also repeated excluding RRs from Japan.

While these meta-analyses and heterogeneity investigations were based on variation in RRs between studies, some additional investigations were conducted on within-study variation in RRs, based on data from the same publication. For sex, these meta-analyses were based on the ratio of the RR for males to that for females, while for level of adjustment, results were compared based on the ratio of the RR adjusted for multiple potential confounding variables to the RR adjusted for no variables. Where multiple pairs of results were available within a publication, the pair selected was chosen based on the preferences described above. For within-study variation of other characteristics, where there was far less data available, the results were simply summarized in the text.

RESULTS

Literature searches

Flowcharts of the searches are shown in Figure 1 for lung cancer and in Figure 2 for COPD. Starting with over 10000 papers identified in the initial MEDLINE searches for each disease, 53 study reports were identified for lung cancer and 19 for COPD, which provided results for, respectively, 44 and 18 studies.

For lung cancer there were in total 152 RRs available for analysis, 138 for cigarette smoking, six for cigar smoking and eight for pipe smoking, single studies sometimes providing multiple estimates, *e.g.* for separate sexes, for several levels of adjustment for covariates, or for several products. For COPD there were 58 RRs available for analysis, 52 for cigarette smoking, three for cigar smoking and three for pipe smoking. Table 1 (lung cancer) and Table 2 (COPD) gives some details of the studies considered. Eleven of these studies provided data for both diseases.

Table 1 Details of the 44 studies of lung cancer

Study ID[a]	Ref.	Country	Design[b]	Study Population	Start year	Year followed	Age[c]	Sex[d]	Cases	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
ACE	[51,52]	US	Cohort	Regional	1995	10	18+	C	111	0, 8	0	0	Died	2
AEROBIC	[53]	US	Cohort	Regional	1974	29	20-84	M	232	0	0	0	Died	1
AGRICAN	[54]	France	Cohort	Regional	2005	6	18+	M, F	664	1	0	0	Diagnosed	2
AHS	[55]	US	Cohort	Pesticide workers	1993	18	NAR	C	789	0, 8	x	0	Diagnosed	2
AMIANT	[56]	Poland	Cohort	Asbestos workers	2000	14	NAR	C	110	0	0	0	Diagnosed	1
ARIC	[57]	US	Cohort	Regional	1987	19	45-64	M, F	470	0, 3	0	0	Diagnosed	4
ATP	[22]	Canada	Cohort	Regional	2001	16	35-69	M, F	210	0, 1, 7	0	0, x	Diagnosed	10
BIOBANK	[58]	UK	Cohort	National	2006	10	40-73	M, F	1493	0	0	0	Diagnosed	2
BWHS	[59]	US	Cohort	National	1995	18	21-69	F	306	0, 1, 7	0	0	Diagnosed	3
CHANCES	[21]	Multiple	Cohort	International	1982	29	46-74	C	14041	0, 7	0	0	Diag, died	4
COAL	[60]	US	Cohort	Coal miners	1969	38	NAR	M	568	7	0	0	Died	1
CPS-I	[26]	US	Cohort	National	1959	6	49+	M, F	1293	0, 1, 3	x	0	Died	6
CPS-II	[26]	US	Cohort	National	1982	6	49+	M, F	4957	0, 1, 3	x	0	Died	6
EPIC	[31]	Multiple	Cohort	International	1991	14	35-70	M	2995	0, 5	x	0	Diagnosed	6
	[32]					8	30-70	M, F	2995	7	0	0	Diagnosed	2
ESTHER	[61]	Germany	Nested CC	Regional	2000	17	50-75	C	143	0	0	0	Diagnosed	1
FRAMING	[62]	US	Cohort	Regional	1954	59	NAR	C	284	0, 1	0	0	Diagnosed	2
HBC	[63]	Finland	Cohort	Regional	2001	5	55-65	C	121	1	0	0	Diagnosed	1
HPFS	[64]	US	Nested CC	Medical workers	1986	14	40-75	M	210	0, 2, 4	0	0	Diagnosed	3
JP8	[23]	Japan	Cohort	National	1984	25	35+	M, F	4478	0, 2, 5	x	0, x	Diagnosed	8
JPHC	[65]	Japan	Cohort	National	1990	21	40-69	M, F	1663	0	x	0	Diagnosed	2
	[66]					3	40-69	M, F	1663	0, 10	x	0	Died	4
KAISER	[67]	US	Cohort	Regional	1978	30	NAR	C	1415	0, 6	0	0	Diagnosed	2
KRIS	[68]	Lithuania	Cohort	Regional	1972	36	40-59	M	343	0, 1, 4	0	x	Diagnosed	3
LSS	[69]	Japan	Cohort	Atomic bomb	1950	59	5+	M, F	1597	0	x	0	Diagnosed	2

				survivors									
MWOMEN	[24]	UK	Cohort	National	1996	15	50-69	F	6331	0, 10	x	0, x	Died	3
NHANES	[70]	US	Cohort	National	1988	18	40+	C	269	0	0	0	Died	1
NHIS	[71]	US	Cohort	National	1987	28	18-84	C	7420	0, 11	0	0	Died	2
	[72]					9	25-79	M, F	7420	0, 4	0	x	Died	4
NHS	[73]	US	Cohort	Medical workers	1980	24	34-59	F	1729	1, 13	0	0	Died	2
	[74]					24	38-63	F	1729	0	0	0	Diagnosed	1
NIHAARP	[75]	US	Cohort	Regional	1995	11	50-71	M, F	17846	0, 5	x	x	Diagnosed	4
	[76]					16	50-71	C	17846	0	0	0	Diagnosed	1
NLCS	[29]	Netherlands	Nested CC	National	1986	17	55-69	C	3355	0	0	0	Diagnosed	3
	[30]					20	55-69	M, F	3355	0	0	0	Diagnosed	2
NLMS	[28]	US	Cohort	National	1985	26	35-80	C	3890	0, 1, 5	x	0	Died	8
NLST	[77]	US	Cohort	Construction workers	1998	18	NAR	M	352	0, 2	0	0	Died	2
NONMET	[78]	US	Nested CC	Non-metal miners	1947	50	NAR	M	198	0, 7	0	0	Died	2
NOWAC	[79]	Norway	Cohort	National	1991	24	31-70	F	1507	0, 1, 3	0	0	Diagnosed	3
PLCO	[80]	US	Cohort	Regional	1993	15	55-74	C	1040	0	0	0	Died	1
	[81]					15	55-74	F	1040	6	0	0	Died	1
QRESEAR	[82]	UK	Cohort	National	1998	15	25-84	M, F	32187	0, 6	0	0	Diagnosed	4
SCCS	[83]	US	Nested CC	Regional	2002	14	40-79	M, F	1334	0	0	0	Diagnosed	2
	[84]					7	40-79	C	1334	10	0	0	Diagnosed	1
SHEETME	[85]	Multiple	Cohort	Sheet metal workers	1986	24	NAR	M	808	0	0	0	Died	1
THIN	[86]	UK	Cohort	National	2000	12	30-99	C	1015	0	0	0	Diagnosed	1
THREEC	[20]	Norway	Cohort	Regional	1974	33	20-49	M	858	0, 10	0, x	0	Died	6
	[87]					35	35-49	M, F	858	0	0	x	Died	2
USA5	[26]	US	Cohort	National	1986	24	45+	M, F	11420	0, 1, 3	0	0	Died	6
VETERAN	[88]	US	Cohort	Regional	1987	28	21-89	M	105	0	0	0	Diagnosed	1
VITAL	[89]	US	Cohort	Regional	2000	7	50-76	C	797	0	0	0	Diagnosed	1

VLAGT	[27]	Netherlands	Cohort	Regional	1965	43	20-65	M, F	275	0, 3, 4	0	0	Died	4
WHI	[90]	US	Cohort	National	1993	16	50-79	F	901	0, 1, 15	0	0	Diagnosed	3

[a]Study IDs are ACE: The Adverse Childhood Experiences Study; AEROBIC: Aerobics Center Longitudinal Study; AGRICAN: Agriculture and Cancer Study; AHS: Agricultural Health Study; AMIANT: Amiantus; ARIC: Atherosclerosis Risk in Communities study; ATP: Alberta's Tomorrow Project; BIOBANK: The UK Biobank Study, BWHS: The Black Women's Health Study; CHANCES: Consortium on Health and Ageing: Network of Cohorts in Europe and the United States; COAL: Underground coal miners from 31 US mines; CPS-I: Cancer Prevention Study 1; CPS-II: Cancer Prevention Study 2; EPIC: European Prospective Investigation into Cancer and Nutrition; ESTHER: Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung; FRAMING: Framingham Heart Study; HBC: Helsinki Birth Cohorts; HPFS: Health Professionals Follow-up Study; JP8: Pooled analysis of eight prospective studies in Japan; JPHC: Japan Public Health Center-based Prospective Study; KAISER: Kaiser Permanente Medical Care Program Study; KRIS: Kaunas–Rotterdam Intervention Study; LSS: Life Span Study; MWOMEN: Million Women Study; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; NHS: Nurses' Health Study; NIHAARP: National Institutes of Health-American Association of Retired Persons Diet and Health Study; NLCS: Netherlands Cohort Study on Diet and Cancer; NLMS: National Longitudinal Mortality Study; NLST: National Lung Screening Trial; NONMET: Non-metal Mining; NOWAC: Norwegian Women and Cancer study; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer study; QRESEAR: QResearch database; SCCS: Southern Community Cohort Study; SHEETME: Sheet Metal Workers; THIN: The Health Improvement Network; THREEC: Three counties in Norway; USA5: Pooled analysis of five US cohort studies, VETERAN: Veterans Exercise Testing Study; VITAL: Vitamins and Lifestyle; VLAGT: Vlagtwedde-Vlaardingen Study; WHI: Women's Health Initiative Observational Study; US: United States; UK: United Kingdom.

[b]Nested CC: Nested case-control.

[c]NAR: No age restriction.

[d]C: Results only for sexes combined.

[e]Number of adjustment factors for which RR available (0 = unadjusted, 1 = age adjusted, N > 1 = adjusted for N factors).

[f]x: Results available for exclusive use.

[g]x: Results available with deaths excluded in the early period of follow-up.

[h]Number of RRs available.

Cigarette smoking results

The full details of the results summarized below are given in Supplementary material 1 for lung cancer and Supplementary material 2 for COPD. Below, the results are summarized firstly for lung cancer (see also Table 3) and then for COPD (see also Table 4).

Lung cancer

Data available for cigarette smoking: Each of the 44 studies provided data for current cigarette smoking, with data coming from two publications for nine of these studies. Of the 44 studies, 26 were from North America [24 United States (US), one Canada, and one from both the US and Canada], 14 were from Europe [four United Kingdom (UK), two Netherlands, two Norway, and one each from Finland, France, Germany, Lithuania, Poland, and from multiple countries], three were from Japan, and one from multiple countries in North America and Europe. Thirty-nine were cohort studies, and five were nested case-control studies. Eight studies were of workers in specific industries and one was of atomic bomb survivors, the rest considering regional, national or international populations. As shown in Table 1, the studies varied in regard to various factors, including the start year, the length of follow-up, the ages and sexes considered, the number of lung cancer cases studied, and the extent of adjustment for potential confounding factors.

Meta-analyses for cigarette smoking: In total, data were entered on 138 RRs, with up to 10 per study. The initial meta-analyses for cigarette smoking involved 62 of the RRs, selected based on the preferences described in the methods section. As shown in Table 3 and Figure 3, the overall random-effects RR

Table 2 Details of the 18 studies of chronic obstructive pulmonary disease

Study ID[a]	Ref.	Country	Study Population	Start year	Year followed	Age[b]	Sex[c]	Cases	COPD definition[d]	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
CPRD	[91]	UK	Regional	2003	4	40-89	C	14446	3	0	0	0	Diagnosed	1
CPS-I	[26]	US	National	1959	6	49+	M, F	782	DU	0, 1, 3	0, x	0	Died	6
CPS-II	[26]	US	National	1982	6	49+	M, F	2128	DU	0, 1, 3	0, x	0	Died	6
Finn Twins	[92]	Finland	National	1975	27	17+	C	511	5	0, 2	0	0	Diagnosed	2
JACC	[93]	Japan	National	1988	20	40-79	M, F	285	6	0, 1, 9	0	0	Died	6
KAISER	[94]	US	Regional	1978	28	NAR	C	778	4	0, 6	0	0	Diagnosed	2
MWOMEN	[24]	UK	National	1996	15	50-69	F	1910	2	0, 5	x	0	Died	3
NHS-HPFS	[95]	US	Regional	1976	24	30-75	C	832	1	0	0	0	Diagnosed	1
NIH-AARP	[96]	US	Regional	1995	11	50-70	C	3648	1	0	0	0	Diagnosed	1
NLMS	[28]	US	National	1985	26	35-80	C	2091	2	0, 1, 5	x	0	Died	9
NOWAC[i]	[97]	Norway	National	1991	17	26-71	F	68	2	1, 6	x	0	Died	2
PATH	[98]	US	National	2013	3	18+	C	319	1	0	0	0	Diagnosed	1
SMC	[99]	Sweden	Regional	1997	17	48-83	F	1495	8	0	x	x	Diagnosed	1
THIN	[86]	UK	National	2000	12	30-99	C	3901	9	0	0	0	Diagnosed	1
USA5	[26]	US	Regional	1986	24	50+	M, F	9246	DU	0, 1, 3	0, x	0	Died	6
	[100]				25	50+	M, F	9246	2	0, 5	0, x	0	Died	4
VLAGT	[27]	Netherlands	Regional	1965	43	NAR	M, F	313	7	0, 3	0, x	0	Died	4
WHI	[25]	US	Regional	1993	22	50-79	F	4959	1	0	x	0	Diagnosed	1
WHS	[101]	US	Regional	1993	11	45+	F	1604	1	0	x	0	Diagnosed	1

[a]Study IDs are CPRD: Clinical Practice Research Datalink; CPS-I: Cancer Prevention Study 1; CPS-II: Cancer Prevention Study 2; Finn Twins: Finnish Twin Cohort; JACC: Japanese Collaborative Cohort Study; KAISER: Kaiser Permanente Medical Care Program Study; Million: Million Women Study; NHS-HPFS: Nurses' Health Study and Health Professionals Follow-up Study; NIH-AARP: National Institutes of Health–AARP Diet and Health Study; NLMS: National Longitudinal Mortality Study; NOWAC: Norwegian Women and Cancer Study; PATH: Population Assessment of Tobacco and Health Study; SMC: Swedish Mammography Cohort; THIN: The Health Improvement Network; USA5: Five US Cohort Studies; VLAGT: Vlagtwedde-Vlaardingen Study; WHI: Women's Health Initiative Observational Study and; WHS: Women's Health Study; US: United States; UK: United Kingdom.

[b]NAR: No age restriction.

[c]C: Results only for sexes combined.

[d]Disease definition codes: 1 = Self-report; 2 = ICD-10 J40-44; 3 = GP notes and ICD-10 J41-44; 4 = ICD-9 491, 492, 494-496; 5 = Participants entitled to special reimbursement or regularly used anticholinergics; 6 = ICD-10 J41-J44 J47; 7 = ICD-9 490-2, 494, 496 ICD-10 J40-J44, J47; 8 = ICD-10 J44; 9 = GP notes and ICD codes, unstated; DU = definition unstated; COPD: Chronic obstructive pulmonary disease.

[e]Number of adjustment factors for which RR available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).
[f]x: Results available for exclusive use.
[g]x: Results available with deaths excluded in early period of follow-up.
[h]Number of RRs available.
[i]Study included despite only 68 COPD cases as results are available for lung cancer.

estimate was 12.14 (CI 10.30-14.30) based on RR estimates that were highly significantly ($P < 0.001$) heterogeneous.

Table 3 also gives RRs by level of 12 different characteristics of the study or of the RR, with the most striking evidence of variation being for region, where the estimate for Japan (3.61, CI 2.87-4.55) was much lower than those for North America (15.15, CI 12.77-17.96), Europe (12.30, CI 9.77-15.49) or the single study conducted in North America and Europe (13.10, CI 9.91-17.32). This is also shown in Figure 3 (North America, Europe, Japan). There was also much weaker evidence that RRs were higher in studies starting more recently and in those with shorter follow-up periods, where the cigarette smokers may also have smoked cigars and/or pipes, where the endpoint was lung cancer death rather than diagnosis, and where more adjustment factors were taken account of.

When these analyses were restricted to studies in North America and Europe (see detailed results in Supplementary material 1), there was no evidence ($P \geq 0.1$) of variation by sex, region or any of the other factors considered in Table 3 except two. One was whether a latency rule was applied, with a significantly ($P < 0.01$) higher RR (19.52, CI 16.27-23.42) for studies excluding cases occurring shortly after baseline than the RR (13.29, CI 11.42-15.46) for studies considering all cases occurring after baseline. The other was study design, with a significantly ($P < 0.05$) higher RR (14.58, CI 12.71-16.74) based on cohort studies than the RR (10.41, CI 8.04-13.48) based on nested case-control studies.

Within-study comparisons for cigarette smoking: There were 18 otherwise comparable pairs of male and female RRs from the same study (see Supplementary material 1). The male RR exceeded the female RR in 13 pairs, and the random-effects estimate of the male/female ratio was significant (ratio 1.52, CI 1.20-1.92).

There were 36 pairs of unadjusted RR estimates and estimates adjusted for 2 or more covariates. Adjustment increased the RR in 24 of these pairs, and decreased the RR in 12. However, this difference was not significant ($P > 0.1$) and in most cases the effect of adjustment was quite small, with adjustment increasing the RR by a factor > 1.25 in six cases, and decreasing it by the same factor in six cases.

Within the studies considered, current cigarette smoking RRs also varied by four other characteristics: exclusive cigarette smoking; latency; years of follow-up; and endpoint. However, the data available were extremely limited, and some of the variation (and all of it for years of follow-up) related to different publications within the same study, where other characteristics varied as well. When attention was limited to results from the same publication within a study, there was no significant evidence of variation in risk for any of the other three characteristics. Thus, study THREEC[20] reported RRs that were virtually identical for exclusive cigarette smoking (32.58) and non-exclusive cigarette smoking (32.83), while study CHANCES[21] provided RRs for the endpoints died (13.10) and diagnosed (11.50) which clearly did not differ significantly. More data were available for latency, with five pairs of results,

Table 3 Lung cancer and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Heterogeneity test by level (NS = $P \geq 0.1$) and trend if relevant
	All		62	44	12.14 (10.30-14.30)	$P < 0.001$
4	Sex	Combined	12	12	12.93 (10.55-15.84)	
		Males	26	26	12.95 (9.82-17.08)	
		Females	24	24	11.32 (8.46-15.15)	NS
5	Region	N. America	34	26	15.15 (12.77-17.96)	
		Europe	21	14	12.30 (9.77-15.49)	
		Japan	6	3	3.61 (2.87-4.55)	
		Multi	1	1	13.10 (9.91-17.32)	$P < 0.001$
6	Study population	International	3	2	14.45 (6.85-30.50)	
		National	25	16	10.26 (8.03-13.12)	
		Regional	24	17	16.27 (13.39-19.77)	
		Specific	10	9	9.71 (5.41-17.42)	$P < 0.05$
7	Year of start of baseline	< 1980	14	10	8.65 (5.83-12.83)	
		1980-89	19	13	12.92 (9.83-16.98)	
		1990-99	16	12	13.45 (9.76-18.53)	
		2000+	13	9	14.38 (11.40-18.15)	NS trend $P < 0.1$
8	Number of cases	< 500	19	16	11.90 (9.55-14.83)	
		500-1999	24	17	11.68 (8.65-15.75)	
		2000+	19	11	12.76 (9.99-16.31)	NS trend NS
9	Exclusive cigarettes	No	45	35	13.47 (11.55-15.72)	
		Yes	17	11	9.50 (6.61-13.64)	$P < 0.1$
10	Latency rule applied	No	51	38	11.93 (9.97-14.28)	
		Yes	11	7	13.13 (8.69-19.83)	NS
11	Study design	Cohort	55	39	12.35 (10.35-14.73)	
		Nested case control	7	5	10.41 (8.04-13.48)	NS
12, 13	Lowest age considered	< 30	15	10	11.30 (7.37-17.33)	
		30-39	11	8	11.41 (7.80-16.70)	
		40-48	14	9	13.29 (9.15-19.30)	
		49+	14	10	13.62 (10.22-18.16)	NS trend without
		Missing	8	8	10.79 (7.64-15.23)	Missing NS
14	Year of follow-up	< 10	11	7	12.63 (8.49-18.80)	
		10- < 15	11	8	16.05 (12.48-20.65)	
		15- < 20	14	11	16.05 (12.69-20.30)	

		20- < 30	15	11	9.08 (6.26-13.15)	
		30+	11	8	9.57 (6.01-15.26)	$P < 0.05$ trend $P < 0.1$
15	Endpoint	Died	23	17	14.85 (11.99-18.38)	
		Diagnosed	39	27	10.82 (8.61-13.60)	$P < 0.05$
16	Number of adjustment factors	None	20	15	9.65 (7.13-13.05)	
		Age only	4	3	11.80 (5.24-26.56)	
		More	38	28	13.68 (11.46-16.34)	NS trend $P < 0.1$

RR: Relative risk; NS: Not significant.

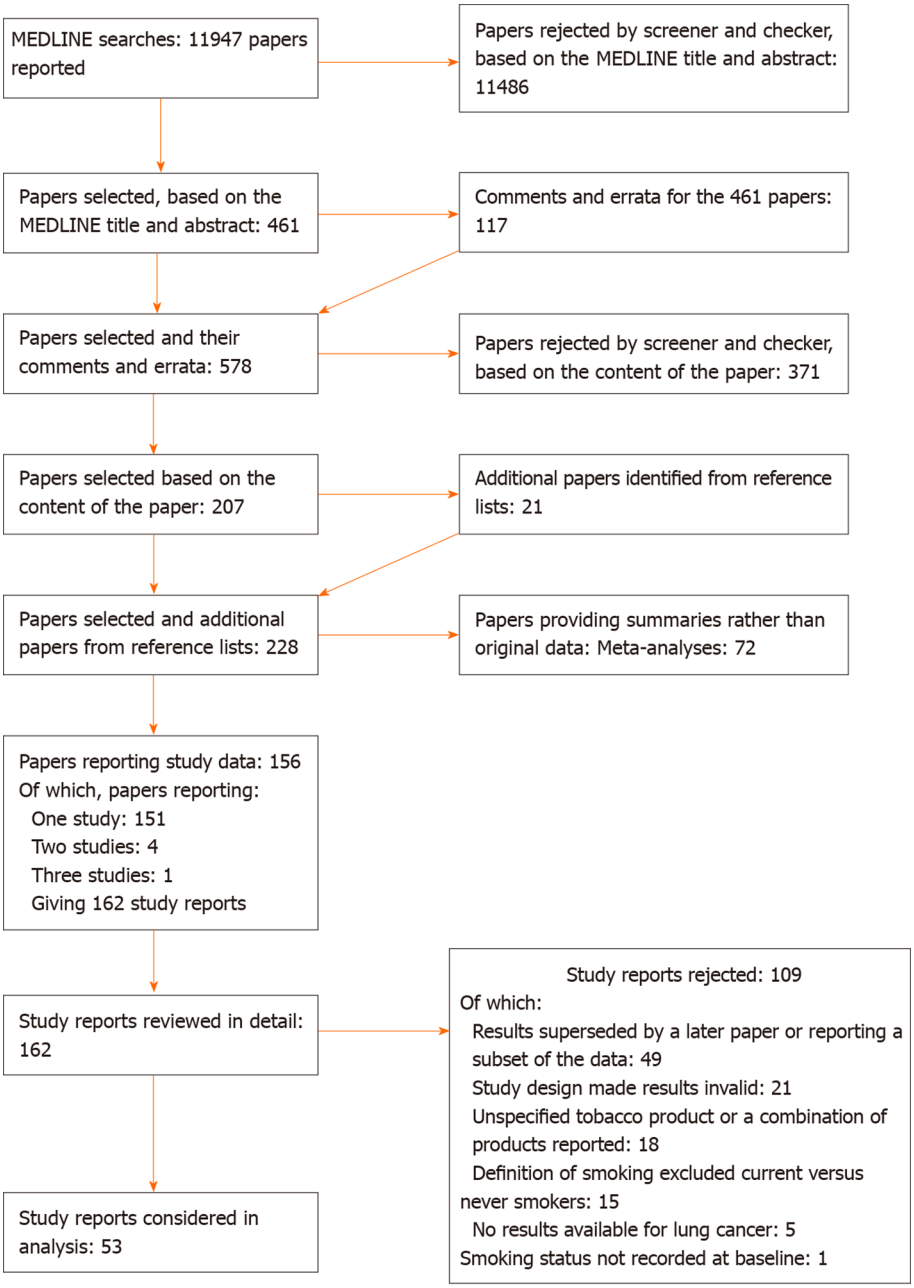

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Figure 1 Literature searches, lung cancer.

Table 4 Chronic obstructive pulmonary disease and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of Studies	RR (95%CI)	Heterogeneity test by level (NS = $P \geq 0.1$) and trend if relevant
	All		23	18	9.19 (6.97-12.13)	$P < 0.001$
4	Sex	Combined	8	8	8.91 (7.05-11.26)	
		Males	5	5	9.56 (4.22-21.64)	
		Females	10	10	9.33 (4.91-17.71)	NS
5	Region	N. America	13	10	8.91 (5.73-13.84)	
		Europe	8	7	10.63 (6.93-16.29)	
		Japan	2	1	6.00 (2.97-12.12)	NS
6	Study population	National	12	9	8.90 (6.47-12.24)	
		Regional	11	9	9.51 (6.16-14.66)	NS
7	Year of start	< 1988	12	8	10.24 (7.26-14.45)	
	of baseline	1988+	11	10	8.14 (5.78-11.47)	NS
8	Number of cases	< 1000	11	8	7.42 (5.65-9.74)	
		1000+	12	10	10.67 (7.26-15.68)	NS
9	Exclusive cigarettes	No	13	12	9.02 (6.78-12.00)	
		Yes	10	10	9.48 (5.25-17.14)	NS
10	Latency rule applied	No	21	16	8.41 (6.38-11.09)	
		Yes	2	2	21.67 (7.74-60.66)	$P < 0.1$
11, 12	Lowest age considered	< 34	5	5	8.36 (7.13-9.80)	
		35-45	5	4	6.26 (4.31-9.08)	
		46-49	5	3	7.92 (5.41-11.58)	
		50+	5	4	15.36 (5.95-39.66)	NS trend without
		Missing	3	2	9.33 (5.00-17.40)	Missing NS
13	Year of follow-up	< 10	6	4	6.85 (5.24-8.94)	
		10- < 20	6	6	11.32 (6.67-19.20)	
		20- < 30	9	7	10.11 (5.21-19.60)	
		30+	2	1	6.29 (3.73-10.59)	NS trend NS
14	COPD definition[a]	Excl. Bronch	6	5	17.45 (8.35-36.44)	
		Incl. Bronch	5	3	7.83 (4.60-13.35)	
		Other	12	10	7.15 (5.19-9.84)	$P < 0.1$
15	Endpoint	Died	13	8	10.95 (7.42-16.15)	
		Diagnosed	10	10	7.49 (5.63-9.95)	NS
16	Number of adjustment factors	None	8	8	6.96 (5.09-9.53)	
		More	15	10	10.83 (7.67-15.29)	$P < 0.1$

[a]Excl. Bronch: Excluding bronchiectasis (codes 2 and 3 in Table 2); Incl. Bronch: Including bronchiectasis (codes 4, 6 and 7). COPD: Chronic obstructive pulmonary disease; RR: Relative risk; NS: Not significant.

one for each sex from ATP[22] and from JP8[23], and one for females from Million Women Study (MWOMEN)[24]. However (see the estimates in Supplementary material 1) the estimates taking and not taking latency into account were very similar.

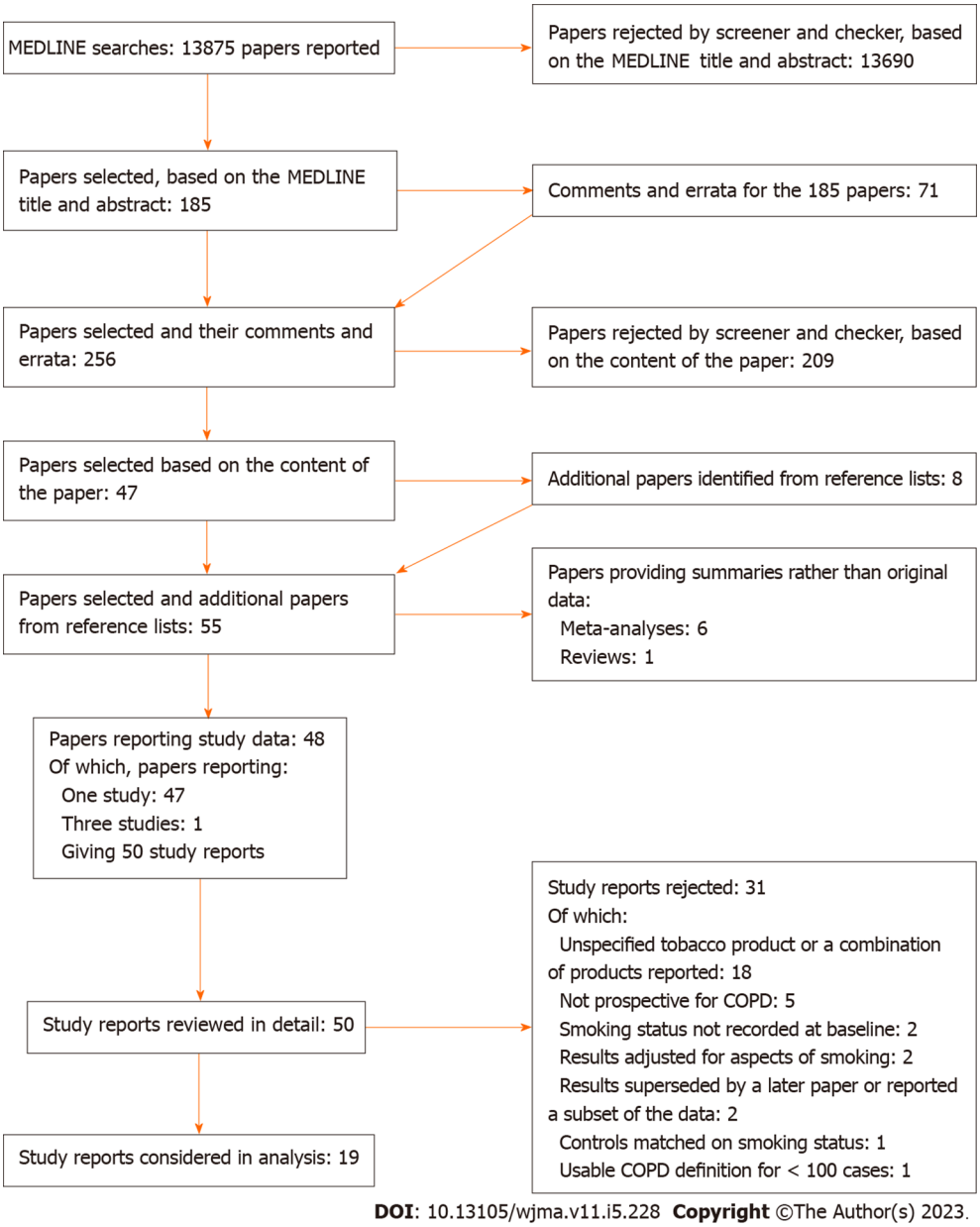

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Figure 2 Literature searches, chronic obstructive pulmonary disease. COPD: Chronic obstructive pulmonary disease.

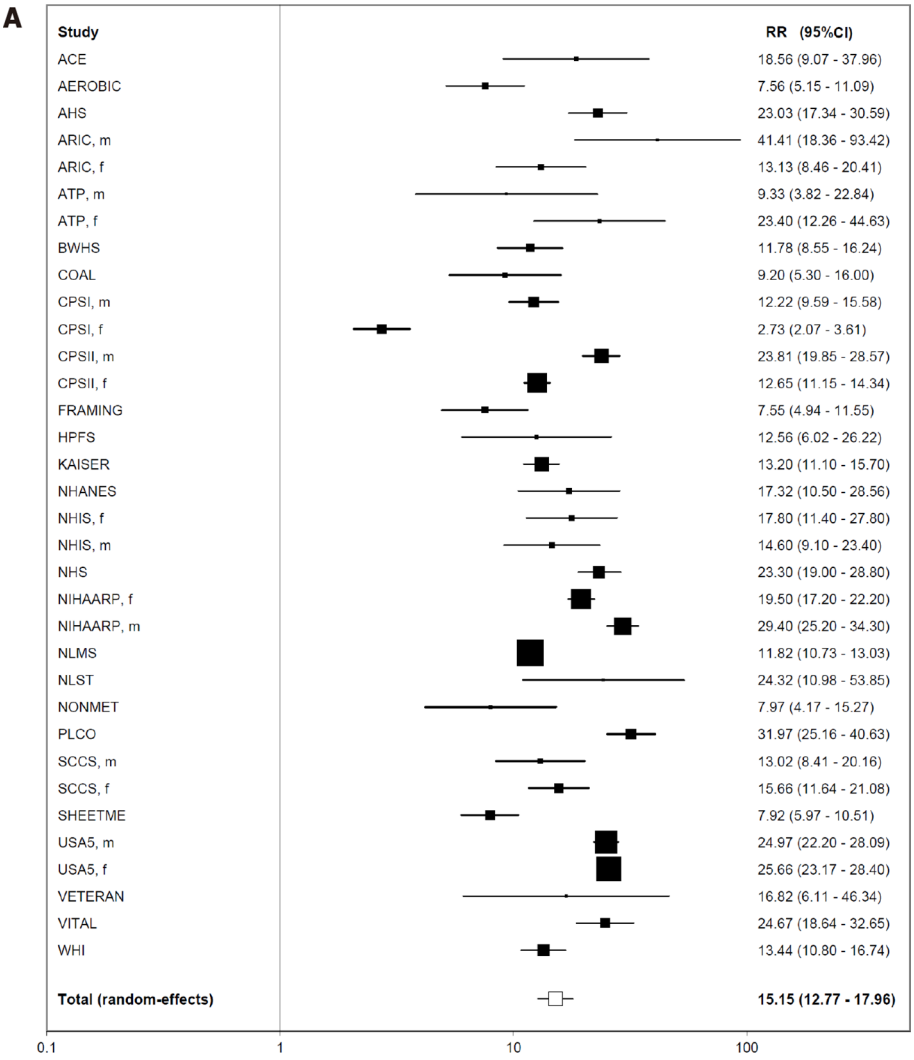
COPD

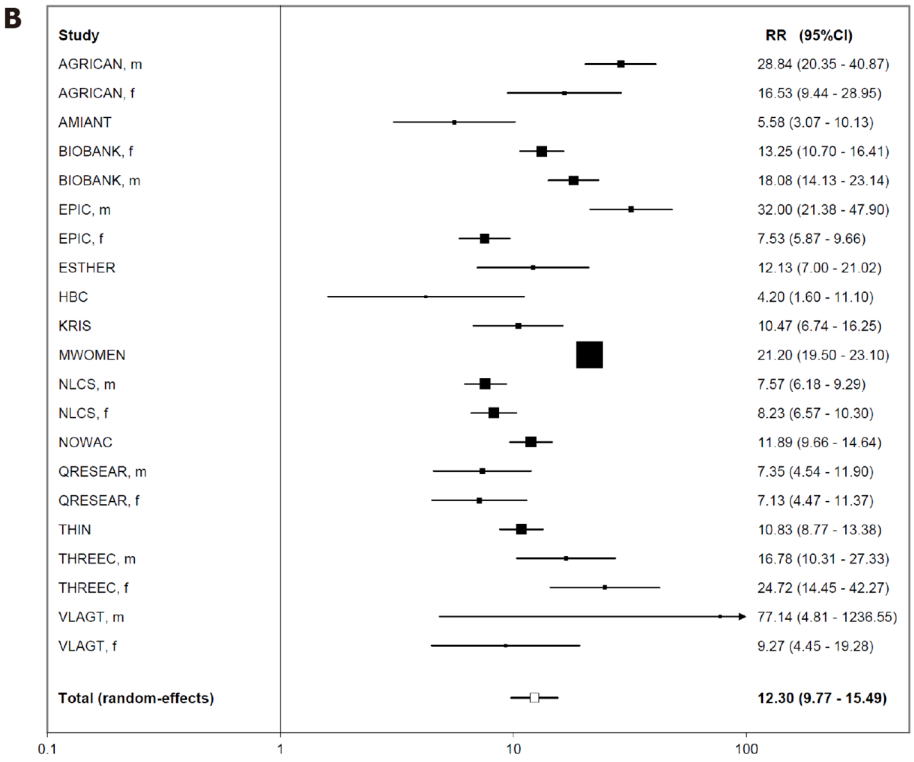
Data available for cigarette smoking: Each of the 18 studies provided data for current cigarette smoking, with data coming from two publications for one of these studies. Of the 18 studies, 10 were from the US, seven from Europe (three UK, and one each from Finland, Netherlands, Norway, and Sweden), and one from Japan. All 18 studies were of cohort design. Nine studies were of national populations and nine of regional populations, with none of workers in specific industries.

As shown in Table 2, the studies varied in regard to several factors, including the start year, the length of follow-up, the ages and sexes considered, the number of COPD cases studied, the definition of COPD used, and the extent of adjustment for potential confounding factors.

Meta-analyses for cigarette smoking: Data were entered on a total of 52 RRs, with up to 10 per study. The initial meta-analyses involved 23 of the RRs, selected based on the preferences described in the methods section. As shown in Table 4 and Figure 4, the overall random-effects RR estimate was 9.19 (CI 6.97-12.13) based on RR estimates that were highly significantly ($P < 0.001$) heterogeneous, the RRs varying from 3.21 (CI 2.96-3.47) in WHI[25] to 36.70 (CI 30.20-44.70) in MWOMEN[24].

Table 4 also gives RRs by level of 12 different characteristics of the study or of the RR. There was some evidence ($0.05 < P < 0.1$) that RRs were greater for three of the characteristics: where a latency rule had been applied; where bronchiectasis had been excluded from the study definition; and where studies had adjusted for potential confounding factors. Nor were they independent, with MWOMEN[24], with its very high RR, having all the three characteristics associated with an increased risk.


A
Study
RR (95%CI)
ACE 18.56 (9.07 - 37.96)
AEROBIC 7.56 (5.15 - 11.09)
AHS 23.03 (17.34 - 30.59)
ARIC, m 41.41 (18.36 - 93.42)
ARIC, f 13.13 (8.46 - 20.41)
ATP, m 9.33 (3.82 - 22.84)
ATP, f 23.40 (12.26 - 44.63)
BWHS 11.78 (8.55 - 16.24)
COAL 9.20 (5.30 - 16.00)
CPSI, m 12.22 (9.59 - 15.58)
CPSI, f 2.73 (2.07 - 3.61)
CPSII, m 23.81 (19.85 - 28.57)
CPSII, f 12.65 (11.15 - 14.34)
FRAMING 7.55 (4.94 - 11.55)
HPFS 12.56 (6.02 - 26.22)
KAISER 13.20 (11.10 - 15.70)
NHANES 17.32 (10.50 - 28.56)
NHIS, f 17.80 (11.40 - 27.80)
NHIS, m 14.60 (9.10 - 23.40)
NHS 23.30 (19.00 - 28.80)
NIHAARP, f 19.50 (17.20 - 22.20)
NIHAARP, m 29.40 (25.20 - 34.30)
NLMS 11.82 (10.73 - 13.03)
NLST 24.32 (10.98 - 53.85)
NONMET 7.97 (4.17 - 15.27)
PLCO 31.97 (25.16 - 40.63)
SCCS, m 13.02 (8.41 - 20.16)
SCCS, f 15.66 (11.64 - 21.08)
SHEETME 7.92 (5.97 - 10.51)
USA5, m 24.97 (22.20 - 28.09)
USA5, f 25.66 (23.17 - 28.40)
VETERAN 16.82 (6.11 - 46.34)
VITAL 24.67 (18.64 - 32.65)
WHI 13.44 (10.80 - 16.74)
Total (random-effects) 15.15 (12.77 - 17.96)
0.1
1
10
100


B
Study
RR (95%CI)
AGRICAN, m 28.84 (20.35 - 40.87)
AGRICAN, f 16.53 (9.44 - 28.95)
AMIANT 5.58 (3.07 - 10.13)
BIOBANK, f 13.25 (10.70 - 16.41)
BIOBANK, m 18.08 (14.13 - 23.14)
EPIC, m 32.00 (21.38 - 47.90)
EPIC, f 7.53 (5.87 - 9.66)
ESTHER 12.13 (7.00 - 21.02)
HBC 4.20 (1.60 - 11.10)
KRIS 10.47 (6.74 - 16.25)
MWOMEN 21.20 (19.50 - 23.10)
NLCS, m 7.57 (6.18 - 9.29)
NLCS, f 8.23 (6.57 - 10.30)
NOWAC 11.89 (9.66 - 14.64)
QRESEAR, m 7.35 (4.54 - 11.90)
QRESEAR, f 7.13 (4.47 - 11.37)
THIN 10.83 (8.77 - 13.38)
THREEC, m 16.78 (10.31 - 27.33)
THREEC, f 24.72 (14.45 - 42.27)
VLAGT, m 77.14 (4.81 - 1236.55)
VLAGT, f 9.27 (4.45 - 19.28)
Total (random-effects) 12.30 (9.77 - 15.49)
0.1
1
10
100

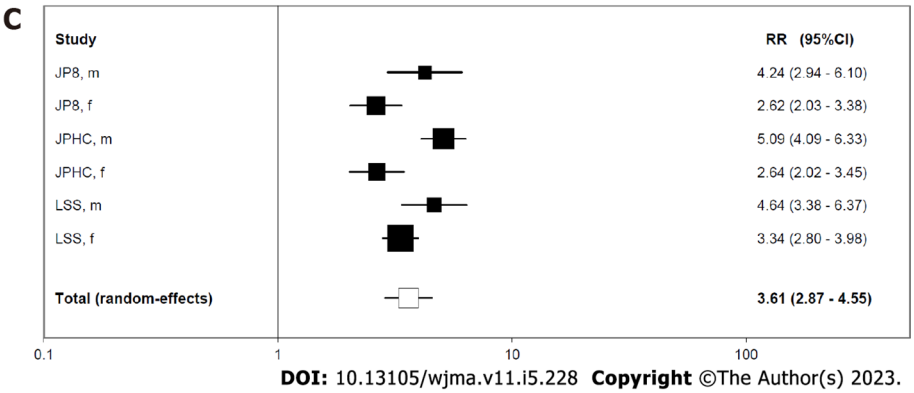


Figure 3 Forest plot for lung cancer and current *vs* never cigarette smoking. A: North America; B: Europe; C: Japan.

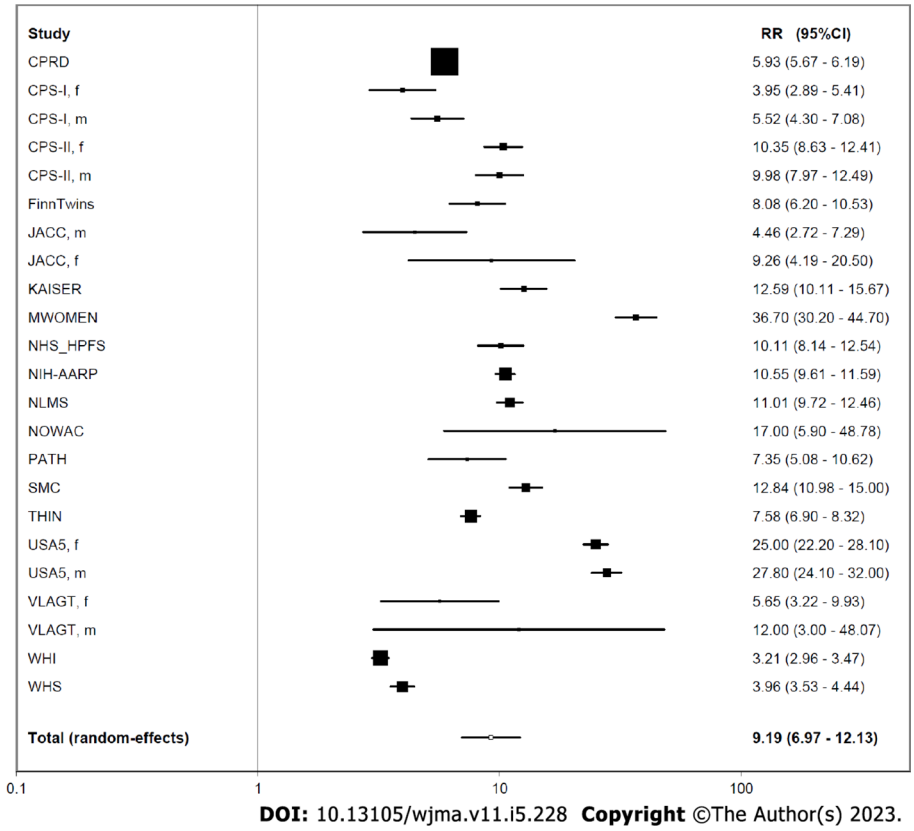


Figure 4 Forest plot for chronic obstructive pulmonary disease and current *vs* never cigarette smoking.

Within-study comparisons for cigarette smoking: There were five otherwise comparable pairs of male and female RRs from the same study (see Supplementary material 2). The male RR was the higher in three pairs, and the female RR was the higher in two, and the random-effects estimate of the male/female ratio was not significant (ratio 1.08, CI 0.88-1.34).

There were 15 pairs of unadjusted RR estimates and estimates adjusted for two or more covariates. Adjustment increased the RR in 13 of these, and decreased it in two ($P < 0.01$), emphasising the conclusion from the previous section. The increase was greater by a factor of 1.5 in 5 of the 14 increases, with a decrease by a similar factor in one case, the adjusted/unadjusted factor varying from 0.65 to 3.17.

Except for in four studies (CPS-I[26], CPS-II[26], USA5[26], VLAGT[27]), where the female RR was taken to be for exclusive cigarette smoking but the male RR was not, the only other characteristic varying within study was latency. Here MWOMEN[24] gave similar adjusted RRs of 35.30 (CI 29.20-42.50) based on analyses involving the whole follow-up, and 36.70 (CI 30.20-44.70) based on analyses excluding occurrences in the first few years of follow-up.

Cigar and pipe smoking results

Lung cancer: The full output for cigar smoking is given in Supplementary material 3. The data are very limited, coming from one study in the US (NLMS[28]), one in the Netherlands (NLCS[29,30]) and one of multiple studies in Europe (EPIC[31,32]), with the RR estimate from NLCS based on far more lung cancer cases in current cigar smokers (520) than seen in NLMS (11) or EPIC (3). Only an unadjusted RR estimate was available from NLCS, while the other studies provided RRs by level of adjustment. All the RR estimates are in the range 2.68 to 4.71, with the combined random-effects estimate, based on the most adjusted data, being 2.73 (CI 2.36-3.15), with no evidence of heterogeneity ($P > 0.1$).

The full output for pipe smoking is given in Supplementary material 4. Again, the data are very limited, coming from the same three studies as for cigar smoking (NLMS, NLCS and EPIC), plus one in Norway (THREEC[20]). The most precise RR estimate comes from NLCS. As for cigars, RR estimates by level of adjustment were available from each study except for NLCS. Based on the most adjusted data the overall random-effect RR estimate was 4.93 (CI 1.97-12.32), the wide confidence interval reflecting the highly significant heterogeneity ($P < 0.001$), with individual study most-adjusted RRs being over 10 for two studies (EPIC 13.30, THREEC 10.32) and under 3 for the other two (NLMS 1.51, NLCS 2.80).

COPD: The data for pipe and cigar smoking, shown in Supplementary material 5, are very limited, coming from only one study, which was conducted in the US (NLMS[28]). This reported combined sex RRs for exclusive cigar smoking *vs* never smoking of 2.21 (CI 0.89-5.47) adjusted for age only, and of 2.44 (CI 0.98-6.05) after additional adjustment for sex, race/ethnicity, education and survey year. The corresponding estimates for exclusive pipe smoking were, respectively, 1.04 (CI 0.27-4.10) and 1.12 (CI 0.29-4.40).

Comparison within study of current cigarette smoking RRs for lung cancer and COPD

There were eleven studies, seven in the US and four in Europe, which provided comparable results for both lung cancer and COPD. For seven of the studies (CPS-II, Kaiser, NIH-AARP, NLMS, THIN, VLAGT and WHI) the RRs were higher for lung cancer than for COPD, while for two (MWOMEN and NOWAC) the RRs were lower. For USA5 the RRs were very similar in both sexes, being slightly higher for lung cancer for females and slightly higher for COPD for males. For CPS-I the RRs were clearly higher for lung cancer in males and slightly higher for COPD in females. (See Supplementary material 1 and 2 for the RRs). These within-study comparisons are consistent with the higher overall RR estimates for lung cancer than for COPD.

DISCUSSION

Lung cancer

Comparison with earlier reviews – cigarettes: Our conclusion that current cigarette smokers have a substantially increased risk of lung cancer is consistent with that of major bodies (*e.g.*[1,2]). Our overall random-effects RR estimate of 12.14 (CI 10.30-14.30) for current *vs* never cigarette smoking is not dissimilar from an estimate of 10.92 (CI 8.28-14.40) from a meta-analysis based on 34 cohort studies published in 2013[13] (though based on current *vs* non rather than current *vs* never cigarette smoking), and somewhat higher than estimates of 7.33 (CI 4.90-10.96) for males and 6.99 (CI 5.09-9.59) for females based on 99 cohort studies published by 2016[16] and of 8.43 (CI 7.63-9.31) based on our earlier meta-analysis, of studies published in the 20th century[4].

We also found much higher RR estimates for North America (15.15) and Europe (12.30) than for Japan (3.61). Strong evidence of regional variation in risk is also evident based on publications in the 20th century[4], where RRs for current *vs* never smoking of any product were 11.68 (CI 10.61-12.85) for North America, 7.53 (CI 5.40-10.50) for the UK, 8.68 (CI 7.14-10.54) for Scandinavia, 8.65 (CI 5.98-12.51) for other regions of Europe, 2.94 (CI 2.23-3.88) for China, 3.55 (CI 3.05-4.14) for Japan and 2.90 (CI 2.04-4.13) for other regions of Asia. Similar, relatively low, RRs have been reported based on meta-analyses conducted in Japan[6,15] or in the whole of Asia[7,17], while relatively high RRs for Europe and the US have been reported in recent meta-analyses or large studies[10,13,33,34]. There is considerable heterogeneity between the estimates from different studies, with, for example, 11 of the 34 selected RR estimates for North America exceeding 20, and 7 less than 10. However, the fact that the highest of our six individual RR estimates for Japan was 5.09 emphasises the regional difference, with a very recent large study in China[35] having also reported similarly relatively low RRs for smoking.

Our analyses show a somewhat higher RR in males than females, with the within-study comparison estimating the ratio as 1.52 (CI 1.20-1.92). A similar difference was also seen in our earlier meta-analyses [4] where the RRs were 9.16 (CI 8.00-10.49) for males and 6.76 (CI 5.65-8.08) for females. Other recent reviews or analyses of large studies have all also reported a higher RR in males, though with one exception, where the RRs from a pooled analysis of case-control studies were 23.6 (CI 20.4-27.2) for males and 7.8 (CI 6.8-9.0) for females[10], the RRs for the others[6,7,15,16] were at most 60% higher in males.

Of the other factors studied in our latest analyses (see Table 2) some were not considered earlier. Of those that were, neither set of analyses showed any clear variation by study size, by study type, by whether the exposed group smoked exclusively cigarettes or not, or by the extent of adjustment for potential confounding factors. There was a tendency for RRs to be greater for studies starting later, more clearly seen in the earlier analyses, a difference which may partially explain why the RRs tend to be somewhat higher for the later than for the earlier analyses.

Comparison with earlier reviews – cigars and pipes: Our combined RR of 2.73 (CI 2.36-3.15) for cigar smoking was based on estimates from only three studies. It is somewhat lower than the RR of 4.67 (CI 3.49-6.25) reported in our earlier review[4] based on 15 estimates, though there the individual study estimates showed marked heterogeneity ($P < 0.001$) with three RRs above 10 and four less than 4, the two having the greatest weight being the RRs of 3.30 (CI 2.68-4.06) and of 5.20 (CI 4.10-6.60) derived from the American Cancer Society CPS I and CPS II studies[36,37]. It is also not dissimilar from estimates of 2.98 (CI 2.08-4.26) from a recent review of US studies[18], of 1.87 (CI 0.53-6.55) from a more recent US study[33,34] and of 2.73 (CI 2.06-3.60) from five US cohorts[14] based on ever *vs* never smoking.

Our combined RR estimate of 4.93 (CI 1.97-12.32) for pipe smoking was based on estimates from only four studies which were markedly heterogeneous ($P < 0.001$). It is similar to that of 5.20 (CI 3.50-7.73) reported earlier[4] based on 12 estimates for current pipe only smoking. These 12 estimates also showed marked heterogeneity ($P < 0.001$), with three RRs above 10 and three less than 4, the two having the greatest weight being that of 5.85 (CI 4.52-7.58) derived from the West European case-control study[38] and of 2.14 (CI 1.46-3.13) from the US veterans study[39]. These estimates are not dissimilar from the more recent estimates of 5.00 (CI 4.16-6.01) from the US CPS II study[40] or of 3.18 (CI 1.35-7.52) from an analysis of five US cohorts[14] based on ever *vs* never smoking.

The available data were too limited to study sources of variation in the results for cigar and pipe smoking in the same way that we addressed them for cigarette smoking.

Comparison of risks by tobacco product: Our results suggested that RRs for current cigar smoking and for current pipe smoking are substantially lower than for current cigarette smoking, though the individual study results for pipe smoking are rather heterogeneous. This conclusion is consistent with the results of our previous review[4]. Although the risks we found for cigar and pipe smoking are lower than for cigarette smoking we agree with McCormack *et al*[31], 2010, who concluded that smoking of these products is "not a safe alternative to cigarette smoking" and suggested that "the lower cancer risk of pipe and cigar smokers as compared to cigarette smokers is explained by lesser degree inhalation and lower smoking intensity". Christensen *et al*[28], 2018, considered that the lower risks for pipe and cigar smoking are probably because "cigar and pipe smokers use these products less frequently per day than cigarette users."

Exceptionally, based on a study in Norway, Tverdal *et al*[20], 2011 concluded that "pipe smoking is not safer than cigarette smoking" but the overall evidence reviewed seems inconsistent with this conclusion. It should be noted that all four of the RRs for pipe smoking given in Supplementary material 3 are lower than the corresponding estimates for cigarette smoking from the same study given in Supplementary material 1 (EPIC 13.30 *vs* 32.00, THREEC 10.32 *vs* 16.78, NLCS 2.80 *vs* 7.57, NLMS 1.51 *vs* 11.82), the results from THREEC being those reported by Tverdal and Bjartveit, 2011[20].

COPD

Comparison with earlier reviews – cigarettes: We found clear evidence that current cigarette smokers, compared to never smokers, have a substantially increased risk of COPD, with an overall RR estimate of 9.19 (CI 6.97-12.13). As for lung cancer, this conclusion of a strong relationship is consistent with that of major bodies (*e.g.*[1,2]). Some earlier reviews have given rather lower RR estimates; 4.01 (CI 3.18-5.05) based on cohort studies published by 2013[13] but for current *vs* non smoking, 3.57 (CI 2.72-4.70) based on studies in Japan published by 2016[15], 3.51 (CI 3.08-3.99) based on studies published by 2006[5] and 3.26 (2.67-3.98) based on studies published by 2014[12].

However, there was considerable heterogeneity between the estimates from the different studies, with the RR estimates varying from 3.21 to 36.70. We found no significant ($P < 0.05$) variation in RR by sex or by region, though the direction of effect – higher RRs in males and in North American and European studies – was the same as that seen more clearly in our earlier review based on 133 studies published up to 2006[5]. Our analyses also found some marginally significant ($0.05 < P < 0.1$) evidence that RRs tended to increase with greater adjustment for potential confounding variables, a finding confirmed by within-study comparisons, but not found in our earlier review[5]. This earlier review also found differing RR estimates of 7.47 (CI 4.63-12.05) for exclusive cigarette smoking, and of 3.06 (CI 2.60-3.60) for cigarette smokers who may also have smoked other products. Though our corresponding estimates of 9.48 (CI 5.25-17.14) and 9.02 (CI 6.78-12.00) are not inconsistent with exclusive cigarette smokers having a higher risk, the difference here was not significant (at $P < 0.05$). As shown in Table 4 there was also marginally significant evidence of increased risk for two factors not considered in our earlier review - where cases occurring shortly after baseline were ignored (so as to avoid an effect of pre-existing symptoms affecting baseline smoking habits), and where bronchiectasis was excluded from the

definition of COPD.

Comparison with earlier reviews – pipes and cigars: We only found one study published in 2010-2020, the NLMS study in the US[28], which reported RRs for current cigar smoking and for current pipe smoking, predominantly occurring in males. The adjusted RRs from this study, 2.44 (CI 0.98-6.05) for current cigar smoking, and 1.12 (CI 0.29-4.40) for current pipe smoking, are imprecise, but seem not inconsistent with earlier published evidence.

For current cigar smoking, a recent review of evidence from the US[18] reported a combined estimate of 1.44 (CI 1.16-1.77) based on four studies, while another review[11], which did not provide meta-analysis results, reported estimates for males from two older studies, 1.30 (CI 0.00-7.45) from the Swedish Census study[41] and 3.70 (CI 1.10-12.0) from the Copenhagen City study[42].

Current pipe smoking estimates from the US included that of 2.36 from the Dorn study[43] (where we derived an approximate CI of 1.12-4.96 from the data provided) and of 2.98 (CI 2.17-4.11) from the CPS II study[40], while estimates from the Swedish study[41] and Copenhagen City study[42] were, respectively, 3.60 (with a derived approximate CI of 2.51-5.14) and 2.40 (CI 0.60-9.60).

Comparison of risks by tobacco product: While the estimates cited above do not allow reliable conclusions as to whether, in the US or Europe, the COPD RR differs between current cigar smokers and current pipe smokers, it is clear that the risks for both products are substantially less than those for current cigarette smokers, where the meta-analysis results shown in Table 4 are 8.91 (CI 5.73-13.84) for the US and 10.63 (CI 6.93-12.24) for Europe.

Comparing risks by tobacco product - similarity of results for lung cancer and COPD

In many ways, the results for the two diseases are quite similar. Thus, our meta-analysis RR estimates for cigarette smoking, 12.14 (CI 10.30-14.30) for lung cancer and 9.19 (CI 6.97-12.13) for COPD, both show a very strong relationship, and indeed every single RR estimate for both diseases shown in the forest plots (Figures 3 and 4) is statistically significantly increased. For both diseases, the meta-analysis estimate for cigarette smoking is also substantially greater than the corresponding estimates for cigar smoking, 2.73 (CI 2.36-3.15) for lung cancer and 2.44 (CI 0.98-6.05) for COPD, and for pipe smoking, 4.93 (CI 1.97-12.32) for lung cancer and 1.12 (CI 0.29-4.40) for COPD, though based on much more limited data. For both diseases, the RR estimates for cigarette smoking are also greater based on studies in North America and Europe than on studies in Japan, most clearly evident for lung cancer. They are also quite similar for males and females, and there is no strong evidence of variation by the other factors studied.

General considerations

While the evidence that cigarette smoking increases the risk of lung cancer and of COPD is absolutely clear, the RR estimates for both diseases show substantial between-study heterogeneity. There are multiple reasons for this, many inter-related, and only some of which we have investigated. Thus, populations in different regions and studies may vary in age and race which may affect precisely what is smoked, the daily amount smoked and the duration of exposure. Males and females may also vary by amount smoked. Study populations may also vary in the extent of exposure to other lung cancer and COPD risk factors, and the extent to which adjustment for this is made in the RR estimation. Variation between studies in the exact definition of the exposed and the unexposed groups is also an issue, only some studies considering exclusive exposure or restricting attention to smoking of some minimum lifetime number of cigarettes. Misclassification of smoking is also an issue, with some of those reporting never having smoked actually being current or former smokers, the studies considered generally not using nicotine biomarkers such as cotinine to check self-reports of smoking. Cohort studies also vary in the extent to which they monitor changes in an individual's smoking over time, some studies only classifying subjects by baseline status, when current smokers may have subsequently quit or switched to other products, including e-cigarettes or heat-not-burn products, and some baseline never smokers may have later taken up smoking. Also, the precise definition of disease may vary between studies, as may changes over time in how lung cancer and COPD are treated, so affecting survival, possibly differently for current and never smokers. Some of these factors may also help to explain variations between our results and those reported in other studies or meta-analyses.

Limitations of our work

While limited to studies in North America, Europe and Japan, our work gives good insight into the magnitude of the RR for current *vs* never use of cigarettes for both lung cancer and COPD, as was the main objective of our meta-analysis. Although heterogeneity of the RR estimates from the individual studies limits the precision of the overall estimates, we have attempted to investigate a range of individual factors that contribute to the heterogeneity. However, it would have been possible to carry out multivariate analyses investigating the extent to which RR estimates varied according to the list of factors studied. For cigar and for pipe smoking, our estimates for both diseases are also limited by the small number of studies that investigated these products. Some limitations are caused by the unfortunate lack of clear definition of the product used in some of the source publications, with the term

"smoking" used variously for any tobacco product use, cigarette smoking or exclusive cigarette smoking. While we have attempted to determine the meaning as best we can, some errors may remain.

Other limitations arose as the objectives of our study were less than those of our earlier meta-analyses of lung cancer studies published in the 20th century[4], or COPD studies published up to 2006[5]. Thus, our investigations did not consider aspects of tobacco smoking, including amount smoked, duration of smoking, age of starting to smoke, the effect of quitting, and risks associated with the use of multiple products. Nor did it consider the role of e-cigarettes which were introduced towards the end of the follow-up period in some of the cohort studies. Nor did it consider results for individual histological types of lung cancer or subgroupings of COPD or for individual types of cigarettes, cigars and pipes. Nor did we attempt to quantify how misclassification of exposure, disease, or confounding variables might have biased the RR estimates.

CONCLUSION

Results from 44 studies published in 2010-2020 confirm the strong association of current cigarette smoking with lung cancer risk, with RR estimates markedly higher for North American and European studies than for studies in Japan, and somewhat higher in males than in females, in cohort than in nested case-control studies, and in studies that excluded cases occurring shortly after baseline. Only limited evidence on lung cancer is available for cigar and pipe smoking, all from North America and Europe. While this indicates lower lung cancer risks than for cigarette smoking, the results for pipe smoking are rather heterogeneous.

Results from 18 studies published over the same period also confirm a strong association of current cigarette smoking with COPD risk, though the RR estimates, which are somewhat lower than for lung cancer, do not vary significantly by region or sex. While the COPD RR estimates are markedly heterogeneous no study or RR characteristic was found that explains a major part of this variation. Only one study, in the US, provided evidence on COPD for current cigar and current pipe smoking, and while this suggested lower risks than for cigarette smoking, its results are uncertain.

It is clear that smoking, particularly of cigarettes, markedly increases the risks of developing lung cancer and COPD. To most effectively reduce these risks, smokers should quit smoking[44,45], though alternative nicotine-containing products may substantially reduce these risks. This is clearest for Swedish snus[46-48] where considerable epidemiological evidence is available. However, it also may be true for much newer products, such as e-cigarettes and heated tobacco products which have toxicant levels that are lower by an average of > 90% compared with cigarette smoke[49]. An earlier expert opinion[50] also considered that e-cigarettes cause about 5% of the harm of cigarettes, and less than the harm caused by cigar or pipe smoking.

ARTICLE HIGHLIGHTS

Research background

While there are extensive data on the risks from smoking, these risks may change over time, and up-to-date evidence is needed for cigarette, cigar and pipe smoking.

Research motivation

To obtain recent evidence comparing the risks of major smoking-related diseases due to the use of various tobacco products.

Research objectives

To summarize data relating current smoking of cigarettes, cigars and pipes in North America, Europe and Japan to the risk of lung cancer and chronic obstructive pulmonary disease (COPD).

Research methods

MEDLINE searches identified English publications in 2010-2020 providing data on risks of one or both diseases relating to current (*vs* never) smoking of cigarettes, cigars or pipes in the three regions. The studies had to be of cohort or nested case-control design or be randomized controlled trials, involve at least 100 cases of the diseases of interest, and not be restricted to specific types of the disease, to patients with specific medical conditions or report results superseded by later results from the same study. Relative risk estimates were extracted for each study and combined using random meta-analyses.

Research results

Results for lung cancer were available from 44 studies and for COPD from 18, predominantly from North America and Europe. For current cigarette smoking, overall RR estimates were 12.14 for lung

cancer and 9.19 for COPD. Estimates were slightly but not significantly higher for males than females. Estimates were relatively low in Japan, particularly for lung cancer, where RRs of 3.61 for Japan compared with those of 15.15 for North America and 12.30 for Europe. No highly significant variations were seen for other factors studied, though for COPD estimates were higher (17.45) where the disease definition excluded bronchiectasis. Few of the studies provided evidence on current cigar or pipe smoking, all from the US or Europe. Estimated RRs for cigar smoking, 2.73 for lung cancer and 2.44 for COPD, and for pipe smoking, 4.93 for lung cancer and 1.12 for COPD, were lower than for cigarette smoking, though based on limited data, with notable heterogeneity for pipe smoking for lung cancer.

Research conclusions

Consistent with evidence from earlier studies, risks for cigar and pipe smoking are much less than for cigarette smoking, both for lung cancer and COPD. Risk of lung cancer from cigarette smoking is much less in Japan than in the US or Europe.

Research perspectives

Smoking significantly increases the risks of developing lung cancer and COPD, with risks highest for cigarette smoking. To most effectively reduce these risks, smokers should quit, though evidence suggests that using alternative nicotine-containing products, such as snus, e-cigarettes and heated tobacco products should also substantially reduce these risks.

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FOOTNOTES

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

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

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REVIEW

Overview of angiogenesis and oxidative stress in cancer

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Abstract

Neoplasms can be considered as a group of aberrant cells that need more vascular supply to fulfill all their functions. Therefore, they promote angiogenesis through the same neovascularization pathway used physiologically. Angiogenesis is a process characterized by a heterogeneous distribution of oxygen caused by the tumor and oxidative stress; the latter being one of the most powerful stimuli of angiogenesis. As a result of altered tumor metabolism due to hypoxia, acidosis occurs. The angiogenic process and oxidative stress can be detected by measuring serum and tissue biomarkers. The study of the mechanisms underlying angiogenesis and oxidative stress could lead to the identification of new biomarkers, ameliorating the selection of patients with neoplasms and the prediction of their response to possible anti-tumor therapies. In particular, in the treatment of patients with similar clinical tumor phenotypes but different prognoses, the new biomarkers could be useful. Moreover, they may lead to a better understanding of the mechanisms underlying drug resistance. Experimental studies show that blocking the vascular supply results in antiproliferative activity *in vivo* in neuroendocrine tumor cells, which require a high vascular supply.

Key Words: Neuroendocrine lung tumors; Angiogenesis; Oxidative stress; Neuroendocrine serum markers; Neuroendocrine tissue markers; Future therapy

Core Tip: There are already several reviews in the literature that contribute to understanding angiogenesis and oxidative stress. However, this is the first review to report the latest cellular and molecular mechanisms of angiogenesis pathways while also discussing the genetics and biochemistry of oxidative stress in neoplasms. We also specifically discuss neuroendocrine lung tumors. These discoveries may be useful for new clinical and translational research studies.

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INTRODUCTION

The angiogenesis process consists of the generation of new blood vessels. The migration and proliferation of endothelial cells from already existing vessels to new vessels are crucial in this process. During embryonic development, these cells are particularly active, whereas in the adult their turnover is slow and limited to certain physiological phenomena, such as ovulation, tissue repair, and scarring processes[1].

Angiogenesis is the result of a well-balanced process between proangiogenic and antiangiogenic factors. This balance can fail due to specific stimuli such as hypoxia, creating a pathological angiogenic process[2]. The prevalence of proangiogenic factors is associated with serious diseases, such as cancer, and with inflammatory and degenerative diseases, such as retinopathies, rheumatoid arthritis, and psoriasis. Insufficient angiogenesis is the basis of obliterating vascular diseases, such as obstructive coronary artery disease or peripheral obstructive arterial disease (Buerger's disease), which are characterized by the downstream tissue ischemia of vascular occlusions[3].

Neoplasms can be considered complex biological structures constituted by aberrant cells and endowed with specific functions; there are mesenchymal-derived cells, inflammatory cells, and vascular cells communicating with one another [4]. To fulfill all their functions, including growth and metastasis, they can promote angiogenesis through the same neovascularization pathway used physiologically. Tumor progression occurs due to the proliferation of the tumor cells themselves and the interactions that the neoplasm sets up within the tumor microenvironment where distinct types of tumor cells secrete key cytokines[5] for tumor progression and metastasis[6].

Cancer cells in active and continuous replication need a constant supply of oxygen and nutrients. For this reason, the first mechanism that cancer cells use to ensure the survival and growth of its cells is angiogenesis. However, neoplastic angiogenesis is an aberrant process associated with the formation of tortuous vessels that are insufficient to fulfill cellular needs. Acidosis is the consequence of altered tumor metabolism in response to hypoxia and the heterogeneous distribution of oxygen between the core and periphery that tumor angiogenesis helps to create. In this way, the acidic environment selects a more aggressive neoplastic cell phenotype with a greater invasive and metastatic phenotype.

Metabolic, hypoxic, and oxidative stress is considered a distinctive marker of cancer[7]. To survive the metabolic stresses, cancer cells activate different types of mechanisms including evasion of apoptosis and immune surveillance, increasing the angiogenic activity to enhance the provision of oxygen and nutrients, activation of the epithelial-mesenchymal transition (EMT), and metastasis[7,8]. Positive feedback between angiogenesis and oxidative stress is evident when a cellular mechanism stands for both the stimulus and the result of this process (Figure 1).

Tumor-induced angiogenesis begins with the release and activation of many growth factors[9]. The most important of which is vascular endothelial growth factor (VEGF) with its receptors. The mechanism of angiogenesis is complex, and it passes through stages well defined by changes in the endothelium and the extracellular matrix[10]. It can be schematically described as follows. The first stage of angiogenesis is characterized by the "destabilization" of pre-existing vessels and the loss of connection between endothelial cells due to increased vascular permeability. The proliferation phase of the endothelial cells follows with the formation of new vessels. Various proteolytic enzymes are released during these phases and alter the density of the extracellular matrix to help the migratory activity of endothelial cells. The third stage of angiogenesis is characterized by the formation of primitive capillaries. Finally, the last stage involves the recruitment of supportive periendothelial cells, such as pericytes and muscle cells, as well as the reorganization of periendothelial cells [11].

The most powerful stimulus for angiogenesis is hypoxia. Hypoxia and angiogenic factors released by the tumor destabilize the pericytes and stimulate continuous angiogenesis[12]. Tumors maintain hypoxia primarily due to the heterogeneous distribution of oxygen between the core and the periphery that cancer cells generate[13]; this situation is also associated with acidosis. By maintaining a low pH, cancer cells can evade immune cells and be chemoresistant[14].

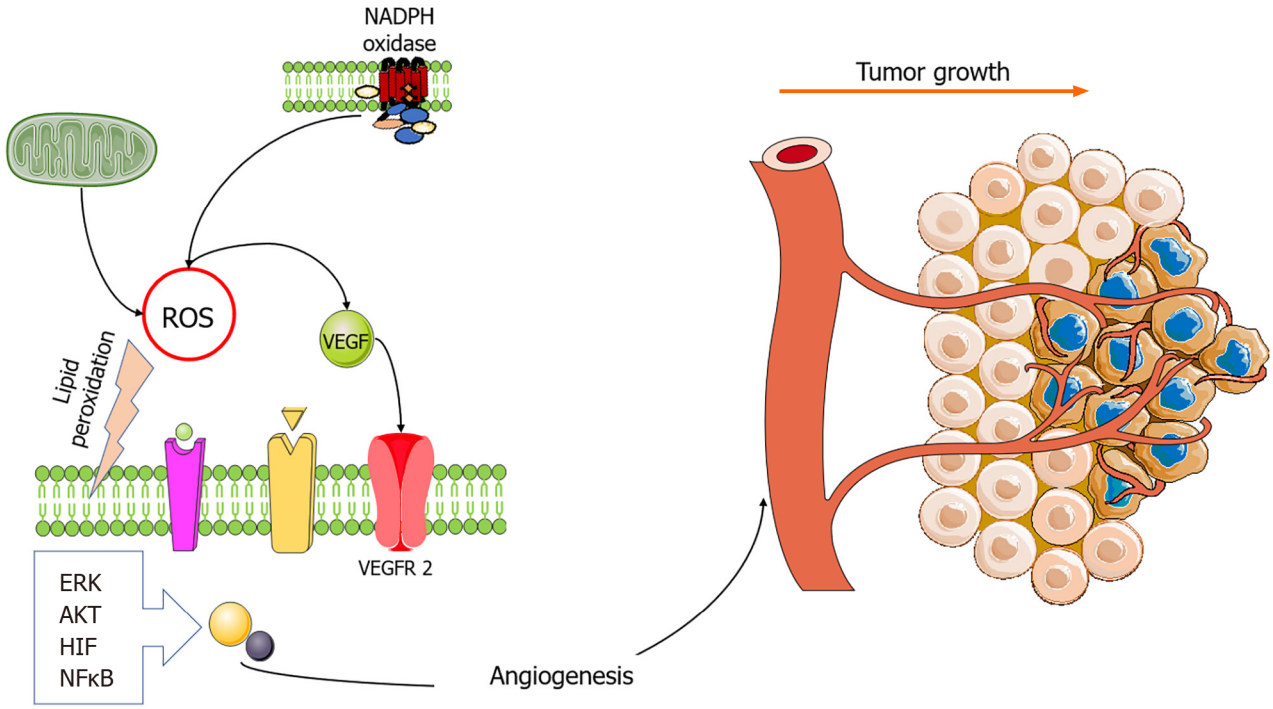

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Figure 1 The two main sources of oxidative stress, mitochondria, and nicotinamide adenine dinucleotide oxidases generate reactive oxygen species that trigger angiogenesis. The vascular endothelial growth factor (VEGF) pathway is modulated by reactive oxygen species (ROS), and oxidative stress stimulates VEGF production in several cell types, including endothelial cells. ROS enhance angiogenesis by increasing hypoxia-inducible factor (HIF) 1 α, protein kinase B (AKT), and regulated extracellular kinase (ERK). However, oxidative stress also induces angiogenesis in a VEGF-independent manner by lipid peroxidation and generating metabolites that act either as ligands or by inducing post-translational modifications of proteins within angiogenic signaling pathways, such as nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) activation pathways. Figure was prepared using images from Servier Medical Art by Servier (https://smart.servier.com), which are licensed under a Creative Commons Attribution 3.0 Unsupported License. NADPH: Nicotinamide adenine dinucleotide; VEGFR2: Vascular endothelial growth factor receptor 2.

Reactive species, mainly represented by reactive oxygen species (ROS), are products generated by metabolic reactions that take place in the mitochondria of eukaryotic cells. If these reach a certain level they can be toxic to the cells. Physiological concentrations of reactive species can generally transduce signals before they are eliminated, whereas tumor cells need high concentrations of ROS to support their high proliferation rate due to their metabolism[15].

Among the several cellular strategies adopted by tumors to develop resistance to ROS are the so-called alternative metabolic pathways. These pathways prevent the accumulation of ROS without reducing the metabolic energy required by the tumor cells. The glycolysis with its parallel pathway and the pentose phosphate pathway, are examples of these pathways. The ROS levels are a sign of the damage that cells can withstand[16].

The therapeutic implications that follow are particularly important since the radiotherapy and chemotherapy currently available conduct their antitumor action precisely through the regulation of ROS levels. Therefore, the clinical response to pro-oxidant therapies has to be considered to enable truly personalized therapies. Consequently, the discovery of biomarkers capable of predicting this response is a challenge[17].

Somatostatin is a ubiquitous polypeptide produced by the delta cells of the digestive system and is present in the intramural plexuses of the intestine. Tumors originating from these cells produce and secrete somatostatin. Somatostatin exists in two biologically active forms, namely SS-14 and SS-28[18].

Several functions of somatostatin in the central nervous system are described. These include neuromodulatory, locomotor, and cognitive functions, inhibition of basal and stimulated secretion of distinct types of endocrine and exocrine cells, and regulation of cell proliferation and differentiation[19]. Specific membrane receptors are bound by somatostatin, of which there are five different subtypes called somatostatin receptors 1-5 (SSTR 1-5). These have maintained structural homology between distinct species (40%-60% of structural homologies) and mediate different biological actions by activating different intracellular signaling pathways[20,21].

Tumors that produce somatostatin have a typical histological architecture common to all neuroendocrine tumors (NETs) and a high somatostatin production. Somatostatin is a powerful inhibitor of neovascularization as many experimental data have shown. SSTR are expressed on endothelial cells, and the activation of quiescent endothelium is associated with an upregulation of SSTR2.

Somatostatin agonists inhibit VEGF, basic fibroblast growth factor, and growth hormone/insulin-like growth factor 1. Consequently, they can negatively regulate angiogenesis[22]. Furthermore, somatostatin can function as a powerful antitumor agent *in vivo* inhibiting both endothelial nitric oxide synthase and mitogen-activated protein kinases (MAPK) through SSTR3[23].

NETs represent a neoplasm that most benefit from metabolic radiotherapy and treatment with antiangiogenesis and pro-oxidant drugs. The presence of marked vascularization is a distinctive feature in most NETs, and this characteristic can be considered one of the diagnostic markers of neuroendocrine pathology[24]. Several studies have shown that microvascular density is 10 to 30 times greater in NETs than in other carcinomas[25].

TUMOR ANGIOGENESIS

As previously mentioned, the most important tumor-induced angiogenesis mediator is VEGF and its receptors[9] (Table 1). Six subtypes of VEGF are recognized: VEGF-A; VEGF-B; VEGF-C; VEGF-D; VEGF-E; and placental growth factor[26]. VEGF-C and VEGF-D take part in lymphangiogenesis. VEGF-A plays a dominant role in the angiogenesis process and is simply referred to as VEGF[27].

VEGF gene transcription is regulated by hypoxia-inducible factor (HIF), which is a protein composed of a constant subunit (HIF-1β) and an oxygen-regulated subunit (HIF-1α or HIF-2α)[28]. In response to hypoxia, the level of VEGF increases significantly in the extracellular space. High concentrations of VEGF determine the degradation of the basement membrane and the destabilization of the pericytes, the growth of endothelial cells, and the formation of new vessels[29]. This process is highly involved in tumor progression and when small tumors receive their nourishment by passive diffusion[30]. Those over 2 mm^2 undergo the formation of a hypoxic central core that stimulates the angiogenesis process [31]. This phase is called the "angiogenic switch" and is the release of many mediators of angiogenesis by the tumor cells in response to the reduced oxygen supply[32].

There are different mechanisms by which neoplasms stimulate angiogenesis[33]. The first and most important mechanism is germinal angiogenesis, which leads to the formation of new vessels from pre-existing capillaries and small venules. The endothelial cells undergo reactivation resulting in the formation of small shoots that grow and migrate into the adjacent connective tissue. Subsequently, an immature vessel is formed, stabilizing after the recruitment of pericytes and the reconstitution of the basement membrane. The new vessels are characterized by fenestrated endothelial cells, a discontinuous basement membrane, and rare pericytes. Consequently, the vascular network is permeable without efficient flow regulation and has an aberrant morphology with irregularly branched and tortuous vessels[34].

Another mechanism of tumor neovascularization is co-optation. In this case, the cancer cells grow along the normal vascular network. This mechanism is mainly observed in the brain, liver, and lung. It is particularly important in the early metastatic processes. Intussusception is the division of a pre-existing vessel into two new vessels and has been described in some aggressive tumors. Finally, in the vascular mimicry mechanism, a formation of vessels from the tumor cells themselves is observed. This process is seen in many aggressive tumors[35].

Pericytes are smooth muscle cells that stabilize the vessel walls and protect the normal vessels themselves from anticancer drugs, guaranteeing and promoting their target action. Hypoxia and angiogenic factors released by the tumor destabilize the pericytes and facilitate continued angiogenesis[8]. The reduction in their number leads to an increase in permeability and consequently the interstitial fluid pressure[36]. This leads to a further reduction in perfusion, the distribution of anticancer drugs, and acidosis[37]. Interstitial fluid pressure can be considered a marker of response to anticancer therapy[38].

Hypoxia can promote chemoresistance by increasing the ATP-binding cassette efflux pumps. Hypoxic cells are less proliferative than their normoxic counterpart and are therefore less subject to the chemotherapeutic cytotoxic effect[39]. Hypoxia also contributes to reducing the response to immunotherapy because it reduces immune activity[40]. An increase in HIF1 levels prevents the activation of CD8+ T-helper lymphocytes, suppresses the cytotoxic effect of natural killer cells, and increases the expression of immunosuppressive mediators such as inducible nitric oxide synthase and interleukin (IL)-10 by dendritic cells.

Different therapeutic strategies have been developed in an attempt to make hypoxia an advantage. Drugs activated by an enzymatic reduction in a hypoxic environment with the production of cytotoxic compounds have been tested without a real confirmation in terms of clinical utility[41]. Similarly, attempts were made to increase the oxygen transport capacity of the plasma using hyperbaric therapy[42].

In 1993, Kim *et al*[43] treated a mouse model of rhabdomyosarcoma, glioblastoma, and leiomyosarcoma with anti-VEGF monoclonal antibodies, obtaining tumor growth arrest. Given the ineffectiveness of these antibodies *in vitro* this pioneering study showed how blocking the action of angiogenesis mediators had a direct effect on tumor growth. However, the effect of these drugs was not constant[44]. There are differences in antitumor responses based on dosage, duration of treatment, and tumor type.

Due to the tremendous vascularization that characterizes them, neuroendocrine lung tumors would most benefit from antiangiogenesis drugs. This observation refers to the architecture of normal endocrine glands that need a well-represented vascular network that allows continuous exchange between endocrine cells and the bloodstream including hormone secretion.

Another characteristic of NETs that would suggest an elective use of antiangiogenic therapy as the treatment of choice is their marked ability to synthesize and secrete elevated levels of VEGF-A[45]. In this aspect, they mimic the endocrine cells with the secretion of peptide hormones[46]. Pancreatic islet β cells show the secretion of elevated levels of VEGF-A, which appears to play a significant role in the development of the dense vascular network of normal endocrine tissues [47]. VEGF-induced angiogenesis is also important for tumorigenesis and tumor progression of NETs. The angiogenic phenotype is necessary for the transition from hyperplasia[48], and it can be blocked pharmacologically[49]. Even in this process, VEGF-A plays a decisive role[50].

Table 1 Proliferation, migration, and differentiation by several factors/inductors implicated in angiogenesis

Inductors	Proliferation	Migration	Differentiation
Heparin-binding peptide growth factors			
VEGF	Yes	Yes	Yes
PlGF	Weak	Yes	Unknown
FGF-1, FGF-2	Yes	Yes	Yes
PTN	Yes	Unknown	Yes
HIV-tat protein	Weak	Weak	Yes
PDGF	Yes	Yes	Yes
HGF/SF	Yes	Yes	Yes
Peptide growth factors that do not bind heparin			
TGF-α	Yes	Yes	Yes
TGF-β	Inhibition	No	Yes
EGF	Yes	Yes	Yes
IGF-I	Yes	Yes	Yes
Inflammatory mediators			
TNF-α	Inhibition	No	Yes
IL-8	Yes	Yes	Unknown
IL-3	Yes	Yes	Yes
Prostaglandins E1, E2	No	No	Yes
Enzymes			
PD-ECGF/TP	No	Yes	Unknown
COX-2	No	Yes	Yes
Angiogenin	No	Yes	Yes
Hormones			
Estrogen	Yes	Yes	Yes
Proliferin	Unknown	Yes	Unknown
Oligosaccharides			
Hyaluronan oligosaccharides	Yes	Yes	Yes
Gangliosides	Unknown	Unknown	Unknown
Hematopoietic factors			
Erythropoietin	Yes	Unknown	Yes
G-CSF	Yes	Yes	Unknown
GM-CSF	Yes	Yes	Unknown
Cell adhesion molecules			
VCAM-1	No	Yes	Unknown
E-selectins	No	Yes	Yes
Integrins	No	Yes	Yes
Semaphorins (Sema3 e 4D)	No	Yes	Yes
Other			
Nitric oxide	Yes	Unknow	Unknow
Angiopoietin-1	No	Yes	Yes

COX-2: Cyclooxygenase 2; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; HGF/SF: Hepatocyte growth factor/scatter factor; IGF: Insulin-like growth factor; IL: Interleukin; PD-ECGF/TP: Platelet-derived endothelial cell growth factor/thymidine phosphorylase; PlGF: Placental growth factor; PDGF: Platelet-derived growth factor; PTN, Pleiotrophin; TGF: Transforming growth factor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; VCAM: Vascular cell adhesion molecule.

The microvascular density of pancreatic NETs is higher in benign tumors than in malignant tumors and in this context is higher in low-grade than in high-grade malignant tumors. It is also characterized by a better prognosis. This observation is called the "neuroendocrine paradox." To explain this phenomenon, it has been hypothesized that in pancreatic NETs the vascular density is a marker of differentiation rather than of aggressiveness[51]. Like their normal counterpart, well-differentiated neuroendocrine cells do keep the ability to promote the formation of a dense vascular network. Conversely, the tumor angiogenesis mechanism of poorly differentiated neoplasms is secondary to hypoxia and aberrant genetic alterations. This does not signify the absence of angiogenic activity in well-differentiated NETs but that it is low per unit of time considered.

Little is known of the process of angiogenesis in NETs originating from organs other than the pancreas, and any available data are scarce and contradictory[52]. As far as the lung is concerned, it appears to be similar to the pancreas, with the presence of high vascular density in well-differentiated NETs and low in high-grade NETs. However, all aspects are not yet completely clear, and further studies are needed, particularly in the area of high-grade and metastatic cancers where antiangiogenic therapies would find their main application.

Several antiangiogenic target drugs have been successfully assessed in metastatic NETs such as anti-VEGFA, anti-VEGFR, and tyrosine kinase inhibitors. However, other drugs already in use in the therapy of NETs have also shown an antiangiogenic action. Among these are the analogues of somatostatin and interferon alpha. Somatostatin analogues have shown antiangiogenic properties *in vitro* by inhibiting the proliferation of endothelial cells and the synthesis and secretion of VEGF. However, data on their use *in vivo* are controversial, probably due to their insufficient ability to compete with VEGF and other proangiogenic factors[53]. The data in favor of the use of interferon alpha for the treatment of carcinoids seems more convincing. There is a significant reduction in intratumor microvascular density, but it is not associated with a reduction in circulating VEGF levels.

The development of resistance to antiangiogenic drugs is one of the major problems linked to their use, which is similar to other targeted therapies. This effect would explain the lack of long-term response and the so-called "angiogenic explosion" after their suspension. When anticancer drugs with antiangiogenic action are used at high dosages, they only have an acute antitumor effect that is not reflected long term.

Acute hypoxia due to massive and non-selective vascular destruction selects and facilitates only the most aggressive cancer cells, preventing immune surveillance, favoring metastases, and promoting resistance to anticancer treatments. Their use at low dosages as an adjuvant in chemotherapy regimens has instead shown efficacy thanks to the establishment of the so-called "vascular normalization" phenomenon[54]. This consists of the selective destruction of only immature and aberrant vascularity while respecting the normal one. Vascular normalization also passes through the fortification of the vessel wall as a result of the recruitment of pericytes. Finally, antiangiogenic drugs also determine a tumor microenvironment[40] effect of normalization due to the reprogramming of many tumor processes that target blood vessels.

Several studies showed[55] that the biological basis of resistance is not found in the genetic mutations that occur in the target molecules but rather in the establishment of a secondary angiogenesis pathway. Malignant cells can simultaneously synthesize and secrete many proangiogenesis factors, among which angiopoietin-2 seems to be the one that plays the most important role. This alternative route was observed in the experimental models of NET[56] and could justify both the increase in serum levels of angiogenic cytokines during anti-VEGF/VEGFR therapy and the simultaneous and effective use of combined therapies that block multiple angiogenic routes.

The use of angiogenesis markers could be a promising way to monitor the efficacy of antiangiogenesis therapy, determine its optimal dosage, avoid related toxicity, and predict its response or resistance. Currently, microvascular density is the best-known tissue biomarker. However, many data from the literature[57] show that it is not predictive in response to antineoplastic therapy. Different approaches have yet to be explored using immunohistochemical, molecular, and serum methods.

OXIDATIVE STRESS

Eukaryotic cells obtain the energy needed from aerobic respiration in the mitochondria. Due to this metabolic process, several reactive species are produced. They are required for signal transduction, enzymatic activity, gene expression, and protein folding in the endoplasmic reticulum and during apoptosis. Commonly, they are harmless. However, about 5% of reactive species can be toxic if they reach high concentrations.

Biochemistry of oxidative stress

The sources of oxidative stress can be both internal and external to the cell. Peroxisomes and P450 complex enzymes, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, and NADPH complexes are all internal sources of oxidative stress. Almost all enzymes act within the mitochondria. Ultraviolet rays, chemicals (*e.g.*,

environmental pollutants, smoking, and alcohol), and exercise are, conversely, external sources of oxidative stress.

Based on the main atom involved we can divide the reactive species into four groups: ROS; reactive nitrogen species (RNS); reactive sulfur species; and reactive chloride species[58]. ROS and RNS are produced during the electron transport chain. ROS, which includes superoxide anion, hydrogen peroxide (H_2O_2), hydroxyl radical, singlet oxygen, and ozone, are the products of oxidative metabolism[59]. Some ROS, such as peroxynitrite anion and $ONOO^-$, can react with nitric oxide. Subsequently, nitric oxide is converted to a hydroxyl radical and a nitrite anion.

The balance between ROS and endogenous antioxidants determines the damage that cells can suffer. After the alteration of this balance, oxidative stress is generated with subsequent damage to DNA, RNA, lipids, and proteins[60]. Reactive species cause DNA damage and malfunctions in the DNA repair mechanisms. The oxidation of DNA that takes place generates 8-hydroxy-2-deoxyguanosine, which is a product capable of causing mutations in DNA and increasing cellular aging and carcinogenesis[61].

Polyunsaturated lipids are abundant in the cell membrane and are also particularly susceptible to oxidation by reactive species. By peroxidation reactions, they release lipids and increase the permeability of the cell membrane, which can lead to cell death[62]. However, proteins are the main target of the reactive species. The carbonyl (aldehydes and ketones) and thiol groups (–SH) can be converted into reactive sulfur radicals[63]. Therefore, there is an alteration in the structure of the protein that leads to changes or loss of function.

The cell has three groups of defense mechanisms: endogenous antioxidants; natural antioxidants; and synthetic antioxidants[64]. The following are endogenous antioxidants: glutathione; alpha-lipoic acid; coenzyme Q; ferritin; uric acid; bilirubin; metallothionein; l-carnitine; melatonin; superoxide dismutase; catalase; glutathione peroxidase; thioredoxin; and peroxiredoxin (PRX). PRX is a group of ubiquitous antioxidant enzymes (PRX I-VI). They can modulate the H_2O_2 levels and transduce intracellular signaling. PRX III eliminates up to 90% of H_2O_2, and PRX V is even more effective against peroxynitrite.

The diet is a source of natural antioxidants such as ascorbic acid (vitamin C), tocopherol (vitamin E), carotene (vitamin A), lipoic acid, uric acid, glutathione, and polyphenolic metabolites. Finally, synthetic antioxidants include N-acetyl cysteine, thyroid hormones, pyruvate, selenium, butylated hydroxytoluene, butylated hydroxyanisole, and propyl gallate [65].

Clinical importance of oxidative stress

Several human diseases, such as neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis), inflammatory diseases (arthritis), cardiovascular disease (atherosclerosis), allergies, immune system dysfunction, diabetes, aging, and cancer[66] are attributable to oxidative stress. During the acute inflammatory response, the chemical mediators released, such as ROS, also affect normal cells. In the case of a chronic inflammatory process, extremely high levels of ROS saturate the antioxidant mechanisms of the cell affecting the surrounding cells.

Oxidative stress in neoplasms

ROS are responsible for some cellular mechanisms implicated in tumor development and progression, including: (1) Cell proliferation (*e.g.*, activation of regulated extracellular kinase 1/2 and ligand-independent kinase receptor tyrosine kinase); (2) Apoptosis inhibition; (3) Tissue infiltration and metastasis (metalloproteinase secretion in the matrix extracellular, Met overexpression, and Rho-Rac interaction); and (4) Angiogenesis (release of VEGF and angiopoietin).

Several biochemical pathways are affected by oxidative stress (from epidermal growth factor receptor to mechanistic target of rapamycin) involving key signaling proteins, such as Nrf2, Keap1, Ras, Raf, MAPK, ERK1/2, MEK, p38, JNK, c-myc, p53, and PKC[67-69]. p38 acts as a key sensor of oxidative stress and is essential in the control of neoplastic development[70]. Unlike other MAPKs, p38 suppresses tumorigenesis by blocking proliferation and promoting apoptosis (Table 2).

Genetics of oxidative stress in neoplasms

A key role in the neoplastic transformation is played by genetic factors. A high level of ROS is associated with the increased metabolism observed in tumor cells; however, oxidative stress is less harmful to cancer cells than it is to normal cells. Cancer cells can adapt to the new conditions and proliferate, creating a new redox balance. This ability of cancer cells allows them to have a greater resistance to oxidation and oxidative stress than normal cells. It follows that the neoplastic cells can increase their metabolic rate and proliferation and avoid the damage caused by free radicals. However, this adaptive response alone cannot explain the high metabolic rate of tumors[71].

Genetic factors implicated in tumorigenesis may also directly or indirectly modulate ROS levels. The physiologic antioxidant activity is mainly regulated by the Nrf2 transcription factor in addition to specific antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, thioredoxin, and PRX. Nrf2 modulates the expression of many genes, including not only those that code for antioxidant enzymes but also genes that control immune and inflammatory responses, carcinogenesis, and metastasis[72]. ROS levels are controlled by Nrf2 and its repressor protein (Keap1). Furthermore, experimental data show that when treated with oxidation-inducing drugs Nrf2-free mice develop more severe intestinal inflammation than controls, suggesting a function for Nrf2 in preventing inflammation and carcinogenesis[73].

While Nrf2 was initially thought to be able to regulate oxidative stress by modulating the production of antioxidant enzyme antioxidant response element, subsequently kinase-dependent mechanisms have been described, such as MAPK, PI3K, and other alternative pathways for activation of Nrf2[74,75]. Somatic mutations that disrupt the Nrf2-Keap1 interaction have been identified in patients with non-small cell lung cancer[76] and esophageal cancer[77]. In breast cancer, the breast cancer tumor suppressor gene 1 (*BRCA1*) is mutated in 40%-50% of hereditary breast cancers, while it is absent or at a low level in 30%-40% of sporadic cases[78]. BRCA1 is responsible for DNA repair and can regulate Nrf2 and

Table 2 Molecular target of oxidative stress to promote tumor progression

Molecular target of ROS	Protein or gene	Function and mechanism	Tumor type
ERK1/ERK2	Protein	Promotion of cell proliferation and angiogenesis	Ovarian, colon, breast, and lung cancer
Nrf2	Protein	Regulation of oxidative stress by modulating the production of antioxidant enzymes	NSCLC and esophageal cancer
Ref1 /APE1	Protein	Reduction of ROS generation	Breast cancer
PTEN	Protein	Involvement in senescence; Association with high levels of Akt and ROS	Lung, liver, and breast cancer
Ras	Protein	Increases mitochondrial mass and ROS levels, causing DNA damage; Regulation of Nox4-p22phox system	30% of human cancer
mTOR	Protein	Promotion of cell proliferation and metabolism that contributes to tumor initiation and progression; Regulation of autophagy and apoptosis	More than 70% of cancers (breast, lung, colorectal, prostate, head and neck, gynecologic, urinary bladder, renal cancer gastric carcinoma, glioblastoma, lymphoma, and medullo-blastoma)
P38	Protein	Regulation of cell proliferation, cell differentiation, cell death, cell migration, and invasion.	Prostate, breast, bladder, live, and lung cancer, transformed follicular lymphoma and leukemia
BRCA	Gene	Regulation of antioxidant response; Controlling the Nrf2 and NFκB activity	40%-50% of hereditary breast cancers
hTERT	Protein	Reduces oxidative stress intracellularly and extracel-lularly; Regulation of apoptosis	Gastric cancer, lung cancer, cervical and head cancer, glioblastoma, breast cancer, and ovarian cancer
Angiopoietin	Protein	Involvement in angiogenesis, lymphangiogenesis, and metastasis; Induction of hypoxia and cytokines	NSCLC

Akt: Protein kinase B; *BRCA*: Breast cancer gene; ERK1/2: Extracellular kinase 1/2; hTERT: Human telomerase reverse transcriptase; NRF2: Nuclear factor erythroid 2-related factor 2; NSCLC: Non-small cell lung carcinoma; PTEN: Phosphatase and homolog of tensin; mTOR: Mammalian target of rapamycin; Ref/APE1: Redox factor/Apurinic/apyrimidinic endonuclease 1; ROS: Reactive oxygen species.

NFκB[79,80]. Nrf2 induces enzymes such as glutathione S-transferase, glutathione peroxidase, and oxidoreductase, which exert a protective action against ROS. In breast cancer cells the *BRCA1* gene reduces RNS damage to cells and helps them cope with oxidative stress. Redox factor 1/AP endonuclease 1 also participates in the reduction of ROS generation[81].

The Ras pathway (Ha-, N- and Ki-ras) is very important for regulating oxidative stress in cancer[82]. Ras activating point mutations are present in tumor cells (approximately 30% of tumors), resulting in a constitutively active protein. These mutations lead to an increase in ROS levels, which induces neoplastic transformation[83]. The *Ras* Val12 mutant activates the NOX4-p22phox NADPH oxidase system, which produces H_2O_2. Consequently, the response to *Ras* Val12-induced DNA damage is impaired by the inhibition of NADPH oxidase. NADPH oxidase, NOX4, can be considered a critical mediator of *Ras* Val12-induced oncogenic DNA damage[84].

If the *Ras* oncogene is overexpressed, cells show an increase in mitochondrial mass and an accumulation of ROS. Among these, the ROS generated by the respiratory chain in the mitochondria and the NOX enzymes in the cytoplasm are particularly important. NOX proteins are oncogenic proteins, and mitochondrial dysfunction is associated with tumorigenesis[85].

Mitochondrial dysfunction leads to DNA damage, decreased ATP levels, and activation of AMPK. The presence of the *K-ras* Val12 mutant in normal epithelial cells leads to increased peroxide levels and increased DNA damage. Peroxides can be generated by the COX-2 enzyme due to their correlation with K-ras[86]. Consequently, the COX-2 enzyme is also involved in many human cancers. Both peroxide production and DNA damage are reduced by pretreatment with the COX-2 antagonist SC58125. Therefore, several proteins including COX-2 and the transcription factor HIF-1α, which is activated in response to low oxygen concentrations, can influence the oncogenic activity of mutant K-rasVal12.

Overexpression of oncogenic proteins [Raf, reverse transcriptase of Mos, MEK, Myc, cyclin E and human telomerase reverse transcriptase (hTERT)] and inhibiting oncosuppressor genes (p53, p21CIP1, PTEN) can cause aging by increasing ROS levels. PTEN deficiency and Ras/MAPK activation could promote metastasis and EMT from prostate precursor cells [87]. Even in glioblastoma cells, PTEN deficiency, associated with high levels of Akt and ROS, leads to senescence. There is evidence that suggests the *hTERT* oncogene acts by modulating the redox system[88]. hTERT is localized in mitochondria, and its activity could influence the redox balance through the recruitment of the same mitochondria. Finally, hTERT inhibitors can induce mitochondrial-dependent apoptosis in target cells[89].

Many other genes are involved in regulating energy metabolism in cancer. *p53*, for instance, is one of the best-known tumor suppressors, and it is implicated in cellular energy balance in the mitochondria between glycolysis and the respiratory chain. Homologous cytochrome oxidase 2 is an important enzyme that mediates this effect, and its activity is very important for the regulation of the COX complex. Reduced homologous cytochrome oxidase 2 synthesis can cause low respiration and a high rate of glycolysis[90].

Sirtuins are a group of proteins involved in many cellular processes (aging, stress response, *etc*). Sirtuins are deacetylase enzymes regulated by NAD (positive activity) and NADH (negative activity). Sirt3 is the most studied of the three mitochondrial sirtuins and is known to act as a tumor suppressor. It is for this reason that it has been linked to longevity in humans. Kim *et al*[91] showed that in Sirt3 (-/-) murine embryonic fibroblasts, increased glycolysis, decreased oxidative phosphorylation, and increased ROS can be observed. Furthermore, the loss of Sirt3 increases cell tumorigenesis[92]. This process is accompanied by the activation of the HIF-1α target gene under hypoxic conditions.

NEUROENDOCRINE LUNG TUMORS

Bronchopulmonary neuroendocrine neoplasms represent a group of rare neoplasms (accounting for almost 20% of all lung neoplasms)[93] arising from the proliferation of cells with both endocrine and nervous phenotypic characteristics that together form the diffuse neuroendocrine system[94].

Based on their morphological, structural, immunohistochemical, and ultrastructural characteristics, they can be divided into four groups according to the 5th edition of the World Health Organization classification on thoracic tumors [95]: typical carcinoid (TC); atypical carcinoid (AC); large cell neuroendocrine (LCNEC); and small cell carcinoma (SCLC). TC and AC are considered well-differentiated NETs, while LCNEC and SCLC are considered poorly differentiated tumors. TC and AC are low (corresponding to G1 NET) and intermediate (corresponding to G2 NET) grades, respectively, whereas LCNEC and SCLC are high grades (traditionally graded as G3 tumors). Although these four subgroups of neuroendocrine neoplasms may represent a continuum in the neuroendocrine differentiation spectrum, histological, immunohistochemical, and molecular studies have demonstrated that pulmonary carcinoids are different from poorly differentiated neuroendocrine carcinomas[96].

The first description of a bronchopulmonary carcinoid dates back to 1831 when Laennec[97], in his treatise on mediated auscultation of the lungs and heart, reported the case of a posthumous endobronchial mass. The clinical presentation can occur with cough, hemoptysis, and recurrent pneumonia (due to the functional exclusion of a bronchus by a growing mass) even if in most cases their clinical course is indolent[93].

The diagnosis is based on imaging methods, such as computed tomography and magnetic resonance imaging, bronchoscopy, bronchial biopsy or fine-needle aspiration biopsy, mediastinoscopy (in selected cases), scintigraphy with 111 In-pentetreotide (octreoscan), and functional studies such as the evaluation of the tumor secretion pattern. Although less than 5% of patients with bronchopulmonary carcinoids have symptoms such as carcinoid syndrome, Cushing's disease, acromegaly, or syndrome of inappropriate antidiuretic hormone secretion, it is possible to detect secretion of amines, peptides, or hormones (endocrine, autocrine, or paracrine)[93].

However, the NETs most striking phenotypical characteristic is the massive vascularization[52] due to their marked ability to synthesize and secrete high levels of VEGF[45]. The experimental data available refer especially to the pancreatic NETs where the presence of high vascular density in NETs and low vascular density in neuroendocrine carcinoma is observed. The precise situation and the angiogenesis mechanism is not completely clear in neuroendocrine lung tumors. This review could provide a starting point for further future studies.

Experimental evidence has shown that the ROS released by the tumor due to metabolic stress are associated with different outcomes depending on their level[31]. Evidence shows that high levels of ROS directly lead cancer cells to cell death whereas low to medium ROS levels increase neoplastic progression, metabolism alteration, cell migration, EMT, and metastasis[98,99]. ROS also stimulate acute inflammation that becomes chronic when associated with prolonged ROS production[100]. NFκB and TGF-β are implicated in the relationships between chronic inflammation and carcinogenesis [101]. ROS are also responsible for p38 MAPK activation and TGF-β1-mediated EMT in many tumors[14]. Mitochondria are very important in determining neoplastic degeneration due to their production of endogenous ROS that subvert the metabolic process and oxidative phosphorylation[102].

Oxidative stress induces the production of ROS-dependent cytokines such as TGF-β, IL-6, IL-13, and VEGFA. A change to the mitochondrial redox and consequently the acid-base balance of the tumor microenvironment could represent a therapeutic strategy to improve the cellular function of T lymphocytes during immunotherapy treatment[103].

CONCLUSION

The use of angiogenesis and oxidative stress markers could be useful for evaluating the efficacy of antineoplastic drugs, establishing the optimal dosage, escaping from the related toxicity, and predicting its response or resistance.

FOOTNOTES

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REVIEW

History, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and treatment of COVID-19: A review

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Abstract

In December, 2019, pneumonia triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surfaced in Wuhan, China. An acute respiratory illness named coronavirus disease 2019 (COVID-19) is caused by a new coronavirus designated as SARS-CoV-2. COVID-19 has surfaced as a major pandemic in the 21st century as yet. The entire world has been affected by this virus. World Health Organization proclaimed COVID-19 pandemic as a public health emergency of international concern on January 30, 2020. SARS-CoV-2 shares the same genome as coronavirus seen in bats. Therefore, bats might be its natural host of this virus. It primarily disseminates by means of the respiratory passage. Evidence revealed human-to-human transmission. Fever, cough, tiredness, and gastrointestinal illness are the manifestations in COVID-19-infected persons. Senior citizens are more vulnerable to infections which can lead to dangerous consequences. Various treatment strategies including antiviral therapies are accessible for the handling of this disease. In this review, we organized the most recent findings on COVID-19 history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and treatment strategies.

Key Words: COVID-19; SARS-CoV-2; Severe acute respiratory syndrome; World Health Organization; Pathogenesis

Core Tip: An acute respiratory illness (COVID-19) is caused by a new coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to β-coronaviruses, and it shares the same genome as coronavirus seen in bats. It primarily disseminates by means of the respiratory passage. Much evidence revealed human-to-human transmission. Fever, cough, tiredness, and gastrointestinal illness are the manifestations in COVID-19-infected persons. Various antiviral therapies are accessible for the handling of COVID-19 disease.

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INTRODUCTION

In December 2019, in Wuhan (China) an outbreak of pneumonia symptomatized by fever, dry cough, fatigue, and occasional gastrointestinal symptoms was revealed. Most of these pneumonia patients were associated with the Huanan Seafood Market, Wuhan, China which deals in fish and various live animal species (poultry, bats, marmots, and snakes) [1].

By using reverse transcription polymerase chain reaction (RT-PCR), researchers determined the reason for the above symptoms and the rapid spread of cases being a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the Coronavirus Disease-2019 (COVID-19)[2-4].

On 30 January 2020, World Health Organization (WHO) stated the novel coronavirus outburst in Wuhan, China, a global crisis[5]. Later on WHO accepted that SARS-CoV-2 has the ability to spread worldwide[6,7]. On 11 March 2020, the WHO announced COVID-19, a pandemic[8]. In successive months, several thousand people in different provinces of China and cities were invaded by the unchecked spread out of this disease[9]. Later, this disease traveled to various countries i.e. Thailand, Japan, Republic of Korea, Vietnam, Germany, United States, Singapore, and India. On comparison COVID-19 cases have overtaken the infected cases and deaths from Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS) at this point of the disease outburst[10]. The early effect of COVID-19 was so dreadful that the various countries had to implement phases of lockdowns. All age groups including children and pregnant women were badly affected due to this infectious disease.

CoVs (Coronaviruses) relates to the order Nidovirales and they have the largest RNA genome[11]. CoVs pertain to Coronaviridae family. They are positive single-stranded RNA-enveloped viruses. Four genera of CoVs are Alpha-, Beta-, Gamma-, and Deltacoronavirus. Seven human coronaviruses (HCoVs) have been revealed till now and they belong to the Alpha- and Betacoronavirus genera. The Alphacoronavirus genus includes HCoVNL63 and HCoV-229E and Betacoronavirus genus includes HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and the novel SARS-CoV-2[12-17]. The alphacoronaviruses (HCoV-NL63 and HCoV-229E) and the betacoronaviruses (HCoV-OC43 and HCoV-HKU1) generally induce common colds, but severe lower respiratory tract infections can also appear, notably in the old age persons and kids[18]. HCoV-NL63 infection causes croup (laryngotracheitis)[19,20], and HCoV-OC43 infection causes severe lower respiratory tract infection among kids[21]. SARS-CoV and MERS-CoV are zoonotic viruses that cause severe respiratory syndrome[11].

This review summarizes the latest findings on the history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and cure of COVID-19.

HISTORY OF THE CORONAVIRUS

Human coronaviruses (229E and OC43) was first diagnosed in late 1960 as a reason for the common cold and were observed safe for human beings[22,23]. In Guangdong province in China in 2002–2003, a disease outbreak resulted in which a new coronavirus (β genera) originated in bats and was crossed to human beings by intermediate host of Himalayan palm civet cats[24]. This virus named SARS-CoV had a fatality rate of 10%[14,25,26]. This virus had been quickly spreading worldwide, particularly in Asia[27].

Almost ten years after SARS in year 2012, another highly pathogenic CoV, MERS-CoV, appeared in Middle East countries[17]. MERS-CoV, was also of bat origin, with dromedary camels as the intermediate host, and intermediate host reservoir species were also observed in goats, sheep, and cows[28]. MERS-CoV affected approximately 2000 people with approximately 34% mortality rate[17].

Recently, in December 2019, the novel Coronavirus 2019 (nCoV) or SARS-CoV-2 surfaced in Huanan Seafood Market, Wuhan (China) which cause pneumonia epidemic of unknown cause[29].

EPIDEMIOLOGY: ORIGIN, RESERVOIRS, AND TRANSMISSION OF COVID-19

COVID-19 was thought to be originated in Wuhan (China). Environment specimens from the Huanan seafood market in Wuhan, China were examined positive, suggesting that the COVID-19 virus originated there[30]. According to several reports, Bat might be the likely pool of SARS-CoV-2[31,32]. Bats are the natural pool of a range of CoVs, including SARS-CoV-like and MERS-CoV-like viruses[33-35]. When the genome of COVID-19 and Bat CoV RaTG13 was compared and analyzed by virus genome sequencing and it revealed 96.2% genome sequence similarity with the Bat CoV RaTG13 genome[24]. It revealed that bat CoV and human SARS-CoV-2 might share the same ancestor[36]. It had > 70% resemblance with the SARS-CoV[37]. The SARS-CoV-2 emanated from bats and intermediate animals through which it reaches humans is unknown. Present suspects are pangolins and snakes[37]. Figure 1 shows the transmission cycle of SARS-CoV-2.

It seems that majority of early COVID-19 cases had a contact record with the seafood market, in Wuhan, China[24,38]. There is the possibility of human-to-human (Transmission *via* Aerosols, Nosocomial-Related Infections & Maternal Transmission) spread in people who did not have vulnerable to the seafood market of Wuhan, China[39]. It is also revealed that 31.3% of COVID-19 patients have traveled a short time ago to Wuhan and 72.3% of patients who are nonresidents of Wuhan, have contact with people of Wuhan[40]. Instances of COVID-19 in different provinces of China and in almost all countries of the world were recorded in people who were returning from Wuhan City, China[37]. COVID-19 cases were observed in countries outside China with no travel history to China indicating human-to-human transmission locally[41].

In India during the early period (from March 2020 onwards), there was an alarming rise in COVID-19 patients but now the recovery rate from this disease is much more and the situation is under control now.

GENOME STRUCTURE OF CORONAVIRUSES

SARS-CoV-2 belongs to beta-coronaviruses. Genome of SARS-CoV-2 is positive-sense single-stranded RNA [(+) ssRNA] with a 5'-cap, 3'-UTR poly(A) tail. The SARS-CoV-2 genome length is < 30 kb, having 14 open reading frames (ORFs) which encode non-structural proteins (NSPs), structural proteins *i.e.* spike (S), envelope (E), membrane/matrix (M) and nucleocapsid (N), and accessory proteins[42,43].

Coronavirus virions have a diameter of about 125 nm and are spherically shaped[44,45]. The genomes of coronaviruses encode five structural proteins: The spike (S), membrane (M), envelope (E) glycoproteins, hemagglutinin esterase (HE), and nucleocapsid (N) protein. All virions have all envelope protein and N protein, but only some beta coronaviruses possess the protein hemagglutinin esterase (HE)[46].

S glycoproteins

These proteins are located outside the virion and contribute to its usual shape. The homotrimers of the S proteins create the sun-like appearance that assigns coronaviruses their name[44,47,48]. Through their C-terminal transmembrane domains, S proteins attach to the virion membrane and also join with M proteins[49]. Virion attachment to particular surface receptors present in the host cell's plasma membrane is made possible by the N-terminus of the S proteins[50].

M glycoproteins

Three transmembrane domains are present in M glycoproteins. Glycosylation of M proteins occurs in the Golgi body[51-53]. Alteration in M protein is required to enter virion into the cell and for protein to become antigenic[54-56]. The M protein aids to regenerate new virions.

E glycoproteins

These are tiny proteins and are made from about 76 to 109 amino acids. The N-terminus of the E proteins typically has 30 amino acids, which facilitates adhesion to the virus membrane[57]. Additionally, Coronavirus E proteins perform an essential part in the assembly and morphogenesis of virions inside the cell.

N proteins

They are phosphoproteins in nature. They possess flexible viral genomic RNA and have the ability to bind to helixes. N proteins perform a vital part in coronavirus virion structure, replication, and transcription[58,59].

The complete genome of Wuhan-Hu-1 coronavirus, a strain of SARS-CoV-2 (taken from a COVID-19 pneumonia patient), is of 29.9 kb size[36]. The CoVs genome contains between 6 and 11 ORFs[60]. Two polyproteins named pp1a and pp1ab, encode 16 non-structural proteins, which are translated by approximately 66% of the viral RNA present in the first ORF (ORF1a/b). The remaining ORFs form structural and accessory proteins. Spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein[11] are the four structural proteins encoded by the remaining part of the virus genome. SARS-CoV-2 is found to be more similar to SARS-like bat CoVs when compared with the known SARS-CoV and MERS-CoV genomes. The majority of genome-encoded proteins of SARS-CoV-2 are alike to those of SARS-CoVs. Zhang *et al*[61] observed that SARS-CoV-2 had been mutated in various patients in China. Tang *et al*[62] categorized two strains of SARS-CoV-2, the L type, and the S type. The L-type strains (derived from S-type) are more infectious and dangerous in terms of evolution than the S-type. As a result, virologists and epidemiologists must carefully examine the novel coronavirus and conduct additional research to determine its virulence and pandemic.

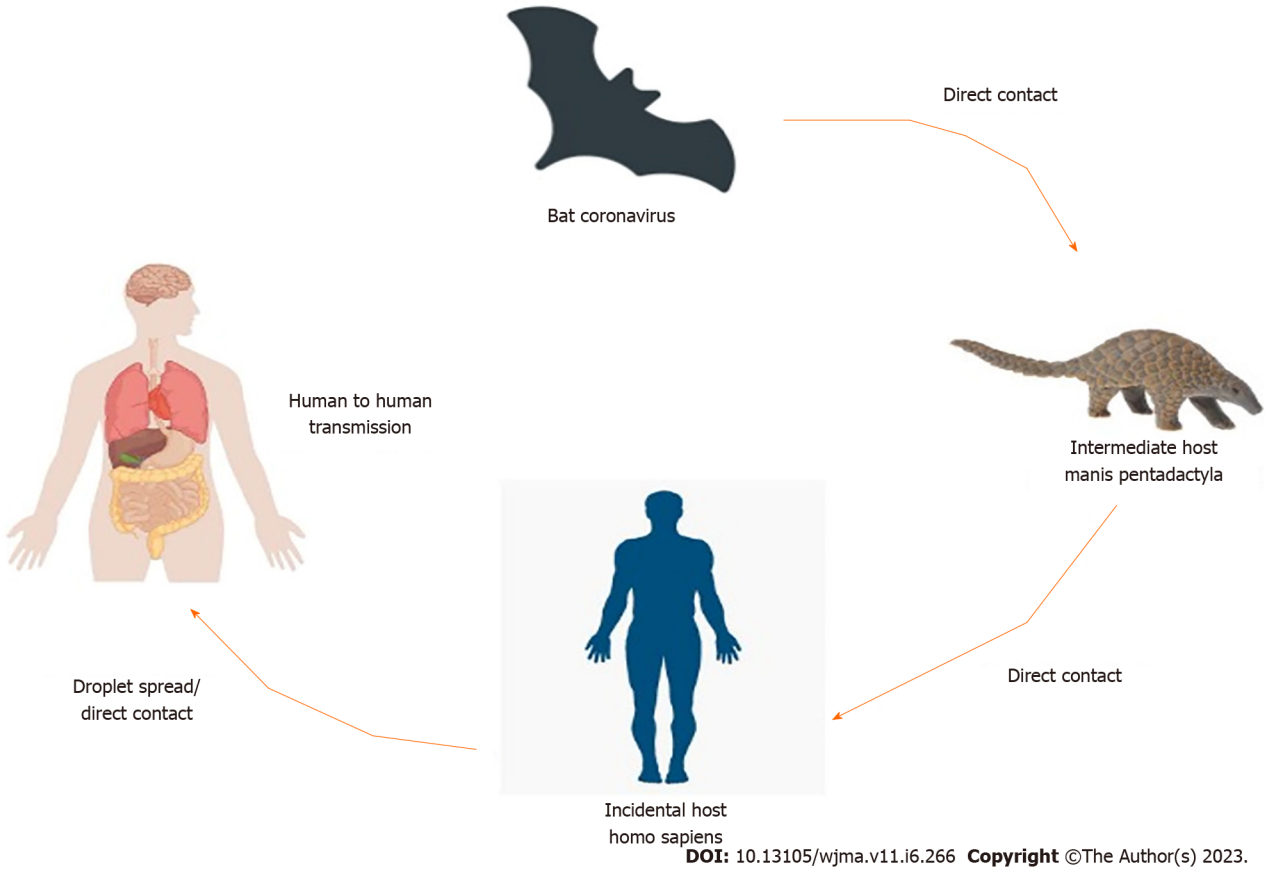

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Figure 1 Transmission cycle of severe acute respiratory syndrome coronavirus 2.

CORONAVIRUS REPLICATION

Here, we summarise the main steps of the SARS-CoV-2 infection cycle.

Entrance into the host cell

The human lower respiratory tract has ACE2, the SARS-CoV receptor[63]. Coronavirus S-glycoprotein may bind to ACE2 receptor present on outer surface of human cells[64]. S glycoprotein comprises of S1 and S2 subunits[65]. S1 subunit specifies the virus-host range and cellular tropism with the help of the RBD domain, whereas S2 subunit helps the fusion of virus with cell membrane with the help of heptad repeats 1 (HR1)[66] and heptad repeats 2 (HR2)[67] domains.

RNA synthesis and virion assembly

After fusing with the membrane, genomic RNA of virus is delivered inside the cytoplasm. This RNA forms pp1a and pp1ab polyproteins after translation[68], which further form non-structural proteins, and replication-transcription complex (RTC) in two-layered vesicles[69]. RTC replicates repeatedly and forms a set of subgenomic RNAs[70], which further form accessory proteins and structural proteins. Newly generated genomic RNA, nucleocapsids, and envelope glycoproteins unite to form new viral particles in the ER and Golgi apparatus[71].

Virion release

At last, virion-containing vesicles combine along with the plasma membrane, and viruses are released outside.

EPIDEMIOLOGY AND PATHOGENESIS

This infection can affect people of any age. In humans, it is very contagious, especially in the elders and those who already have illnesses like fever, cold, or cough[72,73]. Large droplets released by symptomatic patients when coughing and sneezing are used to spread the infection; however, this can also happen from asymptomatic individuals prior to the start of symptoms[44]. COVID-19 infection transmits mainly by way of respiratory droplets, respiratory secretions, and direct contact[38]. Further, SARS-CoV-2 was also observed in faeces of severe pneumonia patients. Even after patients have recovered from the sickness, patients with symptoms can still spread infections. The infected droplets can deposit on surfaces and spread infection up to 1-2 meters away. In a suitable atmosphere, the virus can survive on surfaces for days. Disinfectants like hydrogen peroxide and sodium hypochlorite can destroy viruses[74]. Infection can be gained by

inhaling infectious droplets or by touching surfaces that have been exposed to the virus and subsequently contacting mouth, nose, and eyes. Further, virus is found in faeces and affects the water reservoirs and then spreads by faeco-oral route or through aerosolization[75]. Transplacental transfer from pregnant women to their foetuses has not yet been documented. Although, post-natal transmission in neonates is reported[76]. The incubation period of this virus ranges from 2 to 14 d[77].

CLINICAL FEATURES

The clinical characteristics of patients with COVID-19 are shown in Figure 2. Asymptomatic state, acute respiratory distress syndrome, and multi-organ failure are all possible clinical manifestations of COVID-19[37]. Fever, coughing, sore throat, headaches, sputum production, sore throat, lethargy, myalgia, shortness of breath, and conjunctivitis are frequent clinical symptoms[37]. Acute respiratory distress syndrome (ARDS), arrhythmia, shock[78], acute renal injury, acute cardiac injury, liver dysfunction, and secondary infection were the disorders related to this infection[40]. This infection can lead to pneumonia, respiratory failure, and even death after the first week. IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα are inflammatory cytokines that have dramatically increased during the advancement of this disease[79]. Recovery from this infection began in the second or third week. Elderly persons are more likely to experience negative effects which can lead to death[37]. Additionally, it has been noted that this disease in neonates, kids, and children is substantially less severe than in adults[37].

DIAGNOSTIC CRITERIA

An individual having fever, sore throat, and cough who has a traveling record to China or different locations with chronic community transmittance, or has contacted individuals having the same traveling experiences, or who have come into contact with a confirmed COVID-19 infected person is considered a suspected COVID-19 case[72]. A confirmed COVID-19 case is a suspected one having a positive molecular diagnostic test[72].

Until recently, the standard clinical diagnosis approach for COVID-19 is nucleic acid identification in swabs taken from nose, throat, or other parts of the respiratory system by using real-time polymerase chain reaction and furthermore verified by sequencing[80].

TREATMENT STRATEGIES FOR COVID-19

General precautions

COVID-19 patients are adequately isolated to stop infection to other persons in contact, patients, and health personnel. Keeping adequate water in the body and a proper diet plan while managing fever and cough are the best ways to treat moderate infection at home. It is advised to provide oxygen to hypoxic patients using nasal prongs, face masks, a high-flow nasal cannula, or non-invasive ventilation[72].

Four classes of medicines have been identified based on how they work: (1) Viral entry and membrane fusion inhibitors; (2) protease inhibitors; (3) RdRp inhibitors; and (4) immunomodulatory medicines.

Table 1 shows various therapeutic agents used for the treatment of COVID-19.

Umifenovir, camostat mesylate, ACE inhibitors, angiotensin receptor-1 blockers, soluble recombinant human ACE2, chloroquine phosphate, and hydroxychloroquine sulfate are the various medications that were tested to prevent attachment and fusion of the virus to the cell membrane[81]. Due to their increased production capacity and lower danger of antibody-dependent enhancement, MAbs act more efficient than convalescent plasma as medication for COVID-19 patients[82]. A new MAb cocktail called REGN-COV2 binds to the receptor-binding domain of S1 or S2 subunits of the SARS-CoV-2 spike protein to stop the virus from entering the host cell[83]. Three more MAbs (B38, H4, and CR3022), might be potent against SARS-CoV-2 in upcoming studies[84,85].

Another class of medications that have been used for a long time to treat AIDS is protease inhibitors. Under the trade name Kaletra®, lopinavir is commonly compounded with ritonavir (LPV/r). The LPV/r effectiveness has been demonstrated earlier in cell culture as opposed to SARS-CoV-1 and MERS-CoV[86] and in recent times opposed to SARS-CoV-2[87].

RdRp inhibitors, in particular, demonstrated encouraging results in COVID-19 patients[88-90]. For instance, Remdesivir (RDV, GS-5734, Gilead) inhibited the spread of SARS-CoV-2 at smaller doses[89]. Another RdRp inhibitor, favipiravir (T-705, Avigan®), has demonstrated efficacy against SARS-CoV-2 in Vero E6 cells at higher concentrations[89]. Another RdRp inhibitors, such as β-D-N4-hydroxycytidine (EIDD-1931), were very effective at stopping SARS-CoV-1, SARS-CoV-2, and MERS-CoV replication in *in vitro* condition[91].

To lessen the intensity and complexities of COVID-19 and escape the inflammatory immune reactions (in serious patients), a variety of therapy is frequently applied[92]. Proinflammatory cytokine-suppressing medications, including MAbs (tocilizumab and sarilumab) and IL receptor inhibitors (anakinra), are now available[93]. In Vero E6 cells, nitazoxanide showed antiviral activity as opposed to SARS-CoV-2[89].

Table 1 Various therapeutic agents used for the treatment of coronavirus disease 2019

Sr. No.	Therapeutic agents	Examples
1	Antiviral agents	1 Remdesivir
		2 Favipiravir
		3 Ribavirin
		4 Interferons
		5 Ritonavir/Lopinavir
		6 Arbidol
		7 Chloroquine/Hydroxychloroquine
		8 Recombinant soluble ACE2
		9 Azithromycin
		10 Ivermectin
		11 Nitazoxanide
		12 Camostat mesylate
		13 Paxlovid
2	Biologic agents	1 Monoclonal antibodies
		2 Convalescent plasma
		3 Hyperimmune sera
		4 Exogenous surfactant delivery
3	Anti-inflammatory agents	1 Corticosteroids
		2 Fluvoxamine
		3 Anakinra
		4 Granulocyte-macrophage colony-stimulating factor inhibitors
		5 Intravenous immunoglobulin
		6 Janus kinase inhibitors
		7 Colchicine
4	Herbal agents	Various Chinese herbal medicine
5	Preventive agents	Vaccines

ACE2: Angiotensin converting enzyme 2.

Corticosteroids aid to escape ARDS and acute lung injury by lowering cytokine storm and lung inflammation[94]. Induced pluripotent stem cells, mesenchymal stromal cells, and T cells are various cell therapy techniques that have been researched[95-98].

PREVENTION

Currently, only a few approved medications are available to treat COVID-19 infection. Preventive measures play an important role to prevent this infection. It is advisable to keep confirmed or suspected cases having mild sickness isolated at home. Patients should wear a face mask and follow cough hygiene. Additionally, caregivers need to wash their hands regularly and should wear a surgical mask in the patient ward. Frequent sanitization of the rooms, surfaces, and equipment should be done with sodium hypochlorite. N95 respirators, safety suits, and goggles should be provided to healthcare professionals and workers. Healthcare professionals should also be frequently checked for various signs of COVID-19. Once a patient has been apyretic for at least three days and has two successive negative molecular tests with a sample gap of one day, they could be discharged from isolation. The only requirement for discharge was not the results of negative molecular tests[72].

Community-wide precautions include avoiding crowded places, forbidding large-scale gatherings, and delaying unnecessary travel to locations where transmission is still occurring. People should inculcate habit of good hand hygiene frequently, and exercise good cough hygiene by coughing into their sleeves or tissue paper rather than in their hands[99].

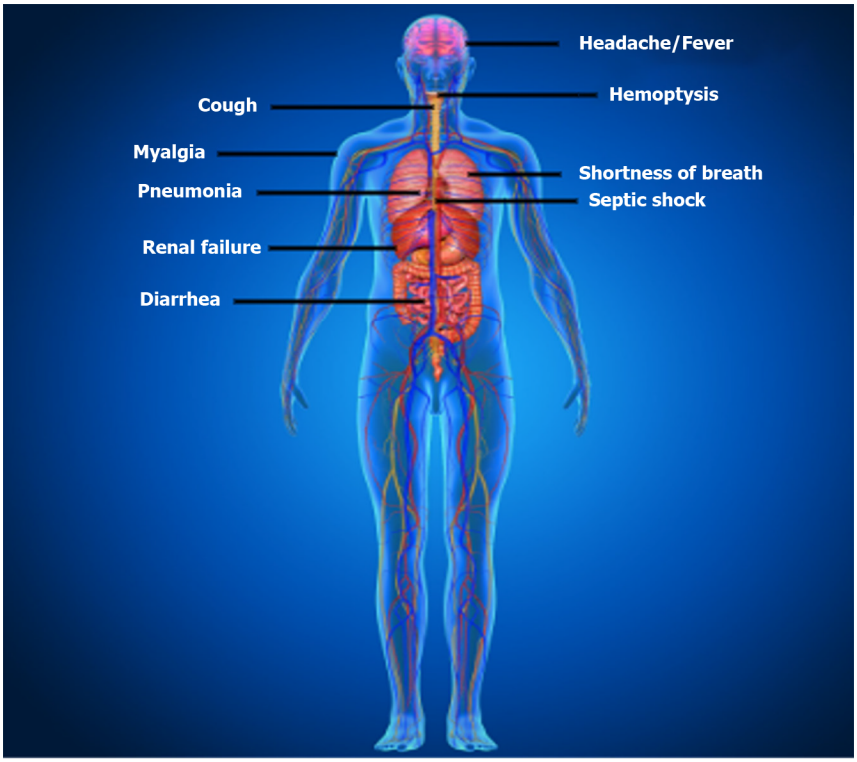

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Figure 2 Clinical Features of patients with coronavirus disease 2019.

A law of banning the sale and trade of wild animals is also being introduced in China[100].

CONCLUSION

In this review, we outline the history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical characteristics, diagnosis, and treatment of COVID-19. The COVID-19 disease propagates rapidly across China and has disseminated to different countries of the world. Due to this viral epidemic, the economic, clinical, and public health frameworks of almost all countries of the world had affected. We wish that the horrible scenario created by this pandemic will not affect our life further.

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FOOTNOTES

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META-ANALYSIS

Endoscopic *vs* radiologic gastrostomy for enteral feeding: A systematic review and meta-analysis

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Abstract

BACKGROUND

Percutaneous endoscopic gastrostomy (PEG) and percutaneous radiological gastrostomy (PRG) are minimally invasive techniques commonly used for prolonged enteral nutrition. Despite safe, both techniques may lead to complications, such as bleeding, infection, pain, peritonitis, and tube-related complications. The literature is unclear on which technique is the safest.

AIM

To establish which approach has the lowest complication rate.

METHODS

A database search was performed from inception through November 2022, and comparative studies of PEG and PRG were selected following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. All included studies compared the two techniques directly and provided absolute values of the number of complications. Studies with pediatric populations were excluded. The primary outcome of this study was infection and bleeding. Pneumonia, peritonitis, pain, and mechanical complications were secondary outcomes. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2) and we used The Risk of Bias in Nonrandomized Studies (ROBINS-I) to analyze the retrospective studies. We also performed GRADE analysis to assess the quality of evidence. Data on risk differences and

95% confidence intervals were obtained using the Mantel-Haenszel test.

RESULTS

Seventeen studies were included, including two randomized controlled trials and fifteen retrospective cohort studies. The total population was 465218 individuals, with 273493 having undergone PEG and 191725 PRG. The only outcome that showed a significant difference was tube related complications in retrospective studies favoring PEG (95%CI: 0.03 to 0.08; $P < 0.00001$), although this outcome did not show significant difference in randomized studies (95%CI: -0.07 to 0.04; $P = 0.13$). There was no difference in the analyses of the following outcomes: infection in retrospective (95%CI: -0.01 to 0.00; $P < 0.00001$) or randomized (95%CI: -0.06 to 0.04; $P = 0.44$) studies; bleeding in retrospective (95%CI: -0.00 to 0.00; $P < 0.00001$) or randomized (95%CI: -0.06 to 0.02; $P = 0.43$) studies; pneumonia in retrospective (95%CI: -0.04 to 0.00; $P = 0.28$) or randomized (95%CI: -0.09 to 0.11; $P = 0.39$) studies; pain in retrospective (95%CI: -0.05 to 0.02; $P < 0.00001$) studies; peritonitis in retrospective (95%CI: -0.02 to 0.01; $P < 0.0001$) studies.

CONCLUSION

PEG has lower levels of tube-related complications (such as dislocation, leak, obstruction, or breakdown) when compared to PRG.

Key Words: Gastrostomy; Adverse events; Meta-analysis; Percutaneous endoscopic; Radiological gastrostomy

Core Tip: Gastrostomy is a routine and preferred feeding route in patients who require enteral nutrition for prolonged period. This metanalysis compared percutaneous endoscopic gastrostomy and percutaneous radiological gastrostomy multiple outcomes, such as bleeding, infection, pneumonia, pain, and tube-related complications. Based on this meta-analysis, gastrostomy technique is related to a lower complication rate of tube-related complications and thus, should be preferred. Costs, devices availability, personal and local experience as well as patients preference should be considered when choose the best technique.

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INTRODUCTION

Patients unable to tolerate oral intake for a prolonged period have an indication for an alternative route of enteral feeding, such as gastrostomy[1]. Gastrostomy involves connecting the stomach to an outflow in the skin with a tube, providing an alimentary route.

The first gastrostomy was performed in the 19th century, and Stamm's technique, surgical gastrostomy described in 1894, was long considered standard for performing a prolonged enteric access. The surgical technique became less performed with the emergence of the endoscopic technique. The method of percutaneous endoscopic gastrostomy (PEG) was first used in 1980 by Gauderer and Ponsky[2]. The technique was developed as a minimally invasive feeding route for neurologically impaired patients.

In 1981, percutaneous radiologic gastrostomy (PRG) was described[3], expanding the options available. This was an important development for scenarios such as head and neck tumors, where endoscopy is sometimes not an option, due to upper obstruction.

Endoscopic and radiological gastrostomy are both considered effective, safe and minimally invasive[4,5]. The preferred method is often based on specialist opinion or institution preference. We aim to perform a systematic review of the literature and meta-analysis to establish which approach has the lowest complication rate.

MATERIALS AND METHODS

Protocol and registration

This study was performed in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[6] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the file number CRD42022377213.

Information source and literature search

The electronic databases searched were MEDLINE (via PubMed), Embase, Scopus, LILACS, the Cochrane Library (via BVS), and Google Scholar from inception until November 2022. The search was performed with the following mesh terms: [(Gastrostomy or Gastrostomies) and (Endoscopic)].

Eligibility criteria

The selection criteria were studies that contained patients undergoing gastrostomy, that compared the two interventions (PEG and PRG) and that included the following outcomes: Bleeding, infection, pain, peritonitis, tube-related complications with their results in absolute values.

Eligibility assessment was performed independently and standardized by 2 authors according to PRISMA guidelines [6]. Discrepancies between reviewers were resolved by consensus. A third reviewer was consulted in case of disagreements.

Case reports, reviews and letters were excluded. Studies that exclusively analyzed patients under 18 years of age, compared other techniques or did not consider the desired outcomes were excluded. Studies with the pediatric population were excluded because of anatomical differences with the adult population and consequently different complications.

To assess the quality of eligible studies we used The Risk of Bias in Nonrandomized Studies (ROBINS-I)[7] to analyze the comparative studies and the Cochrane risk-of-bias tool for randomized trials (RoB2)[8] to analyze the randomized studies. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria using the GRADE pro Guideline Development Tool software (Mc Master University, Ontario, Canada)[9].

Data analyses

The randomized controlled trials (RCT) studies were analyzed separately from the observational studies since they have different levels of evidence. This allowed us to compare the outcomes separately and to make a global analysis of the results.

The analysis was performed using Review Manager (RevMan 5.4) from the Cochrane Informatics & Knowledge Management Department website. Risk differences for dichotomous variables were computed using a fixed-effects model and the respective forest and funnel plots were obtained. Data on risk differences and the 95% confidence intervals (CI) for each outcome were calculated using the Mantel-Haenszel test. Inconsistency (heterogeneity) was qualified and reported using the Chi-squared (Chi^2) and Higgins methods and was termed I^2. I^2 values > 50% were considered to indicate substantial heterogeneity. We performed an analysis using a funnel plot to identify possible outliers. If the sample became homogeneous after excluding possible outliers, the studies were permanently excluded. We used random effects to reduce the influence of heterogeneity on the final result[10]. Outcome measures are described as the mean difference or risk difference (RD), with their corresponding 95%CI.

RESULTS

The initial search showed 15585 results, after removing the duplicate articles, 6490 remained. A total of twenty studies passed the screening stage and were included in qualitative synthesis, seventeen studies met criteria to be included in the metanalysis, two were prospective randomized studies and fifteen were retrospective cohort studies. The search strategy can be visualized in the following diagram (Figure 1).

Study characteristics

Seventeen studies were included in the systematic review, including two RCTs, one prospective, and 14 retrospective cohort studies. A total of 465218 individuals, with 273493 received PEG and 191725 PRG. The characteristics of the studies can be seen in Table 1[11-27]. Early outcomes were analyzed.

Risk of bias within studies

The ROBINS-I and ROB-2 scoring system were used to evaluate risk of bias for observational[12-18,20-27] and randomized studies[11,19], respectively (Table 1). We identified a low risk of bias in the two RCT studies (Figure 2), and a strong methodological quality. As for the observational studies, we note that 5 of them present serious risk of bias[13,15,25,27] and 5 moderate risk[12,14,18,21,23], mostly due to issues in the dissemination of results (Figure 3).

Quality of evidence

The objective criteria of GRADE analysis to evaluate the quality of evidence identified moderate certainty for pain and infection, low certainty for peritonitis and very low certainty for bleeding and pneumonia (Figure 4).

Infection

A total of 465198 patients from 17 studies[12-27] were analyzed. There was no difference in the incidence of infection in retrospective (95%CI: -0.01 to 0.00; $P < 0.00001$; $I^2 = 74\%$) or randomized (95%CI: -0.06 to 0.04; $P = 0.68$; $I^2 = 0\%$) studies. In the overall analysis there was no difference in the meta-analysis of observational and RCT studies combined (95%CI: -0.01 to 0.00; $P = 0.56$; $I^2 = 70\%$) (Figure 5A).

Table 1 Early outcomes were analyzed

Ref.	Country	Design	Period	PEG (N)	RIG (N)	Mean age PEG	Mean age RIG	Single (S) or Multicenter (M)
Hoffer *et al*[11], 1999	United States	Randomized	1993-1994	69	66	58.2	51.9	S
Möller *et al*[12], 1999	Sweden	Retrospective	1990-1994	12	94	48	64	S
Laasch *et al*[13], 2002	United Kingdom	Prospective	2000-2002	50	50	73	68	M (3)
Silas *et al*[14], 2005	United States	Retrospective	1997-2001	177	193	68	63	S
Rustom *et al*[15], 2006	United Kingdom	Retrospective	2002-2005	40	28	63.6	64.8	S
Galaski *et al*[16], 2009	Canada	Retrospective	2004-2005	30	44	55	65	S
La Nauze *et al*[17], 2012	Australia	Retrospective	2007-2009	80	97	61	61	S
Rio *et al*[18], 2010	United Kingdom	Retrospective	1999-2006	21	122	64	64	S
Lewis *et al*[19], 2014	United Kingdom	Randomized	2012-2013	34	31	73	71	S
ProGas Study Group[20], 2015	United Kingdom	Retrospective	2010-2014	121	163	64.2	63.6	M (24)
Vidhya *et al*[21], 2018	Australia	Retrospective	2013-2015	85	52	65	64	S
Park *et al*[22], 2019	South Korea	Retrospective	2010-2015	324	94	66	66.2	M (5)
Strijbos *et al*[23], 2019	Netherlands	Retrospective	2008-2016	291	469	66	66.2	S
Lainez *et al*[24], 2020	Spain	Retrospective	2019	25	23	63.98	62.41	S
Maasarani *et al*[25], 2020	United States	Retrospective	2004-2014	232164	26477	NI	NI	M
Kohli *et al*[26], 2020	United States	Retrospective	2014-2017	16384	154007	53.7	67.2	M
Kohli *et al*[27], 2021	United States	Retrospective	2011-2021	23566	9715	70.7	69.6	M

PEG: Percutaneous endoscopic gastrostomy; PRG: Radiologically guided gastrostomy; NI: Not informed.

Bleeding

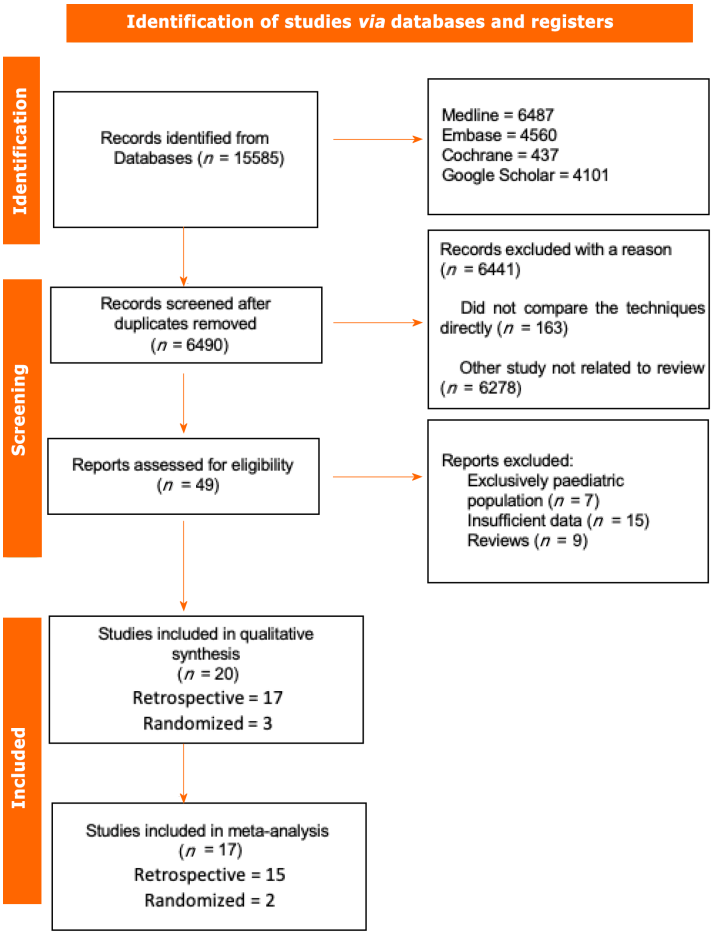
A total of 464618 patients from fourteen[11-13,16,17,19-27] studies were analyzed. There was no difference in the incidence of bleeding in observational studies (95% CI: -0.00 to 0.00; $P < 0.00001$; $I^2 = 76\%$) or RCTs (95%CI: -0.06 to 0.02; $P = 0.43$; $I^2 = 0\%$). In the overall analysis there was no difference in the meta-analysis of observational and RCT studies combined (95%CI: -0.00 to 0.00); $P = 0.81$; $I^2 = 73\%$) (Figure 5B).

Pneumonia

A total of 1796 patients from eight[11,13,17,19-21,23,24] studies were analyzed. There was no difference in the incidence of pneumonia in comparative studies (95%CI: -0.00 to 0.04; $P = 0.28$; $I^2 = 20\%$) or RCT (95%CI: -0.10 to 0.10; $P = 0.39$; $I^2 = 0\%$) studies. In the overall analysis there was no difference in the meta-analysis of observational and RCT studies combined (95%CI: -0.00 to 0.03; $P = 0.44$; $I^2 = 0\%$) (Figure 5C).

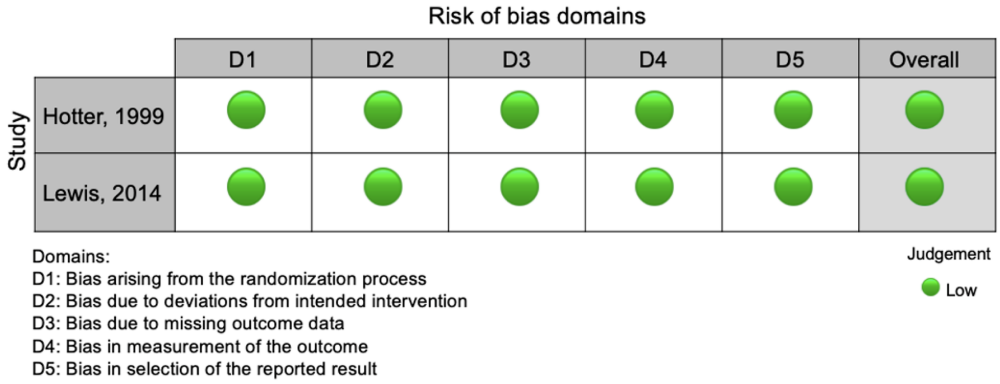
Peritonitis

A total of 34461 patients from five[12,17,21,23,27] were analyzed. There was no difference in the incidence of peritonitis in retrospective (95%CI: -0.02 to 0.01; $P < 0.0001$; $I^2 = 86\%$) studies. It was not possible to evaluate the peritonitis outcome in RCT studies because this outcome was not included in these studies (Figure 5D).



DOI: 10.13105/wjma.v11.i6.277

Figure 1 Flow diagram showing study selection process.



DOI: 10.13105/wjma.v11.i6.277

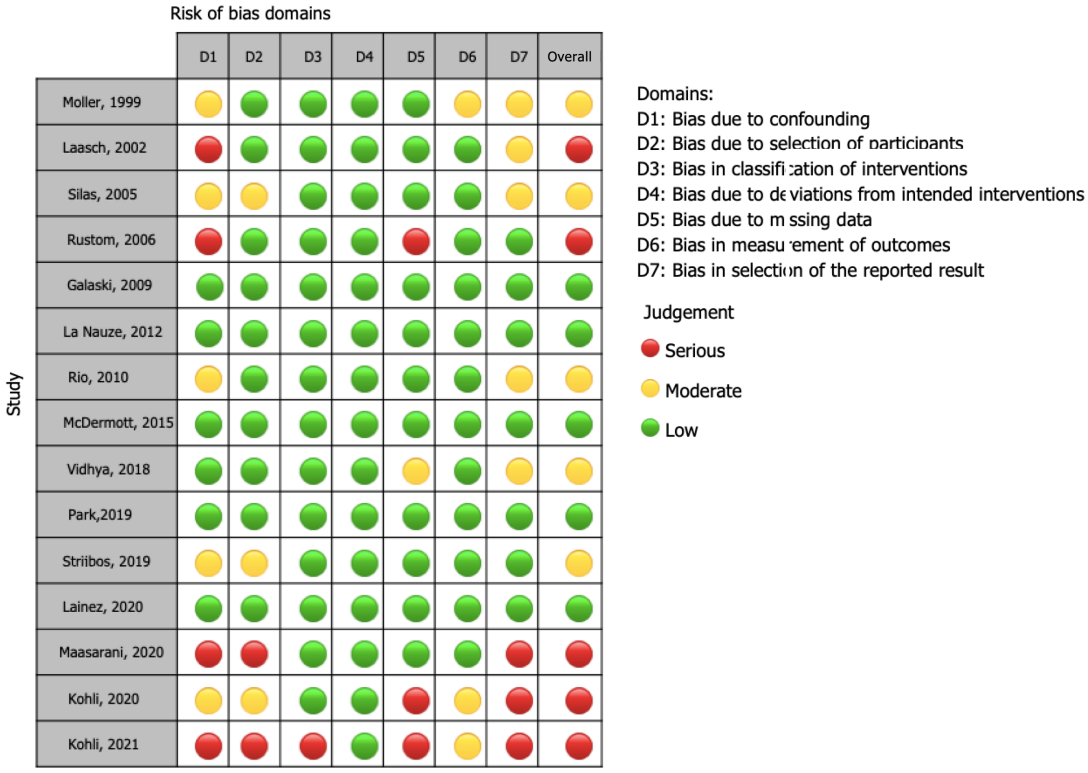
Figure 2 Risk of bias according to ROB-2.

Pain

A total of 260793 patients from seven[14,17,18,20,22,23,25] studies were analyzed. There was no difference in the incidence of pain in retrospective (95%CI: -0.05 to 0.02; $P < 0.00001$; $I^2 = 91\%$) studies. It was not possible to evaluate the pain outcome in RCT studies because this outcome was not included in these studies (Figure 5E).

Tube related complications

A total of 464689 patients from 14 studies[11-19,21-23,25,26] were analyzed. This analysis showed a significant difference in tube related complications in observational studies favoring PEG (95%CI: -0.03 to -0.08; $P < 0.00001$), although there was no significant difference in randomized studies (95%CI: -0.07 to 0.04; $P = 0.13$). In the global analysis there was a difference, favoring PEG (95%CI: -0.07 to -0.03; $P < 0.00001$) (Figure 6).



DOI: 10.13105/wjma.v11.i6.277

Figure 3 Risk of bias according to ROBINS-I.

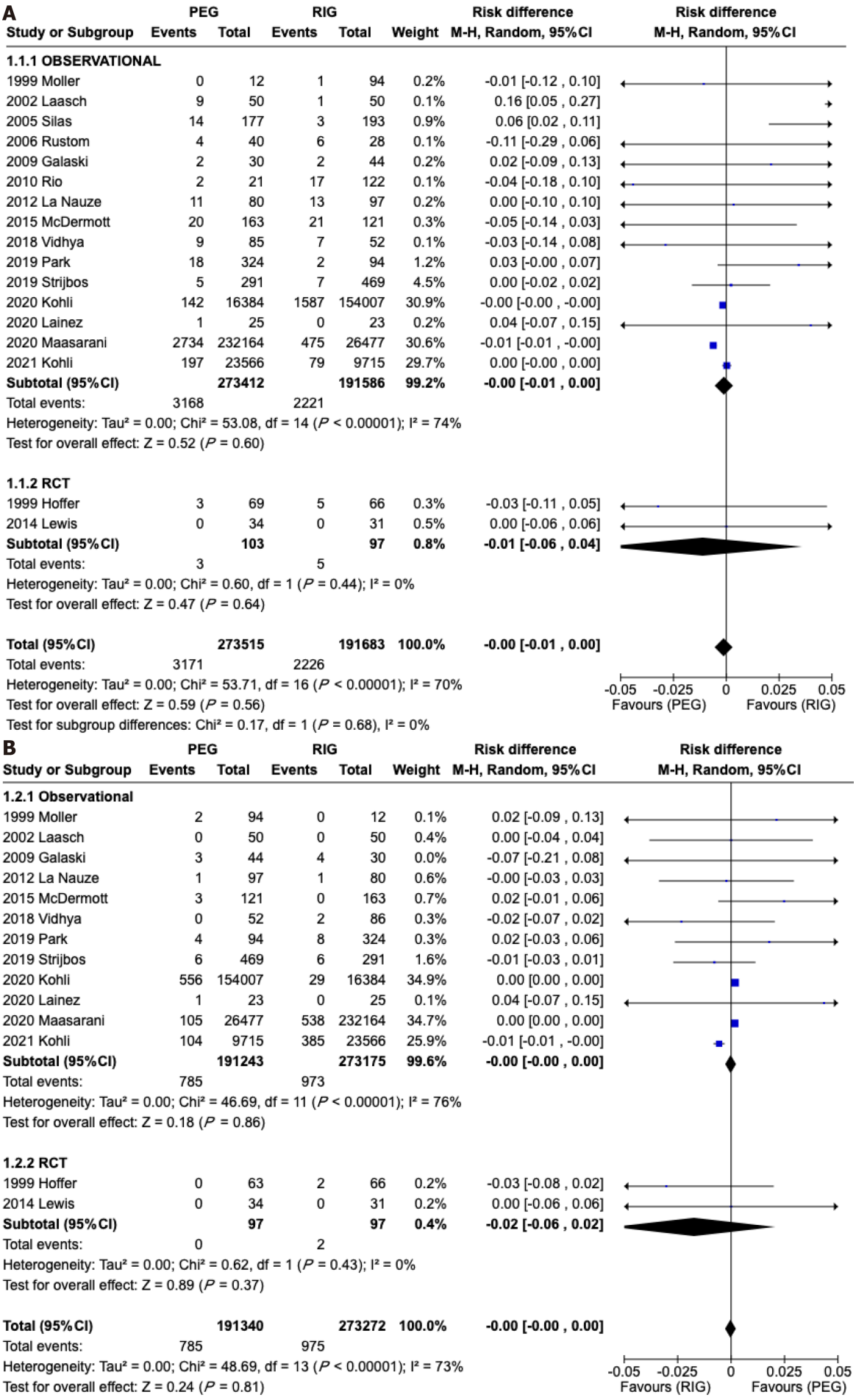
Certainty assessment							N° of patients		Effect		Certainty
N° of studies	Study desing	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain	Placebo	Relative (95% CI)	Absolute (95% CI)	
Pain											
7	observational studies	not serious	not serious	serious	not serious	none	12230/27573 (44.4%)	96205/233220 (41.3%)	**RR 1.11** (1.09 to 1.12)	**45 more per** 1.000 (from 37 more to 50 more)	◉◉◉◎ Moderate
Infection											
17	observational studies	not serious	serious	not serious	not serious	none	2226/191683 (1.2%)	3171/273515 (1.2%)	**RR 1.10** (0.87 to 1.38)	**1 more per** 1.000 (from 2 fewer to 4 more)	◉◉◉◎ Moderate
Peritonitis											
5	observational studies	not serious	not serious	not serious	not serious	none	28/10427 (0.3%)	455/24034 (1.9%)	**RR 0.54** (0.11 to 2.56)	**9 fewer per** 1.000 (from 17 fewer to 30 more)	◉◉◎◎ Low
Bleeding											
14	observational studies	not serious	serious	not serious	not serious	none	785/191277 (0.4%)	973/273206 (0.4%)	**RR 1.16** (0.69 to 1.95)	**1 more per** 1.000 (from 1 fewer to 3 more)	◉◎◎◎ Very low
Pneumonia											
8	observational studies	serious	not serious	not serious	not serious	none	28/909 (3.1%)	39/797 (4.9%)	**RR 0.72** (0.46 to 1.14)	**14 fewer per** 1.000 (from 26 fewer to 7 more)	◉◎◎◎ Very low

DOI: 10.13105/wjma.v11.i6.277

Figure 4 Quality of evidence assessed by Grading of Recommendations Assessment, Development, and Evaluation.

DISCUSSION

This meta-analysis shows that both PEG and PRG techniques are similar in terms of safety profile, except potentially in tube-related complications, which was higher for PRG in observational studies (Evidence 2A). We included 20 studies in this review (3 randomized and 17 comparative studies) and 17 in our meta-analysis, totaling 465218 individuals, with 273493 undergoing PEG and 191725 undergoing PRG. While other metanalyses compared these 2 approaches[28-34], this analysis is unique as it includes the largest number of adult patients and also separates RCT and observational studies providing further insight. This approach follows Cochrane recommendations and thus provides for a more reliable


A
PEG
RIG
Risk difference
Risk difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
1.1.1 OBSERVATIONAL
1999 Moller 0 12 1 94 0.2% -0.01 [-0.12 , 0.10]
2002 Laasch 9 50 1 50 0.1% 0.16 [0.05 , 0.27]
2005 Silas 14 177 3 193 0.9% 0.06 [0.02 , 0.11]
2006 Rustom 4 40 6 28 0.1% -0.11 [-0.29 , 0.06]
2009 Galaski 2 30 2 44 0.2% 0.02 [-0.09 , 0.13]
2010 Rio 2 21 17 122 0.1% -0.04 [-0.18 , 0.10]
2012 La Nauze 11 80 13 97 0.2% 0.00 [-0.10 , 0.10]
2015 McDermott 20 163 21 121 0.3% -0.05 [-0.14 , 0.03]
2018 Vidhya 9 85 7 52 0.1% -0.03 [-0.14 , 0.08]
2019 Park 18 324 2 94 1.2% 0.03 [-0.00 , 0.07]
2019 Strijbos 5 291 7 469 4.5% 0.00 [-0.02 , 0.02]
2020 Kohli 142 16384 1587 154007 30.9% -0.00 [-0.00 , -0.00]
2020 Lainez 1 25 0 23 0.2% 0.04 [-0.07 , 0.15]
2020 Maasarani 2734 232164 475 26477 30.6% -0.01 [-0.01 , -0.00]
2021 Kohli 197 23566 79 9715 29.7% 0.00 [-0.00 , 0.00]
Subtotal (95%CI) 273412 191586 99.2% -0.00 [-0.01 , 0.00]
Total events: 3168 2221
Heterogeneity: Tau² = 0.00; Chi² = 53.08, df = 14 (P < 0.00001); I² = 74%
Test for overall effect: Z = 0.52 (P = 0.60)
1.1.2 RCT
1999 Hoffer 3 69 5 66 0.3% -0.03 [-0.11 , 0.05]
2014 Lewis 0 34 0 31 0.5% 0.00 [-0.06 , 0.06]
Subtotal (95%CI) 103 97 0.8% -0.01 [-0.06 , 0.04]
Total events: 3 5
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Total (95%CI) 273515 191683 100.0% -0.00 [-0.01 , 0.00]
Total events: 3171 2226
Heterogeneity: Tau² = 0.00; Chi² = 53.71, df = 16 (P < 0.00001); I² = 70%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%
-0.05 -0.025 0 0.025 0.05
Favours (PEG) Favours (RIG)
B
PEG
RIG
Risk difference
Risk difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
1.2.1 Observational
1999 Moller 2 94 0 12 0.1% 0.02 [-0.09 , 0.13]
2002 Laasch 0 50 0 50 0.4% 0.00 [-0.04 , 0.04]
2009 Galaski 3 44 4 30 0.0% -0.07 [-0.21 , 0.08]
2012 La Nauze 1 97 1 80 0.6% -0.00 [-0.03 , 0.03]
2015 McDermott 3 121 0 163 0.7% 0.02 [-0.01 , 0.06]
2018 Vidhya 0 52 2 86 0.3% -0.02 [-0.07 , 0.02]
2019 Park 4 94 8 324 0.3% 0.02 [-0.03 , 0.06]
2019 Strijbos 6 469 6 291 1.6% -0.01 [-0.03 , 0.01]
2020 Kohli 556 154007 29 16384 34.9% 0.00 [0.00 , 0.00]
2020 Lainez 1 23 0 25 0.1% 0.04 [-0.07 , 0.15]
2020 Maasarani 105 26477 538 232164 34.7% 0.00 [0.00 , 0.00]
2021 Kohli 104 9715 385 23566 25.9% -0.01 [-0.01 , -0.00]
Subtotal (95%CI) 191243 273175 99.6% -0.00 [-0.00 , 0.00]
Total events: 785 973
Heterogeneity: Tau² = 0.00; Chi² = 46.69, df = 11 (P < 0.00001); I² = 76%
Test for overall effect: Z = 0.18 (P = 0.86)
1.2.2 RCT
1999 Hoffer 0 63 2 66 0.2% -0.03 [-0.08 , 0.02]
2014 Lewis 0 34 0 31 0.2% 0.00 [-0.06 , 0.06]
Subtotal (95%CI) 97 97 0.4% -0.02 [-0.06 , 0.02]
Total events: 0 2
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
Total (95%CI) 191340 273272 100.0% -0.00 [-0.00 , 0.00]
Total events: 785 975
Heterogeneity: Tau² = 0.00; Chi² = 48.69, df = 13 (P < 0.00001); I² = 73%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%
-0.05 -0.025 0 0.025 0.05
Favours (RIG) Favours (PEG)

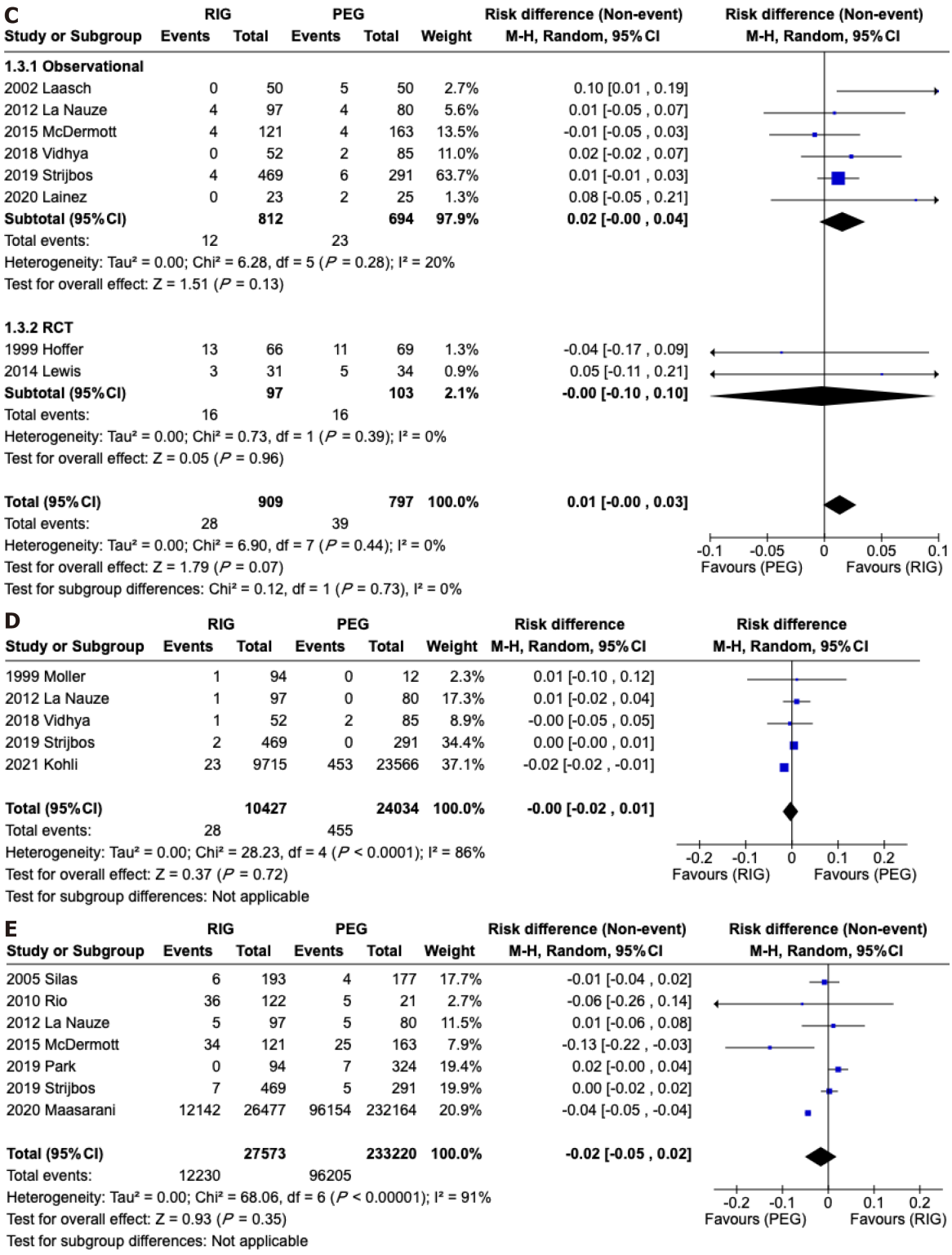


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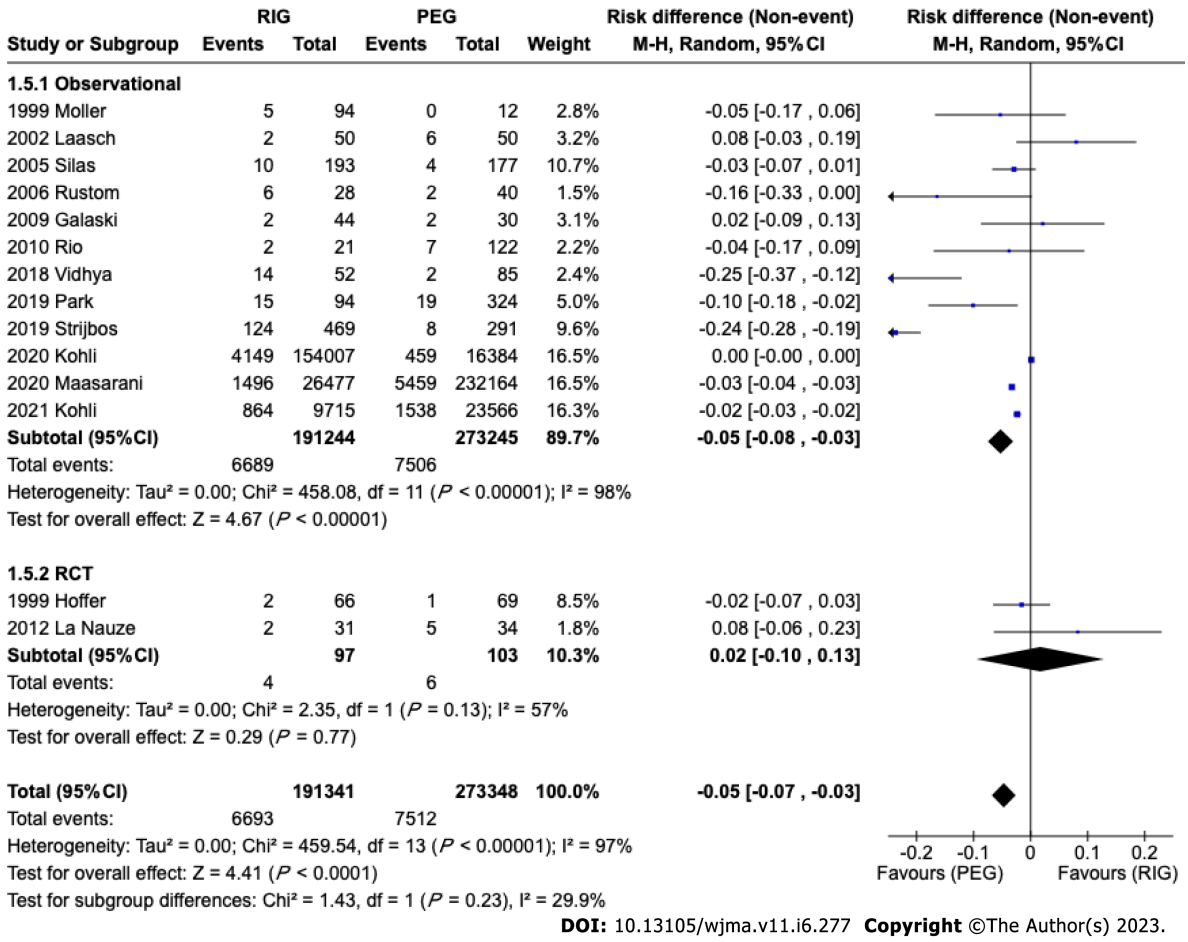
Figure 5 Forest plot studies reporting. A: Outcomes infection; B: Outcomes bleeding; C: Pneumonia; D: Outcomes peritonitis; E: Pain.

comparison. Additionally, we separated all adverse events, including pain and pneumonia, which have not been individually analyzed to date. The adverse effects chosen were based on previous publications showing the most frequent complications related to the method[4].

The three most common techniques for performing gastrostomy are endoscopic, radiologic, and surgical. Although surgical gastrostomy was the first described approach, it is now less used due to its invasiveness. A meta-analysis including RCT (evidence 1A) comparing endoscopic and surgical techniques demonstrated a lower number of minor complications for endoscopic procedures[35].

Until now, there is no consensus regarding the superiority of either endoscopic or radiologic gastrostomy. Our results clarify that both approaches are similar in terms of safety as shown in our meta-analysis including only RCTs.



DOI: 10.13105/wjma.v11.i6.277

Figure 6 Forest plot with studies reporting tube related complications.

Furthermore, a recent RCT including 42 patients comparing the two techniques[36], showed similar results to this meta-analysis. Unfortunately, this RCT was not included due to a lack of data available in the published manuscript, despite our attempt to contact the author.

Local infection is a common adverse outcome of gastrostomy. For this reason, the American Society for Gastrointestinal Endoscopy[37] and the Society for Interventional Radiology[38,39] recommends administering periprocedural antibiotics. The studies utilized in this meta-analysis did not expressly state if antibiotics were administered or not, but as this is a common practice, it was likely used. Our meta-analysis did not demonstrate a significant difference regarding infection in both RCT and non-RCT analysis.

In previous publications[26,27], it has been stated that patients undergoing PEG have a higher rate of bleeding since PEG is preferentially performed in patients with diseases requiring antiplatelets or anticoagulants such as stroke and vascular dementia[27,40]. We expected to prove this hypothesis, however, this meta-analysis demonstrated a low risk of bleeding due to the gastrostomy procedure, without a statistically significant difference between PEG and PRG in both RCT and observational studies. Data on antiplatelet and/or anticoagulant medications among patients who bled were not available.

This study showed no significant difference in the incidence of pneumonia. In previous studies it was observed that gastrostomy compared to nasogastric feeding has a lower incidence of pneumonia, however, this complication is a major cause of mortality in patients undergoing gastrostomy[16]. It is important to state that we were not able to evaluate gastrostomy and gastrojejunostomy separately due to a lack of data. Gastrojejunostomy is associated with a theoretically lower rate of reflux and pneumonia[11,19].

Pain and peritonitis are complex outcomes to measure objectively. Since the definition of these outcomes differs in several studies[13,14,17,18,20-25]. There was no statistical difference between the two methods in our study.

In the analyzed studies, the types, brands, and sizes of tubes were not differentiated. This heterogeneity may influence the results of this analysis. The meta-analysis of observational studies demonstrated a statistically significant difference in the incidence of tube-related complications of a PEG and PRG, such as dislocation, leak, obstruction, or breakdown, showing a higher incidence in PRG. In the RCT meta-analysis, there was no difference. However, the observational studies included 464489 patients versus 200 patients from RCT studies and this should be considered if the RCTs were underpowered to detect a small difference between the techniques. A difference may be expected due to the size difference between endoscopic and radiological techniques. PEG is usually performed using 20FR or 24FR tubes whereas PRG uses 14-16 FR[41]. The size of the gastrostomy ostium influences the incidence of migration; a smaller caliber is associated with a higher incidence of migration and obstruction. The feeding tube can become blocked due to various

reasons, such as the accumulation of food formula, medications, or debris. Smaller tubes increase the probability of the tube becoming blocked. Leaks can occur around the insertion site or through the tube itself, which can cause skin irritation and infection, so if the size of the skin insertion is larger than the tube caliber there is a greater chance of leakage.

Tube-related complications are usually associated with longer hospital stays, the need for further procedures, and potentially increased costs[16,33,42]. Evaluating costs is challenging since procedure cost varies significantly between countries. A study comparing the two techniques published in 2009 showed that the costs of the procedures are also different, with PEGs being 43% more expensive than PRGs[16] but the costs are related only to the procedure and not to the overall cost. In Brazil, PEG has a low cost, being more cost-effective than a CT scan. Although few studies provide information regarding costs, this information would be useful, given that these procedures are performed on a large scale worldwide[11,16].

The strengths of this study include a large number of patients from different continents, dedicated analysis of RCT data, use of a validated quality assessment tool, and application of the GRADE process to assess the quality of our data.

Although systematic review and meta-analysis represent the most thorough assessment of available evidence comparing the risks of PEG and PRG, our study has limitations as discussed above. Most data was gathered from observational studies. Additionally, lack of data on tube size, antibiotic, and anticoagulant use, indications for the gastrostomy procedure, and inclusion of both gastrostomy and gastrojejunostomy all limit understanding of potential nuances that differentiate PEG from PRG.

In summary, both approaches are safe. Thus, individual evaluation is required considering several factors including local and personal experience, device availability, cost, and patient preference.

CONCLUSION

PEG and PRG present a similar safety profile. However, PRG is associated with a slightly higher rate of tube-related complications, potentially related to the small caliber of the gastrostomy tube.

ARTICLE HIGHLIGHTS

Research background

Gastrostomy feeding is superior to nasogastric tube feeding when medium to long-term enteral feeding (≥ 4 wk) is indicated. The optimal technique for long-term enteral feeding is not yet well established. Therefore, we performed a meta-analysis comparing the two methods.

Research motivation

This paper motivation is to demonstrate which technique for performing a gastrostomy has the lowest incidence rate of adverse events.

Research objectives

The aim of the paper is to compare the technique of endoscopic gastrostomy (PEG) and gastrostomy *via* interventional radiology (PRG) and establish which technique is the safest for the patient.

Research methods

Comparative studies of PEG and PRG were selected. Included studies had outcomes such as infection, bleeding, pneumonia, pain, peritonitis and tube related complications. The risk of bias and quality of evidence were assessed. The analysis was performed using Review Manager (RevMan 5.4) from the Cochrane Informatics & Knowledge Management Department website.

Research results

Seventeen studies were included, with a total of 465218 patients. The only outcome that showed a significant difference was tube-related complications in retrospective studies favoring PEG (95%CI: 0.03 to 0.08; $P < 0.00001$), although this outcome did not show significant difference in randomized studies (95%CI: -0.07 to 0.04; $P = 0.13$). There was no difference in the analyses of the following outcomes: Infection in retrospective (95%CI: -0.01 to 0.00; $P < 0.00001$) or randomized (95%CI: -0.06 to 0.04; $P = 0.44$) studies; bleeding in retrospective (95%CI: -0.00 to 0.00; $P < 0.00001$) or randomized (95%CI: -0.06 to 0.02; $P = 0.43$) studies; pneumonia in retrospective (95%CI: -0.04 to 0.00; $P = 0.28$) or randomized (95%CI: -0.09 to 0.11; $P = 0.39$) studies; pain in retrospective (95%CI: -0.05 to 0.02; $P < 0.00001$) studies; peritonitis in retrospective (95%CI: -0.02 to 0.01; $P < 0.0001$) studies.

Research conclusions

The study concluded that RIG has a higher incidence of tube-related complications than PEG. This difference is probably associated with the caliber of the tubes used. There was no statistical difference in the other outcomes evaluated.

Research perspectives

This study aimed to determine which technique is safer for the patient, and both methods proved to be safe. We can conclude that the choice of technique depends on the type of patient, the experience of the service, the cost, and the availability of the method.

FOOTNOTES

Author contributions: dos Santos ESV contributed acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; de Oliveira GHP, dos Santos ESV and Hirsch BS contributed analysis and interpretation of data, revising the article; de Moura DTH contributed analysis of data, interpretation of data, drafting the article, revising the article, final approval; Bernardo WM contributed analysis of data, interpretation of data, drafting the article, revising the article, final approval; de Moura EGH contributed analysis and interpretation of data, drafting the article, revising the article, final approval.

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P-Editor: Zhao S

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META-ANALYSIS

Evidence relating cigarettes, cigars and pipes to cardiovascular disease and stroke: Meta-analysis of recent data from three regions

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Abstract

BACKGROUND

More recent data are required relating to disease risk for use of various smoked products and of other products containing nicotine. Earlier we published meta-analyses of recent results for chronic obstructive pulmonary disease and lung cancer on the relative risk (RR) of current compared to never product use for cigarettes, cigars and pipes based on evidence from North America, Europe and Japan. We now report corresponding up-to-date evidence for acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke.

AIM

To estimate, using recent data, AMI, IHD and stroke RRs by region for current smoking of cigarettes, cigars and pipes.

METHODS

Publications in English from 2015 to 2020 were considered that, based on epidemiological studies in the three regions, estimated the current smoking RR of AMI, IHD or stroke for one or more of the three products. The studies should involve at least 100 cases of stroke or cardiovascular disease (CVD), not be restricted to populations with specific medical conditions, and should be of cohort or nested case-control study design or randomized controlled trials. A literature search was conducted on MEDLINE, examining titles and abstracts initially, and then full texts. Additional papers were sought from reference lists of selected papers, reviews and meta-analyses. For each study identified, we entered the most recent available data on current smoking of each product, as well as the characteristics of the study and the RR estimates. Combined RR estimates were derived using random-effects meta-analysis for stroke and, in the case of CVD, separately for IHD and AMI. For cigarette smoking, where far more data were available, heterogeneity was studied by a wide range of factors. For cigar and pipe smoking, a more limited heterogeneity analysis was carried out. A more limited assessment of variation in risk by daily number of cigarettes smoked was also conducted.

Results were compared with those from previous meta-analyses published since 2000.

RESULTS

Current cigarette smoking: Ten studies gave a random-effects RR for AMI of 2.72 [95% confidence interval (CI): 2.40-3.08], derived from 13 estimates between 1.47 and 4.72. Twenty-three studies gave an IHD RR of 2.01 (95%CI: 1.84-2.21), using 28 estimates between 0.81 and 4.30. Thirty-one studies gave a stroke RR of 1.62 (95%CI: 1.48-1.77), using 37 estimates from 0.66 to 2.91. Though heterogeneous, only two of the overall 78 RRs were below 1.0, 71 significantly ($P < 0.05$) exceeding 1.0. The heterogeneity was only partly explicable by the factors studied. Estimates were generally higher for females and for later-starting studies. They were significantly higher for North America than Europe for AMI, but not the other diseases. For stroke, the only endpoint with multiple Japanese studies, RRs were lower there than for Western studies. Adjustment for multiple factors tended to increase RRs. Our RR estimates and the variations by sex and region are consistent with earlier meta-analyses. RRs generally increased with amount smoked. Current cigar and pipe smoking: No AMI data were available. One North American study reported reduced IHD risk for non-exclusive cigar or pipe smoking, but considered few cases. Two North American studies found no increased stroke risk with exclusive cigar smoking, one reporting reduced risk for exclusive pipe smoking (RR 0.24, 95%CI: 0.06-0.91). The cigar results agree with an earlier review showing no clear risk increase for IHD or stroke.

CONCLUSION

Current cigarette smoking increases risk of AMI, IHD and stroke, RRs being 2.72, 2.01 and 1.62. The stroke risk is lower in Japan, no increase was seen for cigars/pipes.

Key Words: Cigarettes; Cigars; Pipes; Cardiovascular disease; Stroke; Meta-analysis; Review

Core Tip: Recent North American and European studies indicate that current, compared to never cigarette smoking, increases risk in each sex by about 3-fold for acute myocardial infarction, about 2-fold for ischaemic heart disease (IHD), and about 1.6-fold for stroke. More limited evidence from Japanese studies suggests a similar increase in risk for IHD, but a lower increase, of about 1.2-fold, for stroke. The increase in risk is greater in heavier smokers. Limited recent data for cigar or pipe smoking, all from North America, finds no evidence of an increased risk of IHD or stroke, one study reporting a significantly reduced risk of stroke in exclusive pipe smokers. Our findings are generally consistent with evidence from earlier studies. Cigarette smoking increases risk of all the three diseases studied, but by a much smaller factor than noted for lung cancer and chronic obstructive pulmonary disease in our companion publication. Any increase in risk from cigar and pipe smoking has not been demonstrated.

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INTRODUCTION

It is known that cigarette smoking increases risk of various diseases, particularly chronic obstructive pulmonary disease (COPD), lung cancer, stroke and various forms of cardiovascular disease (CVD), including ischaemic heart disease (IHD) and acute myocardial infarction (AMI)[1,2]. However, any risk increases from cigar or pipe smoking, or from using other products containing nicotine are less well investigated. In a project based on studies conducted in North America, Europe and Japan (regions commonly studied in predictive modelling exercises[3-8] and which do not include countries such as India, where a wide variety of other tobacco products are commonly used), we are comparing relative risks (RRs) of various diseases for current *vs* never use of different products. In this journal we earlier published two reviews with meta-analyses of recent epidemiological evidence. One related current use of snus (Swedish snuff) or smokeless tobacco to risk of the major smoking-related diseases[9]. Another related current cigarette, pipe and cigar smoking to risk of lung cancer and COPD[10]. Here we systematically review and meta-analyse evidence relating current smoking of cigarettes, pipes and cigars to risk of AMI, IHD and stroke, based on publications in 2015 to 2020. We do not consider either electronic cigarettes or heat-not-burn products in our project, because large long-term studies relating risk of the main smoking-related diseases to their use have not so far been conducted. As in our previous publications we aim only to carry out meta-analyses concerning current product use, and to study how the derived RRs vary by factors like sex and region, and not investigating in detail variation by amount smoked, duration of smoking, time quit, or age at onset.

The work described here partially updates two earlier meta-analyses of ours. One[5], based on data from 15 countries in Europe, Asia or North America, reported analyses comparing risk in current v never cigarette smoking, giving a RR of 2.05 (95%CI: 1.90-2.21) combining 92 estimates for IHD/AMI, and of 1.48 (95%CI: 1.37-1.60) combining 57 estimates for stroke. The other[11], limited to Japan, gave an RR of 2.21 (95%CI: 1.96-2.50) combining 20 estimates for IHD and of 1.40 (95%CI: 1.25-1.57) combining 16 estimates for stroke. Neither of these reviews considered cigar or pipe smoking specifically. We compare our derived RR estimates with those earlier results, and also with findings of other meta-analyses/reviews published between 2000 and 2020, some of IHD and stroke[12-18], one of IHD only[19], some of stroke only[20-23] and some limited to particular types of stroke[24-28]. These reviews generally relate to cigarette smoking, or to undefined smoking, but one[12] gives results for exclusive cigar smokers.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 2015 to 2020 which provided RR estimates for stroke, IHD or AMI comparing current and never smokers of cigarettes, of cigars, or of pipes. These had to be based on epidemiological cohort or nested case-control studies or randomized controlled trials which were conducted in North America, Europe or Japan, and which involved at least 100 cases of the disease of interest. The studies were excluded if they were restricted to specific types of the diseases, or to patients with specific medical conditions, or if the results were superseded by corresponding later results from the same study. Studies providing estimates for equivalent diseases, such as cerebrovascular disease rather than stroke, coronary heart (or artery) disease rather than IHD, or myocardial infarction rather than AMI were also included. However, studies providing estimates only for disease subsets, such as specific types of stroke were not included.

Literature searches

Initially, at stage 0, literature searches were conducted on MEDLINE for publications in 2015 to 2020. Searches were carried out on November 13, 2021 and used the terms "smoking" OR "smoking [MeSH Major Topic]" AND "cardiovascular disease" OR "heart disease" OR "stroke".

Then, at stage 1, titles and abstracts were screened to select publications that appeared to describe studies satisfying the inclusion criteria, and both meta-analyses and reviews that may cite other relevant publications. The initial screening was usually carried out by PNL, with acceptances checked by KJC, though in some cases KJC did the initial screening and PNL the checking. Disagreements were resolved *via* discussion.

Then, at stage 2, the full texts of the selected publications (and of relevant Supplementary files and other publications linked to them in the MEDLINE search) were obtained, and examined by PNL, who classified the publication as being an acceptance (*i.e.* it appeared to include relevant data), a reject (giving reason), a relevant review or a relevant meta-analysis. The rejections were then checked by KJC, with any disagreements resolved.

At stage 3, additional accepted publications not detected by the MEDLINE searches were sought by examination of reference lists of the accepted papers and of the relevant reviews and meta-analyses and, when obtained, dealt with as in stage 2.

Finally, at stage 4, copies of all the accepted publications (not the meta-analyses) were organized, first by country, and then by study within country, with studies conducted in multiple countries considered as a separate group. The aim was to eliminate from consideration those publications giving results for a study that were superseded by a later publication, and those publications which, on more detailed examination, did not fully satisfy the inclusion criteria.

Data entry

Data were entered into a study database and into an associated RR database. The study-specific information recorded was: Study name; country; region (North America, Europe, Japan or multiple); study design (cohort, nested case-control, or randomized controlled), study population (international, national, regional or specific, *e.g.* workers in a particular industry); study size (number of cases of the disease); year of start; length of follow-up; sexes considered (males only, females only, or both); and age range considered. Also recorded was a summary of the definition of each disease used in each study, including the international classification of disease (ICD) codes where they were provided in the source paper.

The information recorded relating to each RR was: The RR itself and its 95% confidence interval (CI), the RR and CI being estimated from the data provided if necessary; the study to which it related; an identifier for the paper providing the estimate; the year of publication of the paper; whether the RR related to exclusive use of the product; the sex to which it related (males, females or combined - combined RRs only being entered if sex-specific RRs were not available); the age range considered; the years of follow-up considered; the endpoint (from death certification only, or involving in-life diagnosis); whether a latency rule was applied (*i.e.* whether cases identified in the first few years of follow-up were ignored), the number of adjustment factors applied to the risk estimate, and whether the definition of disease was standard or not.

Meta-analyses

Meta-analyses could not be conducted for current cigar or current pipe smoking as the data proved to be too limited. Otherwise, individual study RR estimates were combined using fixed- and random-effects meta-analyses[29], with the

significance of between-study heterogeneity also estimated. For current cigarette smoking, where data were much more extensive, more detailed meta-analyses were conducted, separately for AMI, IHD and stroke, as described below.

Initially, meta-analyses were conducted based on either two RR estimates from each study, if separate RRs were available for males and females, or on a single estimate if the study reported only combined sex results or results for only one sex. Where there was a choice of RRs available for a study, those selected were based on a sequence of preferences applied in turn: (1) Exclusive rather than non-exclusive cigarette smoking; (2) a latency rule had been applied rather than not; and (3) adjustment for the most possible confounders.

Where the data permitted, heterogeneity was studied by the following factors: Sex; region; study population; year of start; study size; exclusive use; study design; lowest age considered; years of follow-up; endpoint; number of adjustment factors; and disease definition. Grouped levels of the variables were used as appropriate.

For each disease, forest plots were generated, with results separated by region, each line of the plot showing the study name (and sex where relevant) and giving the RR and 95%CI. Each RR is illustrated as a square with the area proportional to the weight of the estimate, surrounded by lines extending to the upper and lower 95% confidence limit. The plots also similarly present the overall RRs and 95%CIs for each region and for all the regions combined.

While these meta-analyses and heterogeneity investigations were based on between-study variation in RRs, some additional investigations were conducted on within-study variation in RRs, based on data from the same publication. For sex, these meta-analyses were based on the ratio of the RR for males to that for females, while for level of adjustment, results were compared based on the ratio of the RR adjusted for multiple potential confounding variables to the RR adjusted for no variables. Where multiple pairs of results were available within a publication, the pair selected was chosen based on the preferences described above.

Additional investigation of risk related to the number of cigarettes smoked. The papers selected for the meta-analyses relating cigarette smoking to risk of AMI, IHD and stroke were examined to identify those reporting RRs by number of cigarettes smoked. The results were then tabulated in order to assess those showing a tendency for RRs to increase with amount smoked. Formal meta-analyses of these results were not attempted in view of the various different ways in which the number of cigarettes smoked were grouped. Results by pack-years were not considered as this measure makes the invalid assumption that given increases in amount smoked and duration smoked have the same proportional effect on risk.

RESULTS

Literature searches

A flowchart of the searches is shown in Figure 1. Starting with 20,500 papers identified in the initial MEDLINE searches, the 49 papers identified provided results for AMI, IHD and stroke from respectively, 10, 23 and 31 studies (Figure 1).

For AMI, 20 RRs were available for analysis, all for cigarette smoking. For IHD, there were 53, 51 for cigarette smoking and one each for cigar and for pipe smoking. For stroke there were 76, 70 for cigarettes, four for cigars, and two for pipes. It should be noted that some studies provide more than one estimate, *e.g.* by sex, by level of covariate adjustment, or for different products.

Table 1 (AMI), Table 2 (IHD) and Table 3 (stroke) provide details of the studies considered. Some studies gave data for more than one disease.

The definitions of the diseases considered in each study are not shown in the tables, but can be found in Supplementary material 1.

AMI - cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from one publication per study. Of the total of ten studies, two were from North America [one United States of America (USA), one Canada], and eight were from Europe [two each from Sweden and United Kingdom (UK), and one from each of Estonia, Finland, Germany and Norway]. All were cohort studies. Three studies were national, six regional and one based on GP records. As can be seen in Table 1, the studies varied as regards different factors, including start year, length of follow-up, ages and sexes considered, numbers of AMI cases studied, whether cases were dead or diagnosed, and extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied in the definition of AMI, the standard definition being based on ICD-8 or ICD-9 code 410 or ICD-10 code I21.

AMI - cigarette smoking meta-analyses

Data were entered on 20 RRs, with at most four per study. The initial meta-analyses involved 13 RRs, these being selected using the preferences described above. As can be seen in Table 4 and Figure 2, the overall RR estimate (random-effects) was 2.72 (95%CI: 2.40-3.08), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all exceeded 1.00 (range 1.47-4.72) and all but one of the RRs were significantly increased ($P < 0.05$).

Table 4 also shows RRs by level of ten different study or RR characteristics. The the most striking evidence of risk variation was for number of adjustment factors where the estimates adjusted for age only (2.52, 95%CI: 2.34-2.71) and for age and other factors (2.89, 95%CI: 2.48-3.37) were higher than that with no adjustment (1.47, 95%CI: 1.08-2.01). Estimates were also significantly higher for estimates from North America rather than Europe, for studies starting from 1988 onward than for earlier starting studies, for studies with shorter years of follow-up, and for studies using a standard disease definition. The RR for females exceeded that for males, but not significantly.

Table 1 Details of the 10 studies of acute myocardial infarction

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age	Sex[b]	Cases	Adjust[c]	Excl[d]	Latency[e]	Endpoint	NRR[f]
BIOBANK	[37]	United Kingdom	Cohort	National	2006	12	40-69	M, F	5081	2	0	0	Diagnosed	2
CaCHS	[38]	Canada	Cohort	Regional	2001	13	20+	M, F	1133	15	0	0	Diagnosed	2
CALIBER	[39]	United Kingdom	Cohort	GP records	1997	13	30+	F	5628	1	0	0	Diagnosed	1
EPIC-GERM	[40]	Germany	Cohort	Regional	1994	14	35-65	C	507	0, 9	0	0	Diagnosed	2
ESTONGENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	118	0, 1	0	0	Died	4[g]
KIHD	[42]	Finland	Cohort	Regional	1984	18	42-60	M	205	0	0	0	Diagnosed	1
TROMSO	[43]	Norway	Cohort	Regional	1979	33	20-94	F	854	0, 4	0	0	Diagnosed	2
VASTERBOTTEN	[44]	Sweden	Cohort	Regional	1990	19	30-60	C	2062	2, 9	0	0	Diagnosed	2
WHILA	[45]	Sweden	Cohort	Regional	1995	20	50-59	F	205	1, 7	0	0	Diagnosed	2
WHS	[46]	United States	Cohort	National	1992	26	45+	F	629	0, 14	0	0	Diagnosed	2

[a]Study IDs are BIOBANK: The UK Biobank Study; CaCHS: Canadian Community Health Survey; CALIBER: Cardiovascular disease research using linked bespoke studies and electronic health records; EPIC-GERM: European Prospective Investigation into Cancer and Nutrition, German component; ESTON-GENOME: Estonian Genome Center of the University of Tartu; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; TROMSO: Tromsø Study; VASTERBOTTEN: Västerbotten Intervention Programme; WHILA: Women's Health in the Lund Area Study; WHS: Women's Health Study.
[b]C: Results only for sexes combined.
[c]Number of adjustment factors for which relative risk (RR) available (0: Unadjusted, 1: Age adjusted, N > 1: Adjusted for N factors).
[d]No study had results available for exclusive use.
[e]No study excluded deaths in the early period of follow-up.
[f]Number of RRs available.
[g]Some of the RRs used from this study came from personal communication from Professor Koks.

AMI - cigarette smoking within-study comparisons

There were three comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was less than the female one in two pairs, and the overall estimate of the male/female ratio was not significant (ratio 0.74, CI 0.50-1.09).

There were four studies where comparison could be made between estimates adjusted for 2 or more covariates and estimates that were unadjusted or adjusted for age only. In only one of these did adjustment for multiple covariates materially increase the RR.

Within the studies considered, no study has pairs of estimates varying by other factors.

Table 2 Details of the 23 studies of ischaemic heart disease

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age[b]	Sex[c]	Cases[d]	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
7CNTRY-ITALY	[47]	Italy	Cohort	Regional	1960	50	40-59	M	319	3	0	0	Died	1
ARIC	[48]	United States	Cohort	National	1987	30	45-64	C	1798	0, 15	0	0	Diagnosed	2
BIOBANK	[49]	United Kingdom	Cohort	National	2006	12	40-69	C	547	0	0	0	Diagnosed	1
CALIBER	[39]	United Kingdom	Cohort	GP records	1997	13	30+	F	16800	1	0	0	Diagnosed	1
CPS-II	[50]	United States	Cohort	National	1982	22	30+	C	13478	0, 23	0	0	Died	2
CoCHS	[51]	Denmark	Cohort	Regional	1991	22	20-93	F	900	1	0	0	Diagnosed	1
ELSA	[52]	United Kingdom	Cohort	National	2004	13	52+	C	352	0, 7	0	0	Diagnosed	2
EPIC-10	[53]	Multi	Cohort	International	1991	19	35-70	M, F	7198	0	0	0	Diagnosed	2
	[54]	Multi	Nested CC	International	1991	19	35-70	C	7198	0	0	0	Diagnosed	1
EPIC-UK	[55]	United Kingdom	Cohort	Regional	1993	14	45-79	C	2332	0, 2, 6	0	0	Diagnosed	3
ESTON-GENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	696	0, 1	0	0	Died	4[i]
FINRISK	[56]	Finland	Cohort	National	1982	25	25-74	F	NR	3, 8	0	0	Died	2
HAPIEE	[57]	Multi	Cohort	International	2002	9	NAR	C	225	0	0	0	Died	1
HSE-SHS	[58]	United Kingdom	Cohort	National	1994	17	NAR	C	1412	0, 7	0	0	Died	2
JACC	[59]	Japan	Cohort	Regional	1988	21	40-79	M, F	1554	0, 7, 9	x	0	Died	4
MALMO	[60]	Sweden	Cohort	Regional	1991	22	46-67	M, F	3217	0, 6	0	0	Diagnosed	4
MESA	[61]	United States	Cohort	Regional	2000	11	45-84	C	449	1, 14	0	0	Diagnosed	3
	[62]	United States	Cohort	Regional	2000	11	45-84	C	449	0	0	0	Diagnosed	1
NAS	[63]	United States	Cohort	Regional	1991	20	NAR	F	137	0	0	0	Diagnosed	1
NHS	[64]	United States	Cohort	Medical workers	1989	17	43-68	F	3874	0	0	0	Diagnosed	1
NHS-II	[65]	United States	Cohort	Medical workers	1991	20	25-42	F	456	1, 15	0	0	Diagnosed	2
PREVEND	[66]	Netherlands	Cohort	Regional	2001	9	32-80	C	212	0, 2, 10	0	0	Diagnosed	3
USA5	[67]	United States	Cohort	Regional	2000	11	55+	M, F	29931	0, 5	0	0	Died	4
WHI	[68]	United States	Cohort	National	1993	20	50-79	F	2975	11	0	0	Died	1
WHITEHALL	[69]	United Kingdom	Cohort	Civil servants	1967	43	40-69	M	3250	1	0	0	Died	1

[a]Study IDs are 7CNTRY-ITALY: Italian Rural Areas of the Seven Countries Study; ARIC: Atherosclerosis Risk in Communities Study; BIOBANK: The UK Biobank Study; CALIBER: Cardiovascular disease research using linked bespoke studies and electronic health records; CPS-II: Cancer Prevention Study 2; CoCHS: The Copenhagen City Heart Study; ELSA: The English Longitudinal Study of Ageing; EPIC-10: European Prospective Investigation Into Cancer and Nutrition; EPIC-UK: The European Prospective Investigation of Cancer -Norfolk; ESTON-GENOME: Estonian Genome Center of the University of Tartu; FINRISK: The National FINRISK Study; HAPIEE: Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) project; HSE-SHS: Health Survey for England and the Scottish Health Survey; JACC: Japanese Collaborative Cohort Study; MALMO: Malmö Diet and Cancer Study; MESA: Multi-Ethnic Study of Atherosclerosis; NAS: Normative Aging Study; NHS: Nurses' Health Study I; NHS-II: Nurses' Health Study II; PREVEND: Prevention of Renal and Vascular End-Stage Disease; USA5: Cancer Prevention Study II Nutrition, Nurses' Health Study I Women's Health Initiative cohort, National Institutes of Health–AARP Diet and Health Study, and Health Professionals Follow-up Study; WHI: Women's Health Initiative; WHITEHALL: The Whitehall Study.

[b]NAR: No age restriction specified.

[c]C: Results only for sexes combined.

[d]NR: Not reported.

[e]Number of adjustment factors for which relative risk (RR) available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).

[f]x: Results available for exclusive use.

[g]No study excluded deaths in the early period of follow-up.

[h]Number of RRs available.

[i]Some of the RRs used from this study came from personal communication from Professor Koks.

IHD – cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from two publications for one study. Of the total of 23 studies, eight were from the USA, 14 from Europe (six UK, two from more than one country, and one from each of Denmark, Estonia, Finland, Italy, Netherlands, and Sweden), and one from Japan. One was a nested case-control study, the rest being of cohort design. Two studies were international, eight national, nine regional, two of medical workers, one of civil servants and one based on general practitioner records.

As demonstrated in Table 2, the studies varied by various factors, including start year, length of follow-up, ages and sexes considered, numbers of IHD cases studied, whether results were available for exclusive cigarette use, whether cases were dead or diagnosed, and the extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied with the definition of IHD used to identify cases, the standard definition being based on ICD-8 or ICD-9 codes 410-414 or ICD-10 codes I20-I25.

IHD - cigarette smoking meta-analyses

Data were entered on 49 RRs, with at most four per study. The initial meta-analyses involved 28 RRs, these being selected using the preferences described above. As can be seen in Table 5 and Figure 3, the overall RR estimate (random-effects) was 2.01 (95%CI: 1.84-2.21), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all but one exceeded 1.00 (range 0.81-4.30), and 27 were significantly increased ($P < 0.05$).

Table 5 also shows RRs by level of 11 different study or RR characteristics. There was significant ($P < 0.05$) variation for two of these. One was endpoint, where the RR was higher for cases that had died compared to where it had been diagnosed. The other related to the number of adjustment factors where the RR was lower for those adjusted for age only, than for those that were unadjusted or adjusted for multiple factors. As for AMI, the RR for females exceeded that for males, but not significantly.

IHD – cigarette smoking within-study comparisons

There were five comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was lower in all five pairs, and the overall estimate of the male/female ratio was significant (ratio 0.85, 95%CI: 0.80-0.91).

Table 3 Details of the 31 studies of stroke

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age[b]	Sex[c]	Cases	Adjust[d]	Excl[e]	Latency[f]	Endpoint	NRR[g]
7CNTRY-ITALY	[47]	Italy	Cohort	Regional	1960	50	40-59	M	225	3	0	0	Died	1
ARIC	[48]	USA	Cohort	National	1987	30	45-64	C	1106	0, 14	0	0	Diagnosed	2
BIOBANK	[70]	UK	Cohort	National	2006	12	40-69	M, F	4662	2	0	0	Diagnosed	2
CALIBER	[39]	UK	Cohort	GP records	1997	13	30+	F	11842	1	0	0	Diagnosed	1
CPS-II	[50]	USA	Cohort	National	1982	22	30+	C	5582	0, 23	0	0	Died	2
CaCHS	[38]	Canada	Cohort	Regional	2001	13	20+	M, F	1636	15	0	0	Diagnosed	2
	[71]	Canada	Cohort	Regional	2001	11	20+	M, F	1636	0	0	0	Diagnosed	2
ELSA	[52]	UK	Cohort	National	2004	13	52+	C	326	0, 7	0	0	Diagnosed	2
EPIC-10	[54]	Multi	Nested CC	International	1991	19	35-70	C	2187	0	0	0	Diagnosed	1
EPIC-ITALY	[72]	Italy	Cohort	Regional	1993	15	35-74	M, F	386	0, 2, 10	0	0	Diagnosed	6
EPIC-SPAIN	[73]	Spain	Cohort	Regional	1992	16	29-69	F	301	0	0	0	Diagnosed	1
EPIC-UK	[55]	UK	Cohort	Regional	1993	14	45-79	C	385	0, 2, 6	0	0	Diagnosed	3
ESTON-GENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	156	0, 1	0	0	Died	4[h]
HAPIEE	[57]	Multi	Cohort	International	2002	9	NAR	C	109	0	0	0	Died	1
HSE-SHS	[58]	UK	Cohort	National	1994	17	NAR	C	690	0, 7	0	0	Died	2
JACC	[59]	Japan	Cohort	Regional	1988	21	40-79	M, F	3163	0, 7, 9	x	0	Died	4
JHS	[74]	USA	Cohort	Regional	2000	15	21-84	C	183	0, 11	0	0	Diagnosed	2
JP8	[75]	Japan	Cohort	National	1983	30	40+	M	3487	0	0	0	Died	1
MALMO	[76]	Sweden	Cohort	Regional	1991	22	46-67	C	305	0	0	0	Diagnosed	1
MESA	[62]	United States	Cohort	Regional	2000	11	45-84	C	180	0	0	0	Diagnosed	1
MILLION	[28]	United Kingdom	Cohort	National	1996	19	46-66	F	8103	8	0	0	Diagnosed	1
NFBC	[77]	Finland	Cohort	Regional	1966	49	14-46	C	352	0, 10	0	0	Diagnosed	2
NHIS	[78]	United States	Cohort	National	1987	24	18-95	C	2046	0, 5	x	0	Died	2
	[79]	United States	Cohort	National	1987	14	18-95	C	2046	0, 8, 9	0	x	Died	3
	[80]	United States	Cohort	National	1987	28	40-79	M	2046	0, 1, 9	0	x	Died	3

NHS	[64]	United States	Cohort	Medical workers	1989	17	43-68	F	3288	0	0	0	Diagnosed	1
NIH-AARP	[81]	United States	Cohort	Regional	2004	7	70+	C	1369	0, 4	0	0	Died	2
NLMS	[82]	United States	Cohort	National	1985	26	35-80	C	3083	0, 1, 5	x	0	Died	3
OHASAMA	[83]	Japan	Cohort	Regional	1998	12	60+	C	293	2	x	0	Diagnosed	1
PREVEND	[66]	Netherlands	Cohort	Regional	2001	9	32-80	C	83	0, 2, 10	0	0	Diagnosed	3
SCCS	[84]	United States	Cohort	Regional	2002	11	40-79	C	389	7	0	0	Died	1
USA5	[67]	United States	Cohort	Regional	2000	11	55+	M, F	9821	0, 5	0	0	Died	4
WHITEHALL	[69]	United Kingdom	Cohort	Civil servants	1967	43	40-69	M	1061	1	0	0	Diagnosed	1
WHS	[46]	United States	Cohort	National	1992	26	45+	F	887	0, 14	0	0	Diagnosed	2

[a]Study IDs are 7CNTRY-ITALY: Italian Rural Areas of the Seven Countries Study; ARIC: Atherosclerosis Risk in Communities Study; BIOBANK: The UK Biobank Study; CALIBER: cardiovascular disease research using linked bespoke studies and electronic health records; CPS-II: Cancer Prevention Study 2; CaCHS: Canadian Community Health Survey; ELSA: The English Longitudinal Study of Ageing; EPIC-10: European Prospective Investigation into Cancer and Nutrition; EPIC-ITALY: Italian European Investigation into Cancer and Nutrition; EPIC-SPAIN: Spanish European Investigation into Cancer and Nutrition; EPIC-UK: The European Prospective Investigation of Cancer -Norfolk; ESTON-GENOME: Estonian Genome Center of the University of Tartu; HAPIEE: Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) project; HSE-SHS: Health Survey for England and the Scottish Health Survey; JACC: Japanese Collaborative Cohort Study; JHS: Jackson Heart Study; JP8: Pooled analysis of eight prospective studies in Japan; MALMO: Malmö Diet and Cancer Study; MESA: Multi-Ethnic Study of Atherosclerosis; MILLION: Million Women Study; NFBC: Northern Finland Birth Cohort; NHIS: National Health Interview Survey; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health–AARP Diet and Health Study; NLMS: National Longitudinal Mortality Study; OHASAMA: The Ohasama Study; PREVEND: Prevention of Renal and Vascular End-Stage Disease; SCCS: Southern Community Cohort Study; USA5: Cancer Prevention Study II Nutrition, Nurses' Health Study I, Women's Health Initiative cohort, National Institutes of Health–AARP Diet and Health Study, and Health Professionals Follow-up Study; WHITEHALL: The Whitehall Study, and WHS: Women's Health Study.

[b]NAR: No age restriction specified.

[c]C: Results only for sexes combined.

[d]Number of adjustment factors for which relative risk (RR) available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).

[e]x: Results available for exclusive use.

[f]x: Results available with deaths excluded in early period of follow-up.

[g]Number of RRs available.

[h]Some of the RRs used from this study came from personal communication from Professor Koks.

There were 14 study/sex combinations where comparison could be made between estimates adjusted for two or more covariates and estimates that were unadjusted or adjusted for age only. In all but two of the 14, adjustment for multiple covariates increased the RR ($P < 0.05$).

Within the studies considered, no study has pairs of estimates varying by other factors.

Stroke - cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from three publications for one of these studies, and from two for another. Of the 31 studies, 12 were from North America (11 from USA, one from Canada), 16 from Europe (seven UK, two Italy, two from multiple countries, and one each from Estonia, Finland, Netherlands, Spain and Sweden), and three from Japan. One was a nested case-control study, the rest being of cohort design. Two studies were international, 11 national, 15 regional, one of medical workers, one of civil servants and one based on general practitioner records.

Table 4 Acute myocardial infarction and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		13	10	2.72 (2.40-3.08)	< 0.001
5	Sex	Combined	2	2	2.98 (2.20-4.04)	
		Males	4	4	2.30 (1.57-3.37)	
		Females	7	7	2.83 (2.40-3.34)	NS
6	Region	N. America	3	2	3.42 (2.93-3.99)	
		Europe	10	8	2.54 (2.22-2.90)	< 0.01
7	Study population	National	5	3	2.85 (2.16-3.77)	
		Regional	7	6	2.69 (2.18-3.33)	
		Other	1	1	2.51 (2.33-2.71)	NS
8	Year of start of baseline	< 1988	2	2	1.81 (1.28-2.56)	
		1988+	11	8	2.93 (2.58-3.32)	< 0.05
9	Number of cases	< 1000	7	6	2.52 (1.96-3.25)	
		1000+	6	4	2.87 (2.46-3.35)	NS
10	Lowest age considered	< 30	5	3	3.02 (2.09-4.35)	
		30-44	6	5	2.58 (2.20-3.04)	
		45+	2	2	2.88 (2.40-3.46)	NS trend NS
11	Yr of follow-up	10-< 20	10	7	2.78 (2.40-3.23)	
		20-< 30	2	2	2.88 (2.40-3.46)	
		30+	1	1	2.11 (1.81-2.46)	< 0.05 trend < 0.01
12	Endpoint	Died	2	1	2.99 (1.34-6.67)	
		Diagnosed	11	9	2.71 (2.38-3.08)	NS
13	Number of adjustment factors	None	1	1	1.47 (1.08-2.01)	
		Age only	3	2	2.52 (2.34-2.71)	
		More	9	7	2.89 (2.48-3.37)	< 0.001
14	Disease definition standard	No	6	7	2.43 (2.06-2.87)	
		Yes	7	5	3.14 (2.63-3.74)	< 0.05

As can be seen in Table 3, the studies varied as regards different factors, including start year, length of follow-up, ages and sexes considered, numbers of stroke cases studied, whether results were available for exclusive cigarette use, or for cases being excluded during the early period of follow-up, whether cases were dead or diagnosed, and the extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied with the definition of stroke used to identify cases, the standard definition being based on ICD-8 or ICD-9 codes 430-438 or ICD-10 codes I60-I69.

Stroke - cigarette smoking meta-analyses

Data were entered on 70 RRs, with at most six per study. The initial meta-analyses involved 37 RRs, these being selected using the preferences described above. As can be seen in Table 6 and Figure 4, the overall RR estimate (random-effects) was 1.62 (95%CI: 1.48-1.77), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all but one of the 37 RRs exceeded 1.00 (range 0.66-2.91), and 32 were significantly increased ($P < 0.05$).

Table 6 also shows RRs by level of 11 different study or RR characteristics, there being highly significant evidence ($P < 0.001$) of variation for three of them. One related to the RR being higher for studies in North America and Europe than for studies in Japan, one to the RR being higher for non-exclusive cigarette smokers than it was for exclusive cigarette smokers, and one to the RR being higher for studies with a shorter follow-up period.

Table 5 Ischaemic heart disease and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		28	23	2.01 (1.84-2.21)	< 0.001
19	Sex	Combined	10	10	1.94 (1.71-2.21)	
		Males	7	7	1.86 (1.53-2.26)	
		Females	11	11	2.23 (1.86-2.69)	NS
20	Region	N. America	9	8	2.23 (1.92-2.58)	
		Europe	17	14	1.90 (1.67-2.15)	
		Japan	2	1	2.15 (1.73-2.69)	NS
21	Study population	National	9	8	2.10 (1.92-2.30)	
		Regional	12	9	1.85 (1.56-2.19)	
		Other	7	6	2.18 (1.77-2.69)	NS
22	Year of start of baseline	< 1988	5	5	1.89 (1.56-2.27)	
		1988+	23	18	2.04 (1.83-2.28)	NS
23	Number of cases	< 1000	12	11	1.97 (1.58-2.45)	
		1000+	16	12	2.04 (1.83-2.27)	NS
24	Exclusive cigarettes	No	26	22	2.00 (1.82-2.21)	
		Yes	2	1	2.15 (1.73-2.69)	NS
25, 26	Lowest age considered	< 30	5	4	2.45 (1.77-3.39)	
		30-44	11	9	1.81 (1.61-2.05)	
		45+	9	7	2.06 (1.76-2.42)	NS trend without missing NS
		Missing	3	3	2.09 (1.16-3.78)	
27	Yr of follow-up	< 10	2	2	2.52 (1.07-5.90)	
		10-< 20	13	10	2.04 (1.77-2.35)	
		20-< 30	10	8	1.99 (1.78-2.23)	
		30+	3	3	1.68 (1.23-2.29)	NS trend NS
28	Endpoint	Died	13	10	2.23 (1.94-2.57)	
		Diagnosed	15	13	1.83 (1.62-2.05)	< 0.05
29	Number of adjustment factors	None	6	5	2.11 (1.78-2.50)	
		Age only	5	4	1.64 (1.39-1.93)	
		More	17	14	2.10 (1.88-2.35)	< 0.05
30	Disease definition standard	No	13	12	1.83 (1.59-2.10)	
		Yes	15	11	2.17 (1.93-2.45)	< 0.1

Stroke - cigarette smoking within-study comparisons

There were six comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was less than the female one in five of the pairs, and the overall estimate of the male/female ratio was significant (ratio 0.90, 95%CI: 0.82-1.00).

There were 18 study/sex combinations where comparison could be made between estimates adjusted for 2 or more covariates and estimates that were unadjusted or adjusted for age only. In all but one of the 18, adjustment for multiple covariates increased the RR ($P < 0.001$). Within the studies considered, no study has pairs of estimates varying by other factors.

Results relating cigarette smoking to daily amount smoked

The detailed results are given in Supplementary material 3. Fifteen of the studies provided data on RR by amount

Table 6 Stroke and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of Studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		37	31	1.62 (1.48-1.77)	< 0.001
35	Sex	Combined	17	17	1.65 (1.52-1.50)	
		Males	9	9	1.48 (1.21-1.80)	
		Females	11	11	1.66 (1.39-1.99)	NS
36	Region	N. America	14	12	1.64 (1.48-1.83)	
		Europe	19	16	1.71 (1.51-1.94)	
		Japan	4	3	1.18 (1.04-1.34)	< 0.001
37	Study population	National	13	11	1.76 (1.47-2.11)	
		Regional	19	15	1.55 (1.36-1.78)	
		Other	5	5	1.51 (1.39-1.65)	N.S.
38	Yr of start of baseline	< 1988	8	8	1.43 (1.23-1.67)	
		1988+	29	23	1.68 (1.52-1.85)	< 0.1
39	Number of cases	< 1000	18	16	1.66 (1.44-1.91)	
		1000+	19	15	1.59 (1.41-1.78)	NS
40	Exclusive cigarettes	No	32	27	1.67 (1.52-1.84)	
		Yes	5	4	1.31 (1.19-1.45)	< 0.001
41, 42	Lowest age considered	< 36	8	6	1.59 (1.19-2.14)	
		30-44	16	13	1.48 (1.35-1.62)	
		45+	11	10	1.89 (1.68-2.12)	< 0.01 trend without missing < 0.01
		Missing	2	2	1.87 (1.54-2.28)	
43	Yr of follow-up	< 10	3	3	2.13 (1.80-2.53)	
		10-< 20	22	17	1.69 (1.52-1.89)	
		20-< 30	7	6	1.43 (1.29-1.60)	
		30+	5	5	1.44 (1.10-1.89)	< 0.001 trend < 0.001
44	Endpoint	Died	16	13	1.60 (1.41-1.81)	
		Diagnosed	21	18	1.63 (1.46-1.83)	NS
45	Number of adjustment factors	None	7	7	1.32 (1.08-1.62)	
		Age only	4	3	1.70 (1.31-2.20)	
		More	26	21	1.69 (1.53-1.88)	< 0.1
46	Disease definition standard	No	20	18	1.68 (1.51-1.88)	
		Yes	17	13	1.55 (1.36-1.77)	NS

smoked for one or more of the three diseases, with four giving results for AMI, six for IHD and ten for stroke. Given that some studies presented results separately for females and males, there were a total of 29 independent dose relationships. Twelve of these gave RRs (compared to never smokers) by two levels of amount smoked, and fifteen by three or more levels, with the remaining two dose relationships expressed as risk per daily amount smoked. Fifteen of the relationships came from North American studies, the others coming from European studies. With two minor exceptions (where the stroke results from the ARIC and NHIS studies showed virtually the same RR in heavier smokers as in lighter smokers,) the RR was always greater in the heaviest smoking group than in the lightest smoking group, and in the relationships with three or more levels, the risk increase was usually monotonic. These data demonstrate that a dose-response relationship exists between daily amount smoked and the risk of each of the three diseases.

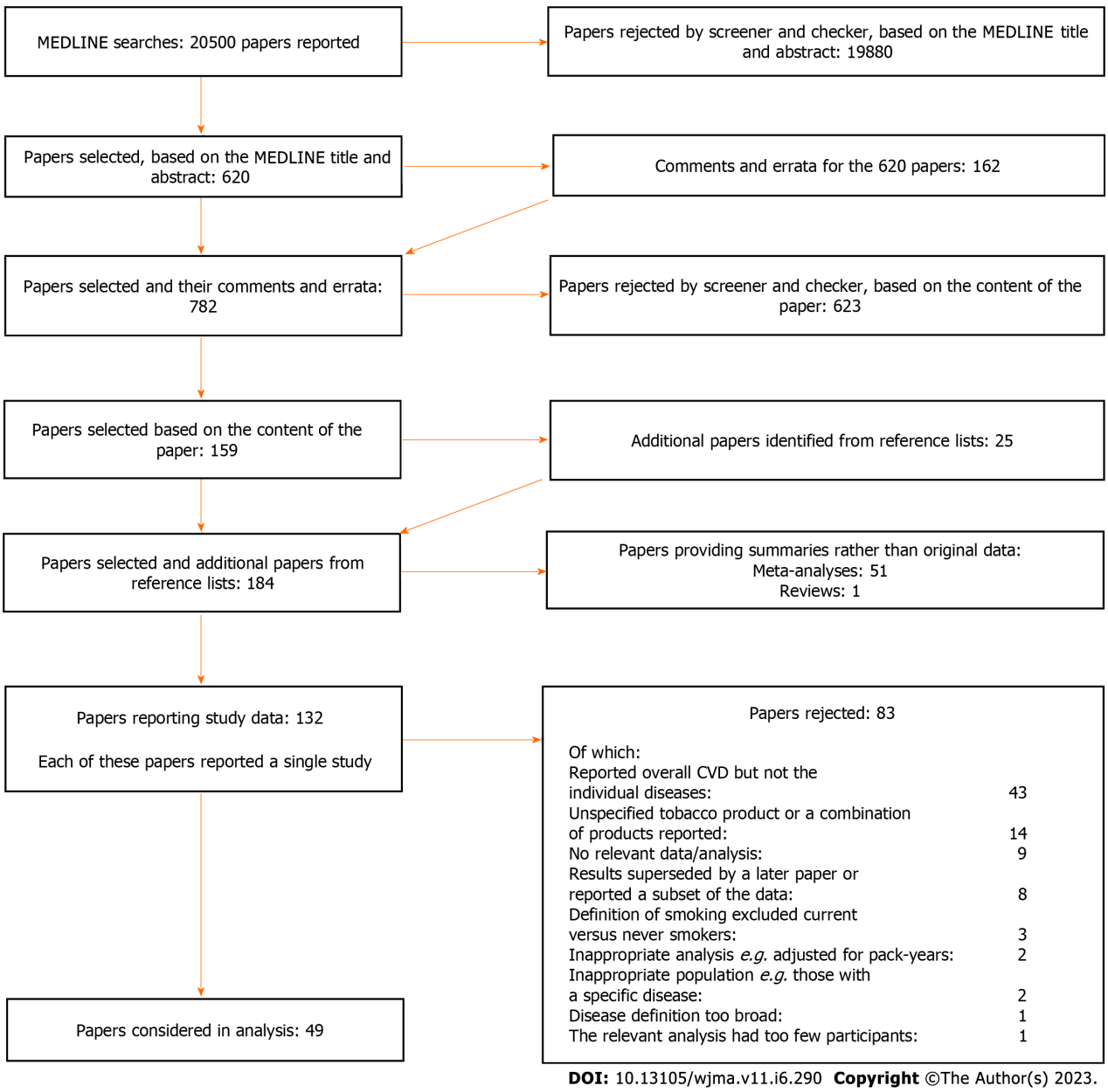

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Figure 1 Flowchart of the literature searches. CVD: Cardiovascular disease.

Results for cigar and pipe smoking

The detailed output for current smoking of cigars or pipes is given in Supplementary material 2. The data are very limited. There are no data at all for AMI. For IHD the only data come from study MESA, where the RRs compared to never smokers are 0.71 (95%CI: 0.35-1.45) for current smoking of cigars and 0.81 (95%CI: 0.26-4.55) for current smoking of pipes, both estimates being reduced but with very wide 95%CI. For stroke, the available data relates to exclusive product use. For exclusive cigar smoking, an estimate from study NHIS of 1.60 (95%CI: 0.72-3.57) is non-significantly increased, but that from study NLMS of 0.50 (95%CI: 0.21-1.22) is non-significantly reduced. For exclusive pipe smoking, the only study providing data is NLMS, where the RR of 0.24 (95%CI: 0.06-0.91) is significantly reduced.

DISCUSSION

Comparison with earlier reviews - cigarettes

We could find no other meta-analysis published in 2001 to 2020 that related cigarette smoking to the risk of AMI. However, there were various published meta-analyses for the other two diseases, as shown in Table 7 (IHD) and Table 8 (stroke) where their results are summarized and compared with our findings.

For IHD (see Table 7) the nine meta-analyses summarized[5,11,13-19] vary by the year of publication, the regions of the world considered, the definition of what is smoked and the comparison group, and the methodology used. However, the

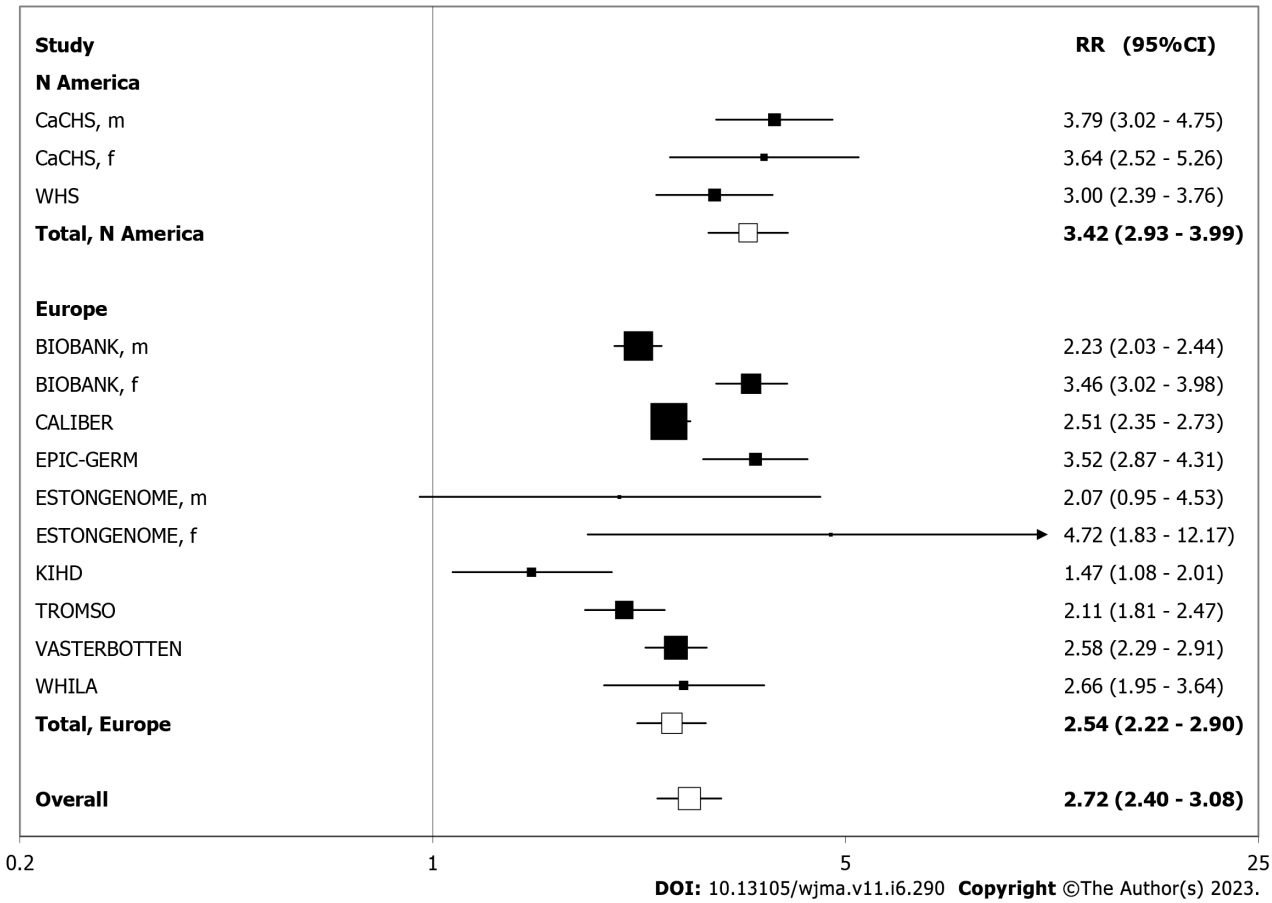


Figure 2 Forest plot for acute myocardial infarction and current *vs* never cigarette smoking, by region.

results are remarkably consistent, with the overall RR estimates varying only from 1.60 to 2.34, as compared with our estimate of 2.01 (95%CI: 1.84-2.21), and all the meta-analyses reporting a somewhat higher RR in females than in males. The consistency of the results, despite the variation in regions considered, also aligns with our finding of similar RRs by continent, though our analysis only included a single study in Japan. Variation in the current smoking RR by any of the factors other than sex or region considered in Table 5 is hardly mentioned at all in any of the earlier meta-analyses. One meta-analysis[11] found no clear relationship, as we did, with study size or number of variables that were adjusted for.

For stroke (see Table 8) data from 11 other meta-analyses[5,11,13-17,20-23] were summarized, these meta-analyses varying by the same factors mentioned above for IHD. Again, the results are quite consistent, with the RRs all significantly raised and varying from 1.32 to 2.27, compared to our estimate of 1.62 (95%CI: 1.48-1.77), and all the meta-analyses reporting a higher RR for females than for males. As previously noted, our analyses found a lower RR for studies in Japan than for studies in North America or Europe (see Table 6), and the earlier results also show relatively low meta-analysis RRs for studies conducted in, or predominantly in, Asia[11,16,17,23]. Few of the earlier meta-analyses considered any of the factors other than sex and region which we had considered in Table 6. One meta-analysis[11] reported higher RRs in studies involving fewer cases, a finding not seen in our analyses (see Table 6) or in another meta-analysis[21]. That meta-analysis reported a non-significantly higher RR in studies with a longer term (> 10 years) follow-up, whereas our analyses reported that the RR declined significantly with increasing follow-up. Our analyses did not consider type of stroke, but a number of the earlier meta-analyses did[17,18,24-28]. It was clear from the RRs reported in these meta-analyses, that the association with smoking was stronger for subarachnoid haemorrhage, where meta-analysis RRs varied from 2.20 to 3.46, than it was for other types of stroke, where RRs varied from 1.19 to 2.17 (data not shown).

For all three diseases our results show strong evidence of a dose-response relationship with amount smoked, a finding consistent with results from earlier meta-analyses (*e.g.*[14]).

Comparison with earlier reviews – cigars and pipes

As noted above, recent data relating to current cigar or pipe smoking are very limited, with no data for AMI, only one study for IHD, and only two for stroke. None of the RRs are significantly increased compared to never smokers, and one, that for stroke and exclusive pipe smoking, 0.24 (95%CI: 0.06-0.91), is significantly reduced. Though there appears to be no recent review for pipe smoking, a recent review[12] reports results from five studies relating current cigar smoking to IHD and from two studies relating current cigar smoking to stroke. From the RRs presented (and using those for primary rather than secondary cigar smoking where both RRs are given for a study) we estimate overall RRs of 1.06 (95%CI: 0.98-1.14) for IHD and 1.00 (0.90-1.11) for stroke, indicating that if any association exists it is much weaker than for cigarettes. It should be noted, however, that all of the RRs cited related to publications in the last century.

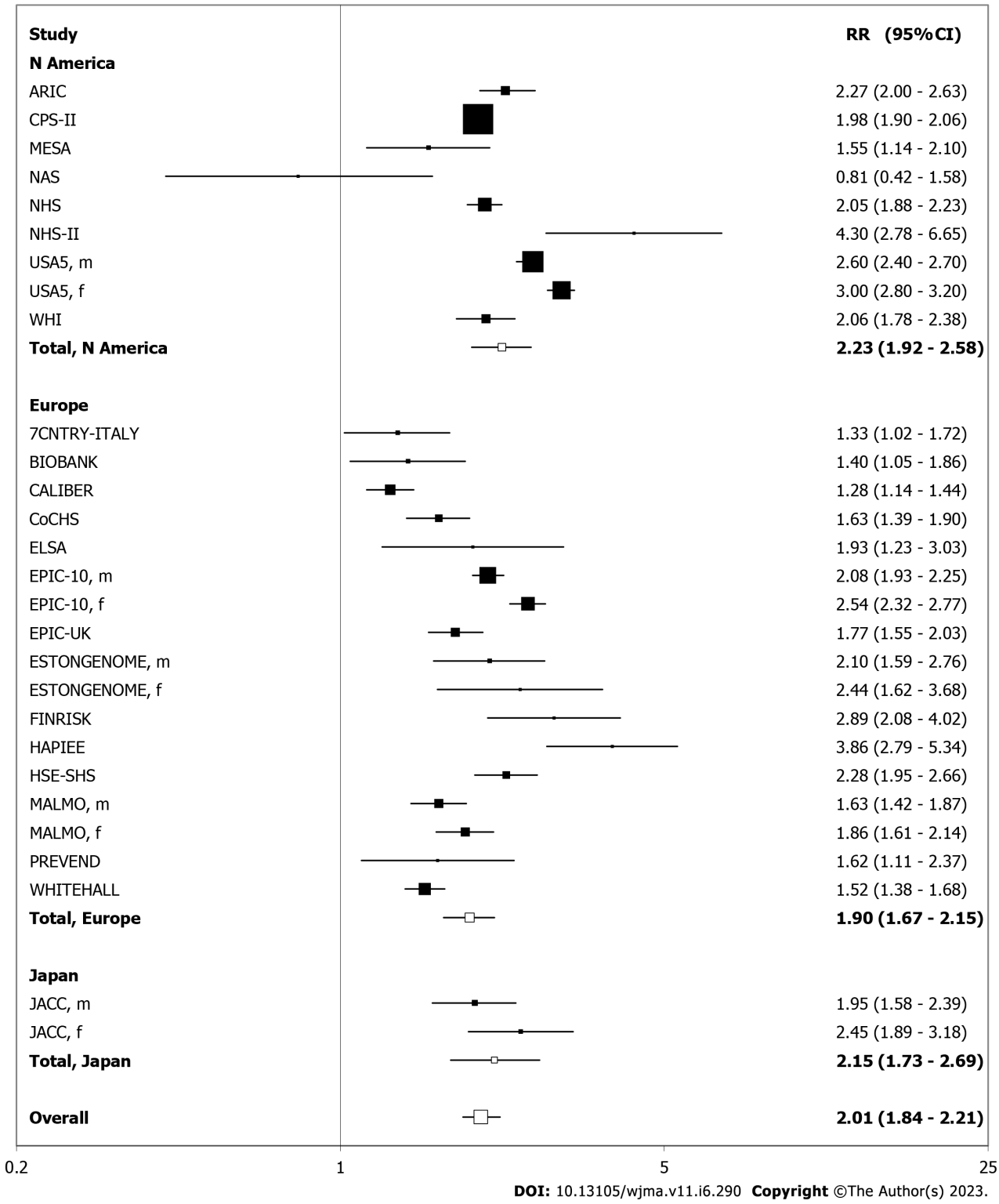
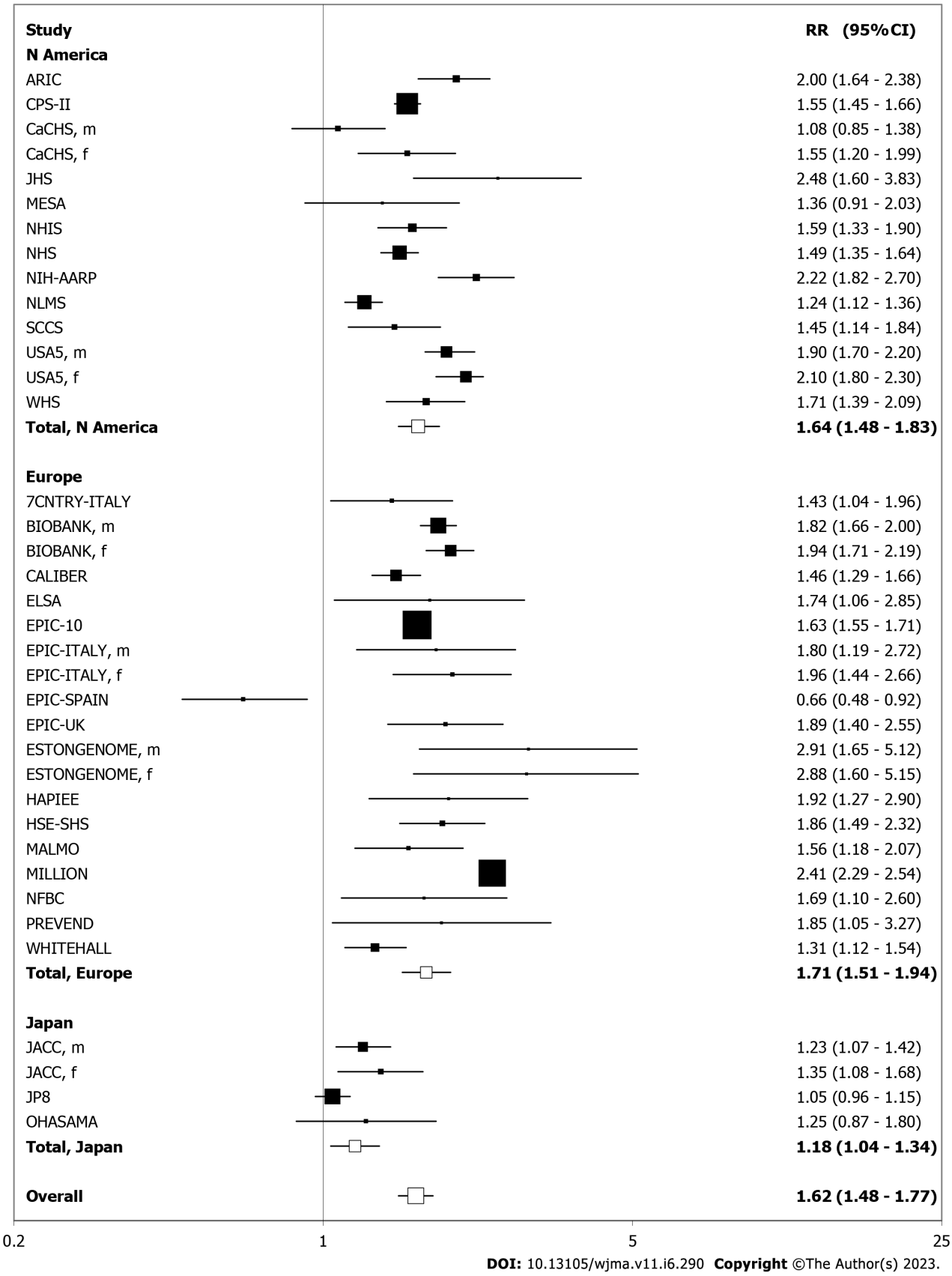


Figure 3 Forest plot for ischaemic heart disease and current *vs* never cigarette smoking, by region.

General considerations

While it is clear that cigarette smoking increases the risk of AMI, IHD and stroke (though by a much smaller factor than for lung cancer and COPD[10]) the RR estimates for all three diseases show highly significant ($P < 0.001$) heterogeneity between the studies. Of the possible reasons for this, many of which are inter-related, we have only investigated some. Thus, populations considered in different studies may vary by race and age, which may affect the product used and extent of exposure. Males and females may also smoke a different amount. The extent of exposure to other risk factors may also vary between studies, as may the extent to which analyses adjust for these factors. As noted previously[10], studies may vary in the definition of exposure, the detail in which changes in smoking over time are monitored or taken into account, the extent to which questions on smoking are answered accurately, the precise definition of disease, and the procedures for diagnosing and treating disease. These factors, not always recorded in the source publications, may help



DOI: 10.13105/wjma.v11.i6.290

Figure 4 Forest plot for stroke and current *vs* never cigarette smoking, by region.

Table 7 Comparison of meta-analysis relative risks for ischaemic heart disease in this study and in other publications

Ref.	Region	What is smoked	Comparison group[a]	RR (95%CI) males	RR (95%CI) females	RR (95%CI) any
Woodward *et al*[17], 2005	Asia-Pacific	Cigarettes	Non	1.56 (1.44-1.70)	1.73 (1.50-2.01)	1.60 (1.49-1.72)
Woodward *et al*[18], 2005	Asia, Australia, New Zealand	Cigarettes	Non			1.86 (1.69-2.06)
Nakamura *et al*[16], 2009	Asia	Undefined	Never			1.97 (1.66-2.33)
Huxley *et al*[19], 2011	Any	Cigarettes	Non	1.72 (1.57-1.88)	1.92 (1.66-2.23)	1.79 (1.61-1.98)
Mons *et al*[15], 2015	Any	Undefined	Never	1.80 (1.51-2.15)	2.26 (1.98-2.59)	2.03 (1.63-2.54)[b]
Lee *et al*[5], 2017[c]	North America, Europe, Asia	Cigarettes[d]	Never	1.99 (1.81-2.19)	2.12 (1.87-2.40)	2.05 (1.90-2.21)
Colpani *et al*[13], 2018	Any	Cigarettes[e]	Never		3.12 (2.15-4.52)	
Hackshaw *et al*[14], 2018	Any	20 cigarettes per day	Never	2.04 (1.86-2.24)	2.84 (2.21-3.64)	2.34 (1.96-2.79)
Lee *et al*[11], 2018[c]	Japan	Cigarettes[d]	Never	1.98 (1.74-2.25)	2.59 (2.06-3.27)	2.21 (1.96-2.50)
This meta-analysis	North America, Europe, Japan	Cigarettes	Never	1.86 (1.53-2.26)	2.23 (1.86-2.69)	2.01 (1.84-2.21)

[a]Former smokers are included among nonsmokers, but are not included among never smokers.
[b]Estimated from data provided.
[c]Includes results for coronary heart disease and acute myocardial infarction.
[d]Includes results for any product if those for cigarettes not available.
[e]Assumed to be cigarettes as study in women.

Table 8 Comparison of meta-analysis relative risks for stroke in this study and in other publications

Ref.	Region	What is smoked	Comparison group[a]	RR (95%CI) males	RR (95%CI) females	RR (95%CI) any
Woodward *et al*[17], 2005	Asia-Pacific	Cigarettes	Non	1.29 (1.20-1.38)	1.42 (1.26-1.62)	1.32 (1.24-1.40)
Nakamura *et al*[16], 2009	Asia	Undefined	Never			1.34 (1.12-1.48)
Peters *et al*[22], 2013	Any	Cigarettes	Non	1.67 (1.49-1.88)	1.83 (1.58-2.12)	1.73 (1.58-1.89)
Chen *et al*[20], 2014	Western	Cigarettes	Never			2.27 (1.76-2.93)
Mons *et al*[15], 2015	Any	Undefined	Never	1.44 (1.23-1.68)	1.78 (1.46-2.17)	1.59 (1.29-1.95)[b]
Lee *et al*[5], 2017	North America, Europe, Asia	Cigarettes[c]	Never	1.42 (1.29-1.56)	1.54 (1.33-1.78)	1.48 (1.37-1.60)
Wang *et al*[23], 2017	China	Undefined	Undefined			1.53 (1.06-2.20)[b]
Colpani *et al*[13], 2018	Any	Cigarettes[d]	Never		2.09 (1.51-2.89)	
Hackshaw *et al*[14], 2018	Any	20 cigarettes per day	Never	1.64 (1.48-1.82)	2.16 (1.69-2.75)	1.90 (1.54-2.35)
Lee *et al*[11], 2018	Japan	Cigarettes[c]	Never	1.32 (1.16-1.51)	1.50 (1.16-1.94)	1.40 (1.25-1.57)
Pan *et al*[21], 2019	Any	Cigarettes[c]	Never[e]	1.54 (1.11-2.13)	1.88 (1.45-2.44)	1.92 (1.49-2.48)
This meta-analysis	North America, Europe, Japan	Cigarettes	Never	1.48 (1.21-1.80)	1.66 (1.39-1.99)	1.62 (1.48-1.77)

[a]Former smokers are included among non smokers, but are not included among never smokers.
[b]Estimated from data provided.
[c]Includes results for any product if those for cigarettes not available.
[d]Assumed to be cigarettes as study in women.

[e]Sex-specific relative risks (RRs) are compared to non-smokers.

to explain variations between studies, and between our results and earlier meta-analyses.

Limitations of our work

Though limited to specific regions, and not providing any information relevant to developing countries, our meta-analyses provide a good idea of the size of the RR for current *vs* never cigarette smoking for all three diseases studied, which was our main objective. Although heterogeneity of the individual RR estimates limits the precision of the overall estimates, we have studied various factors that could contribute in part to the heterogeneity. However, we have not carried out multivariate analyses investigating how RRs vary jointly by the studied factors. For smoking of cigars and pipes, our estimates are limited by the paucity of available information. Our analyses are also limited by the lack of clear description of the factors considered in some studies. Notably, in some studies we cannot always tell with certainty whether the term "smoking" relates to any tobacco product use, to cigarette smoking or to exclusive cigarette smoking.

Other limitations arose as the objectives of our study were limited. Thus we did not consider RRs by duration of smoking, age of starting to smoke or individual types of the product smoked (such as tar level of cigarettes). Nor did we consider RRs for former smokers or users of multiple products, and we carried out only a limited assessment relating to amount smoked. Nor did we study variation by the age when the endpoint was diagnosed or when the subject died from it. Nor did we try to determine the extent of bias arising from misclassification of exposure, disease, or confounding variables.

We did not consider results for different types of stroke, which might have given insight into, for example, whether smoking increases risk differently for lacunar and non-lacunar stroke, a stronger association for lacunar stroke being reported in some studies (*e.g.*[30,31]), but being not clearly evident in others (*e.g.*[32-36]). Clearly there is scope for more detailed investigation.

CONCLUSION

Results from 10 studies of AMI, 23 of IHD and 31 of stroke published in 2015-2020 confirm a dose-related association of current cigarette smoking with all three diseases, with RRs somewhat higher for females than males, and for stroke only, and lower for studies in Japan than for studies in North America and Europe. Very limited evidence for current cigar and current pipe smoking shows no increase in risk for IHD and stroke, no data being available for AMI. Our findings seem generally consistent with data from other reviews and meta-analyses published this century. As noted in our companion paper on lung cancer and COPD, cigarettes smokers should quit to most effectively reduce the risks, though switching to other products containing nicotine, may greatly reduce these risks, as as has been most clearly demonstrated for Swedish snuff ("snus").

ARTICLE HIGHLIGHTS

Research background

While there are considerable data on risks from smoking, such risks may change with time, and recent evidence is required for smoking of cigarettes, cigars and pipes.

Research motivation

To take into account recent data on the risks of acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke associated with current smoking of cigarettes, cigars and pipes.

Research objectives

To summarize recent data on the risk of AMI, IHD and stroke related to current cigarette, cigar and pipe smoking in North America, Europe and Japan.

Research methods

Searches on MEDLINE identified publications in English in 2015-2020 giving data on risks of the three diseases associated with current (*vs* never) cigarette, cigar or pipe smoking in studies conducted in the three regions. Studies were accepted which were of cohort or nested case-control design or were randomized controlled trials, which involved at least 100 cases of the disease of interest, and were not restricted to specific disease subsets, to patients with specific medical conditions or which reported results superseded by later reports of the study. Relative risk estimates were extracted from each study and overall estimates derived using random-effects meta-analyses.

Research results

There were available results from 10 studies for AMI, from 23 studies for IHD, and from 31 studies for stroke, the studies

being mainly conducted in North America and Europe. Overall relative risk (RR) estimates for current cigarette smoking were 2.72 for AMI, 2.01 for IHD and 1.62 for stroke. Estimates were dose-related to daily cigarette consumption, and somewhat higher for females than males. Estimates were relatively low in Japan for stroke. RR estimates tended to be higher for studies starting later and with a shorter follow-up period and where adjusted for multiple covariates. Only a few studies in the United States provided findings for current cigar or current pipe smoking, and then only for IHD and stroke. There was no evidence from these studies that smoking either of these products increased risk of these diseases.

Research conclusions

Consistent with evidence from earlier studies, increased risks for all three diseases are clearly seen for current cigarette smoking, but not for current cigar or pipe smoking.

Research perspectives

Cigarette smoking increases the risks of developing AMI, IHD and stroke, though by a factor much lower than for lung cancer and chronic obstructive pulmonary disease. To reduce these risks most effectively, cigarette smokers should quit, though switching to other products containing nicotine, such as Swedish snuff ("snus"), may also materially reduce these risks.

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FOOTNOTES

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

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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

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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].

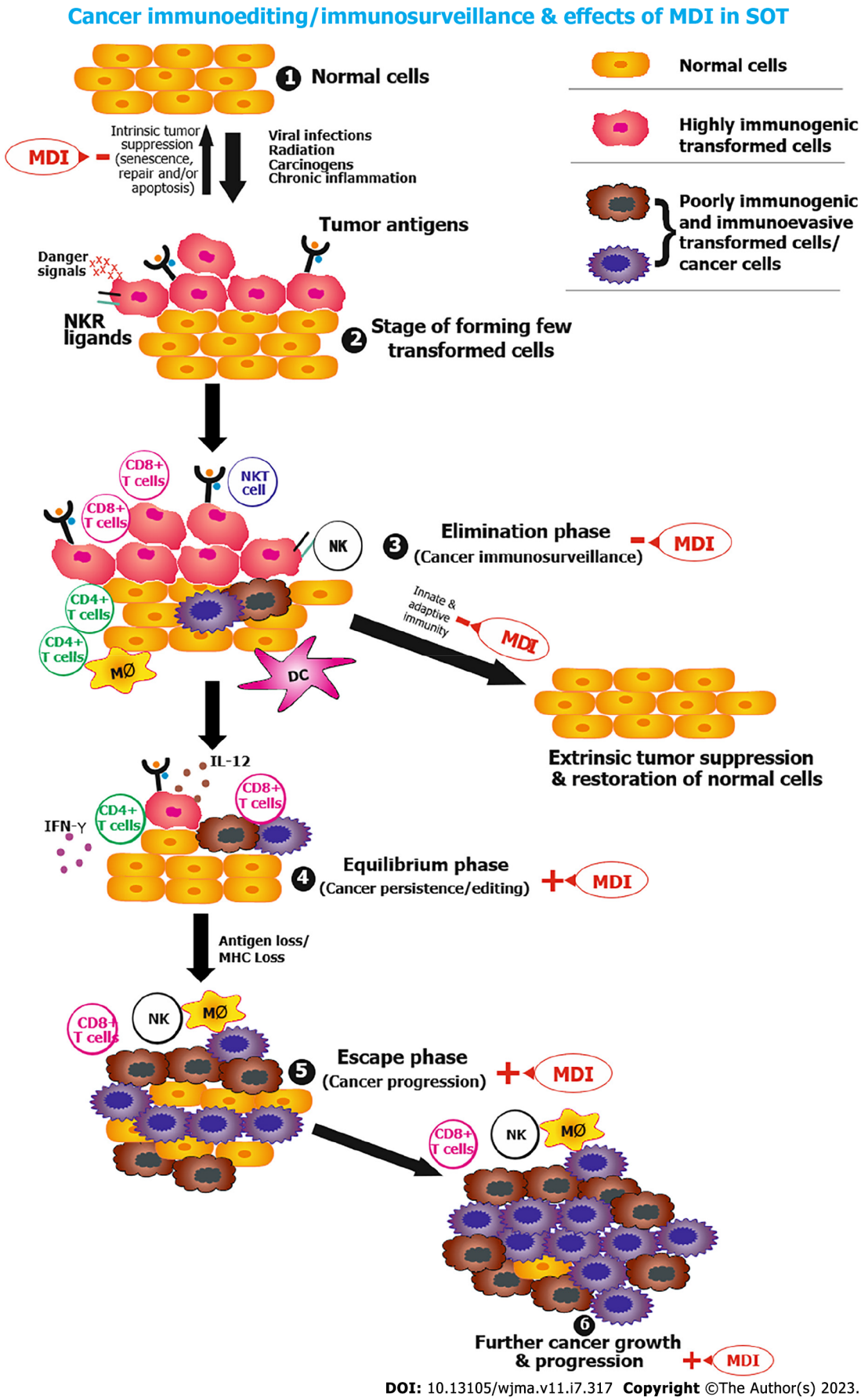

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Figure 1 Cancer immunoediting and influence of immunosuppression after transplantation. +: Promote; –: Inhibit; MDI: Multidrug immunosuppression; MHC: Major histocompatibility complex; NK: Natural killer cell; NKR: Natural killer cell receptor; SOT: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

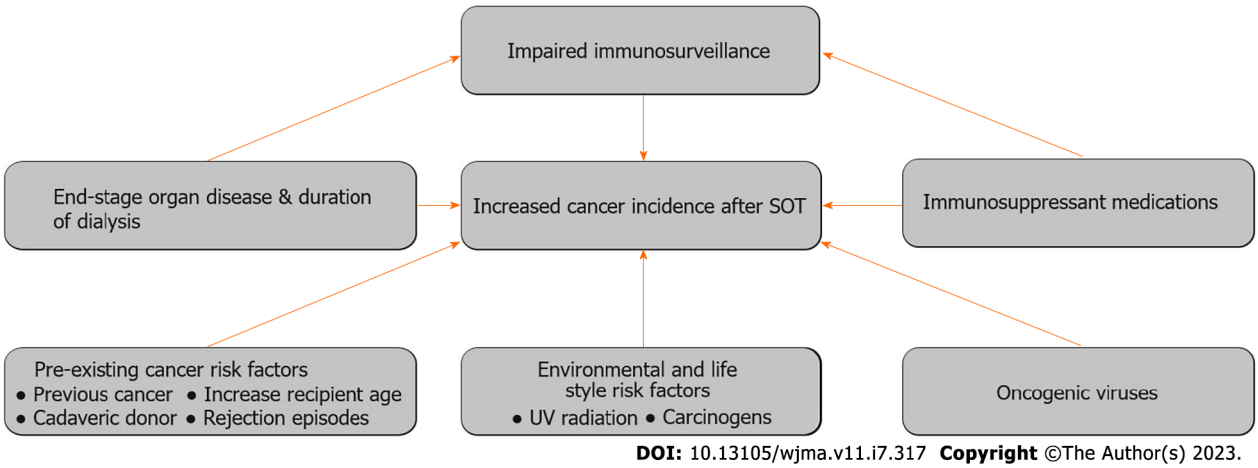

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Figure 2 Summary of etiology of increased cancer incidence after transplantation. SOT: Solid organ transplant; UV: Ultraviolet.

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.

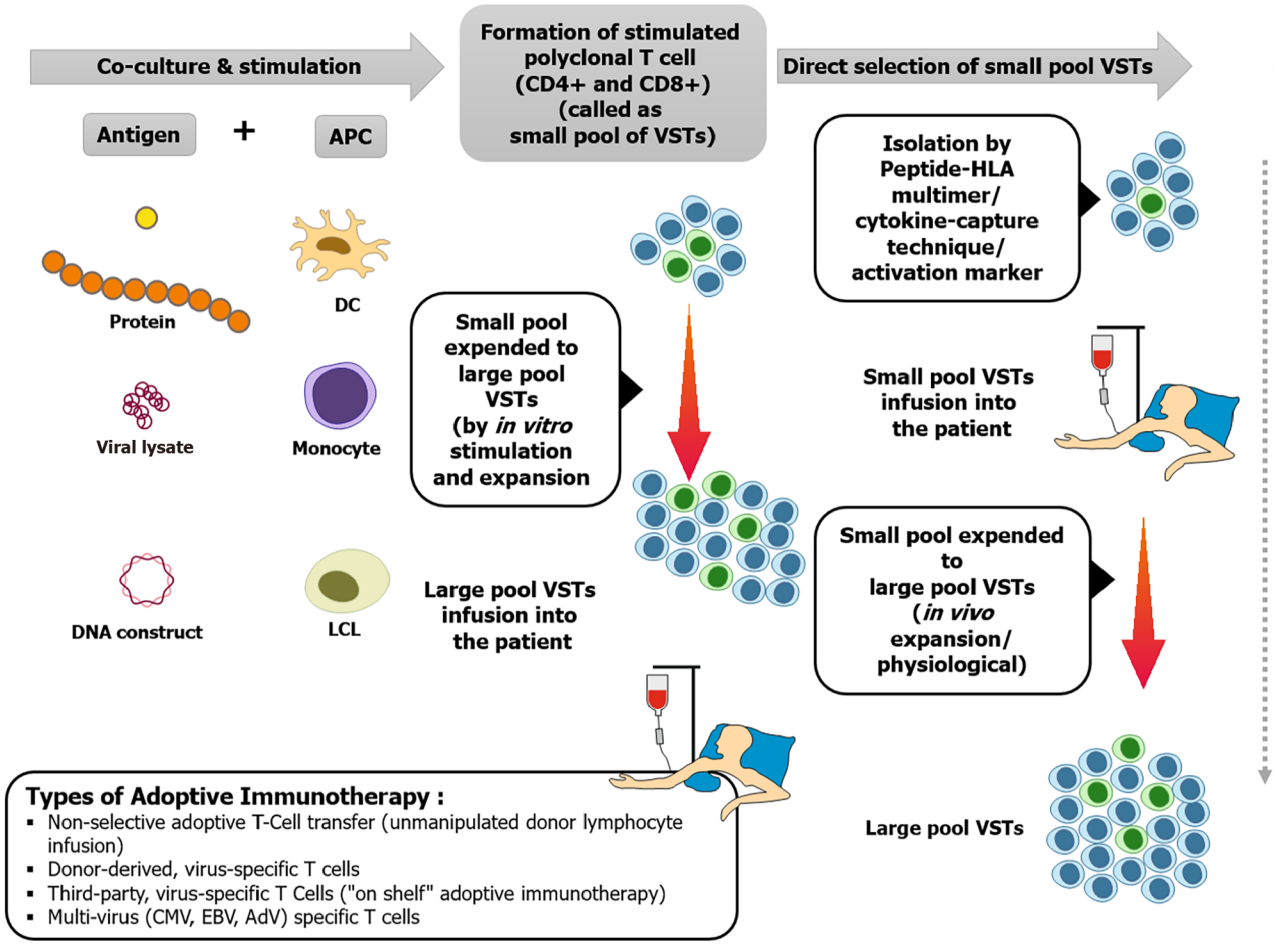

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Figure 3 Technique of adoptive immunotherapy (steps, isolation and types of virus-specific T cells). AdV: Adenovirus; APC: Antigen presenting cells; CMV: Cytomegalovirus; DC: Dendritic cells; EBV: Epstein–Barr virus; HLA: Human leukocyte antigen; LCL: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

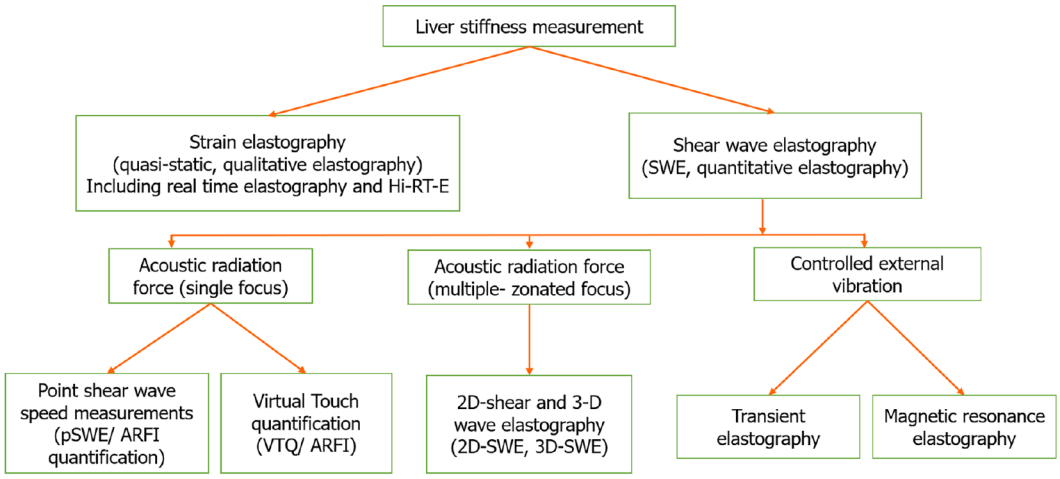

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Figure 1 Classification of ultrasound based elastographic techniques. SWE: Shear wave elastography; pSWE: Point shear wave elastography; APFI: Adolescents' Psychosocial Functioning Inventory; VTQ: Virtual touch quantification.

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.

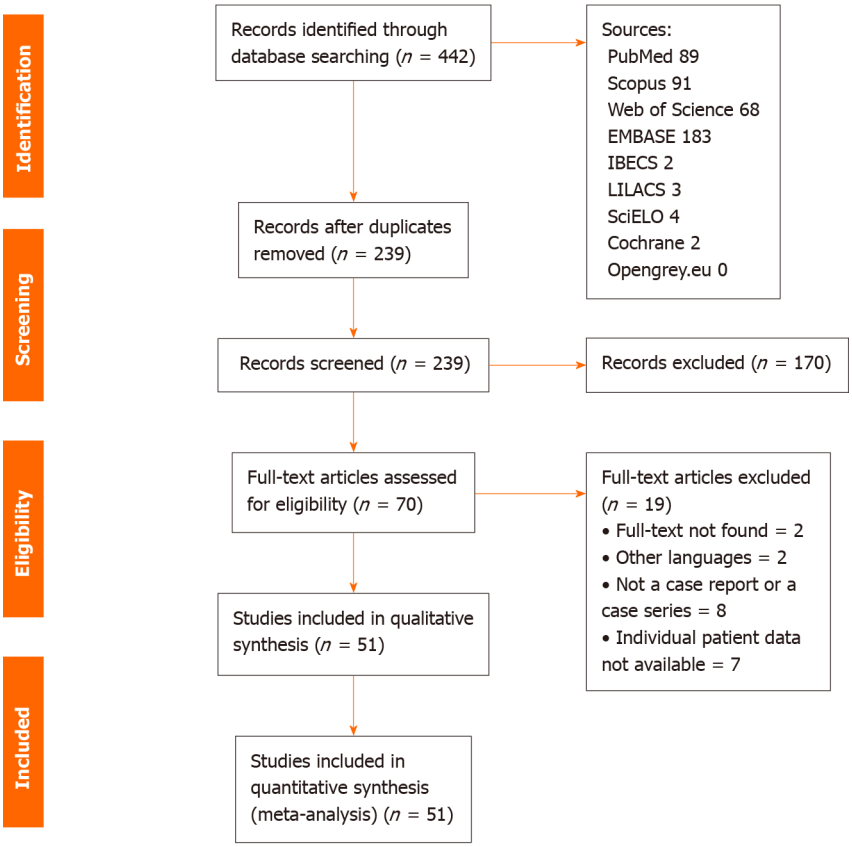

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Figure 1 PRISMA flow diagram.

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

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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.

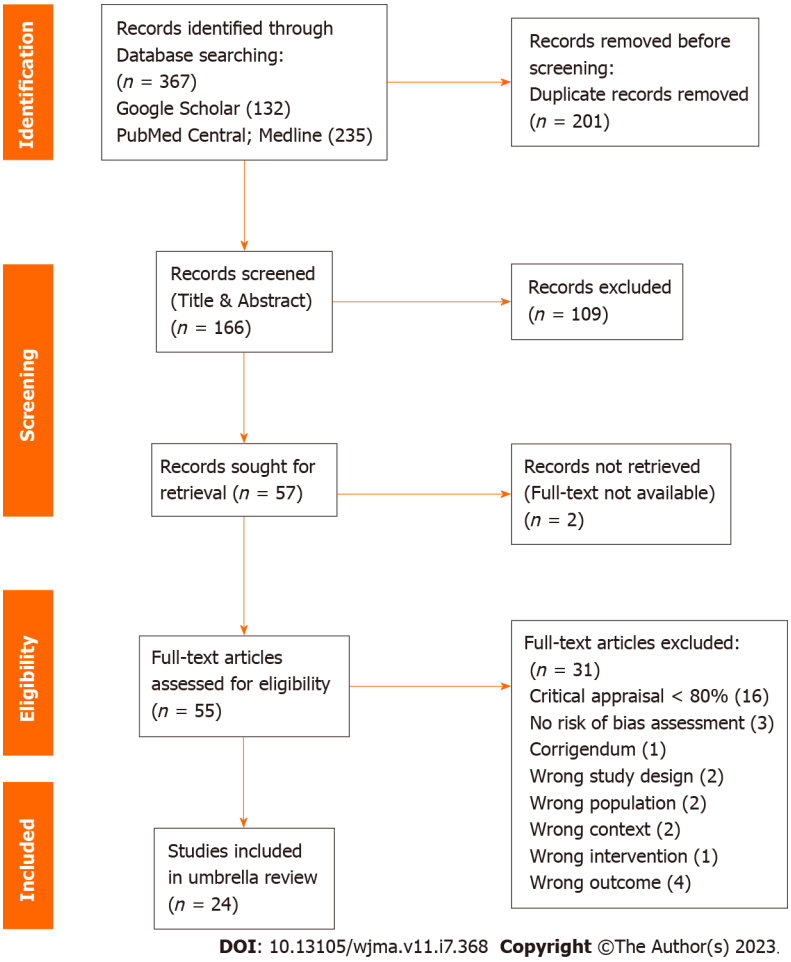

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Figure 1 PRISMA flow diagram.

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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