ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2022 June 28; 10(3): 74-194

Published by Baishideng Publishing Group Inc

WJMA

World Journal of Meta-Analysis

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INDEXING/ABSTRACTING

The *WJMA* is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Saurabh Chandan, Jing Sun

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

PUBLICATION DATE
June 28, 2022

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/GerInfo/288

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World Journal of Meta-Analysis

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World J Meta-Anal 2022 June 28; 10(3): 74-80

DOI: 10.13105/wjma.v10.i3.74

ISSN 2308-3840 (online)

OPINION REVIEW

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

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

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Fakhradiyev I, Kazakhstan; Lopes-Junior LC, Brazil; Tung TH, China

Received: January 12, 2022
Peer-review started: January 12, 2022
First decision: February 21, 2022
Revised: April 19, 2022
Accepted: May 22, 2022
Article in press: May 22, 2022
Published online: June 28, 2022

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Abstract

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

Key Words: Public health; Surgery; Pandemic; Coronavirus

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

Citation: Cawich SO, Narayansingh G, Ramdass MJ, Mencia M, Thomas DA, Barrow S, Naraynsingh V. Responses to disrupted operative care during the coronavirus pandemic at a Caribbean hospital. *World J Meta-Anal* 2022; 10(3): 74-80
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/74.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.74

INTRODUCTION

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

HEALTH CARE IN THE CARIBBEAN

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

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

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

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

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

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

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

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

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

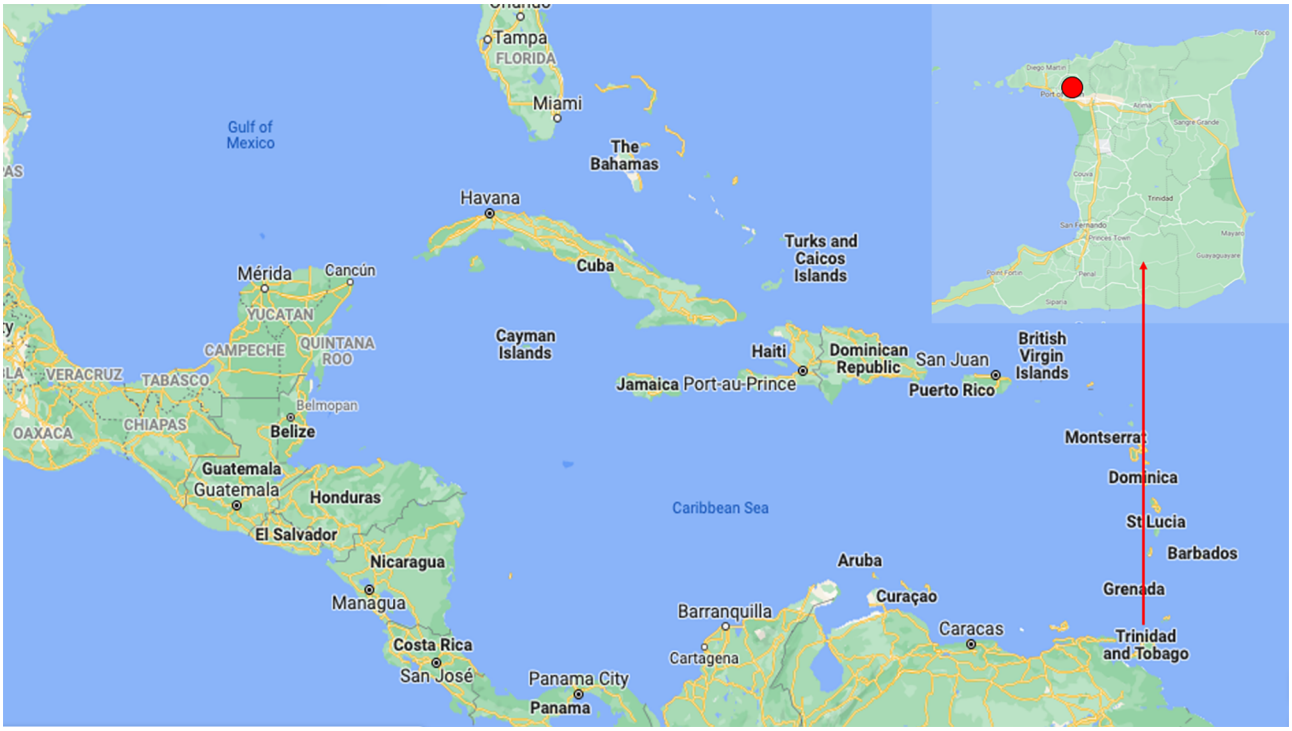
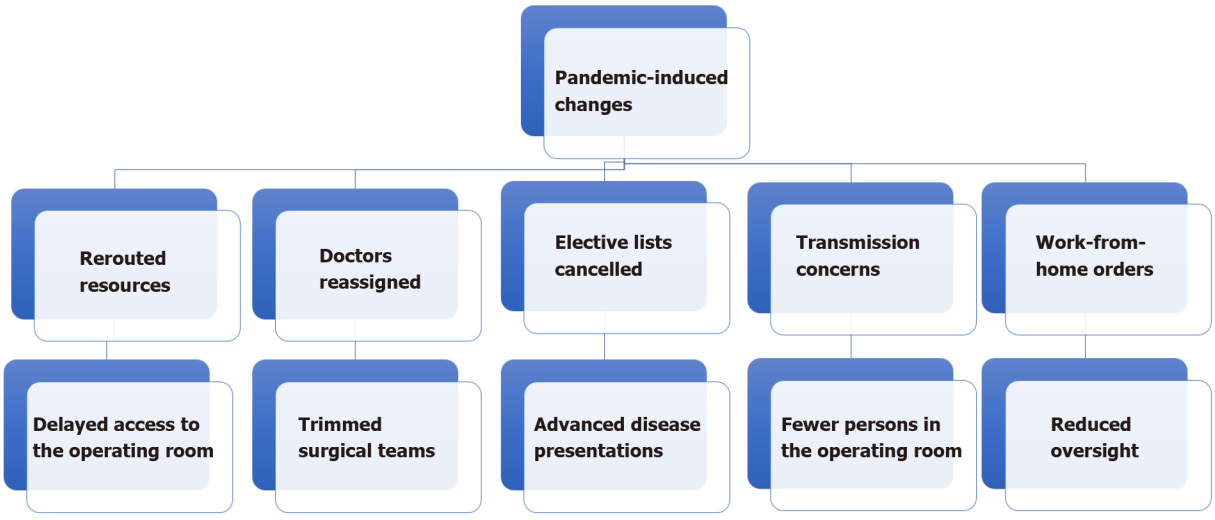


Figure 1 A Map of the Caribbean region. The island of Trinidad & Tobago (inset) is located just off the coast of South America. The Port of Spain General Hospital (red dot) is located in the North-Western part of the island in the nation's capital.



DOI: 10.13105/wjma.v10.i3.74

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

OUTPATIENT CARE

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

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

MULTIDISCIPLINARY CARE

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

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

EMERGENCY SURGICAL CARE

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

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

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

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

OPERATING ROOM RESPONSE

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

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

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

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

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

WAY FORWARD

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

Leadership

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

Critical assessment of the healthcare environment

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

LIMITATIONS

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

CONCLUSION

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

FOOTNOTES

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

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

Country/Territory of origin: Trinidad and Tobago

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Meta-Analysis

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World J Meta-Anal 2022 June 28; 10(3): 81-98

DOI: 10.13105/wjma.v10.i3.81

ISSN 2308-3840 (online)

REVIEW

Mechanism for development of malnutrition in primary biliary cholangitis

Vasiliy Ivanovich Reshetnyak, Igor Veniaminovich Maev

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Feng B, China; Filipec Kanizaj T, Croatia

Received: February 13, 2022
Peer-review started: February 13, 2022
First decision: April 13, 2022
Revised: April 14, 2022
Accepted: May 22, 2022
Article in press: May 22, 2022
Published online: June 28, 2022

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Abstract

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

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

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

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

Citation: Reshetnyak VI, Maev IV. Mechanism for development of malnutrition in primary biliary cholangitis. *World J Meta-Anal* 2022; 10(3): 81-98
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/81.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.81

INTRODUCTION

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

DEFINITION OF MALNUTRITION

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

PREVALENCE OF MALNUTRITION IN PATIENTS WITH LIVER DISEASE

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

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

PBC AND MALNUTRITION

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

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

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

THE PATHOGENESIS OF MALNUTRITION IN PBC

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

Insufficient intake of nutrients in patients with PBC

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

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

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

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

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

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

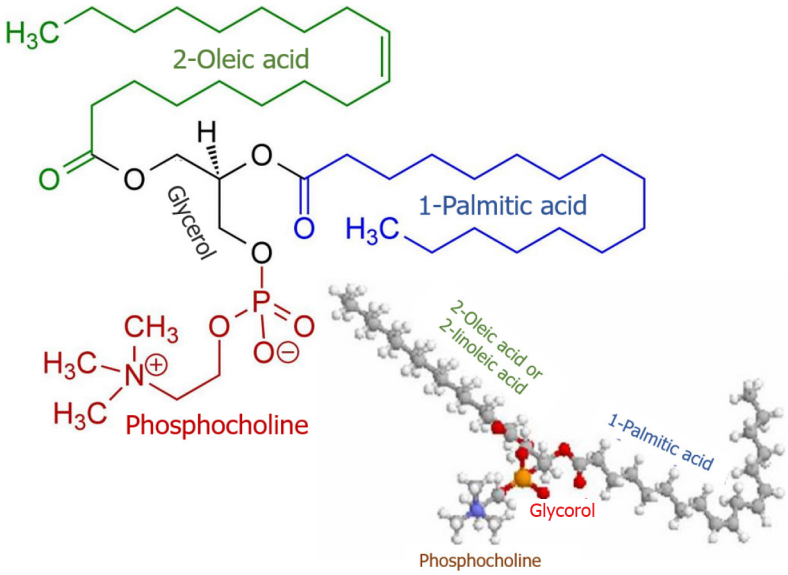
Excruciating insomnia, emotional changes, anxiety, and depression, which develop even in the early stages of the disease, contribute to a decline in glycogen stores and to gradually progressing energy deficiency (a reduction in the level of glucose used as an energy substrate) with the clinical manifestations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

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

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

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

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



DOI: 10.13105/wjma.v10.i3.81

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

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

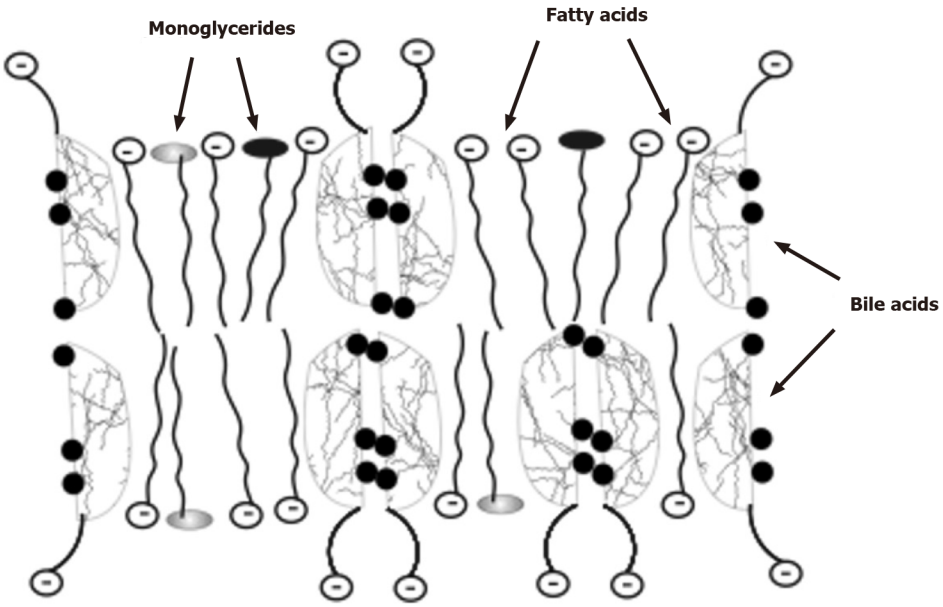
In patients with PBC, the long-term elevated plasma levels of cholesterol in response to the increase in its synthesis in the liver can give rise to xanthelasmas, single or multiple, pale-yellow formations that are slightly raised above the skin. In these patients, the increased levels of cholesterol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

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

Abnormalities in digestion and absorption (maldigestion and malabsorption syndromes)

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

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



DOI: 10.13105/wjma.v10.i3.81

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

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

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

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

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

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

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

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

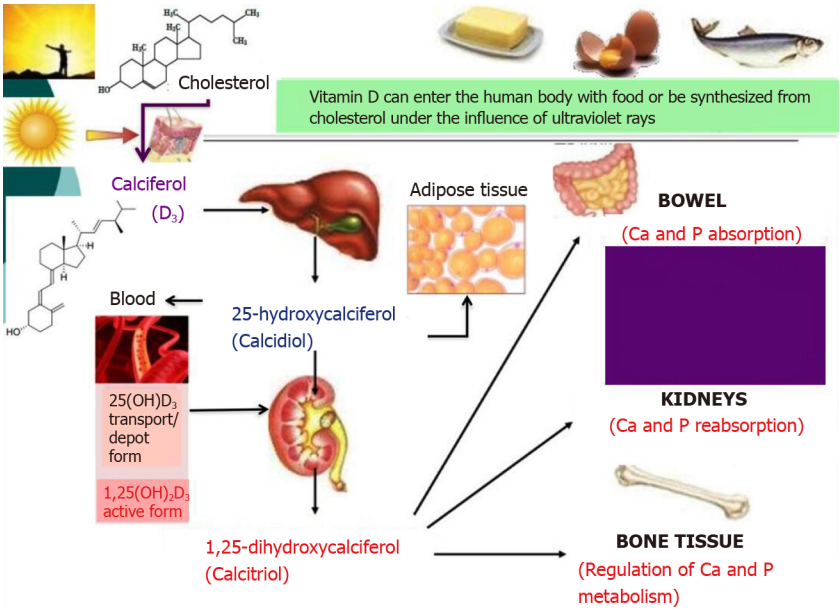


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Figure 3 Metabolism of vitamin D and its involvement in the metabolism of phosphorus and calcium.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Increased metabolic rate (accelerated catabolism)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

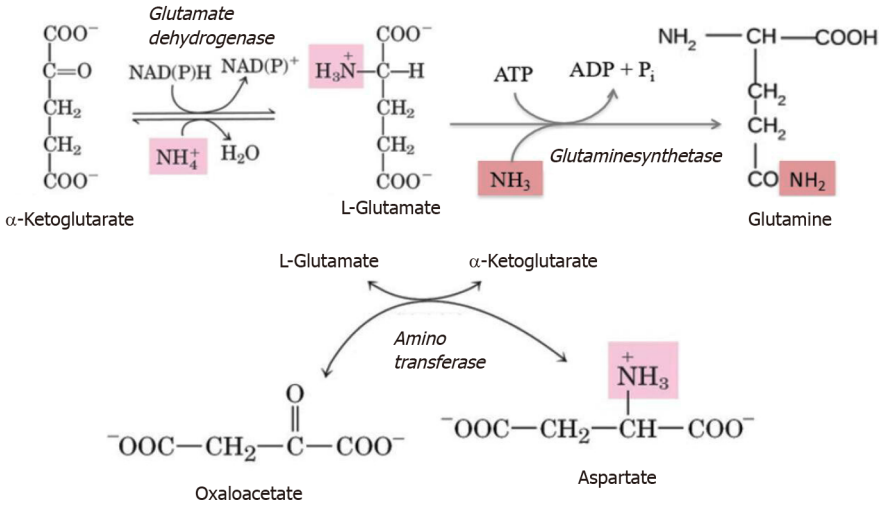

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Figure 4 Use of α-ketoglutarate, glutamate, oxaloacetate, and aspartate to detoxify ammonia.

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

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

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

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

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

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

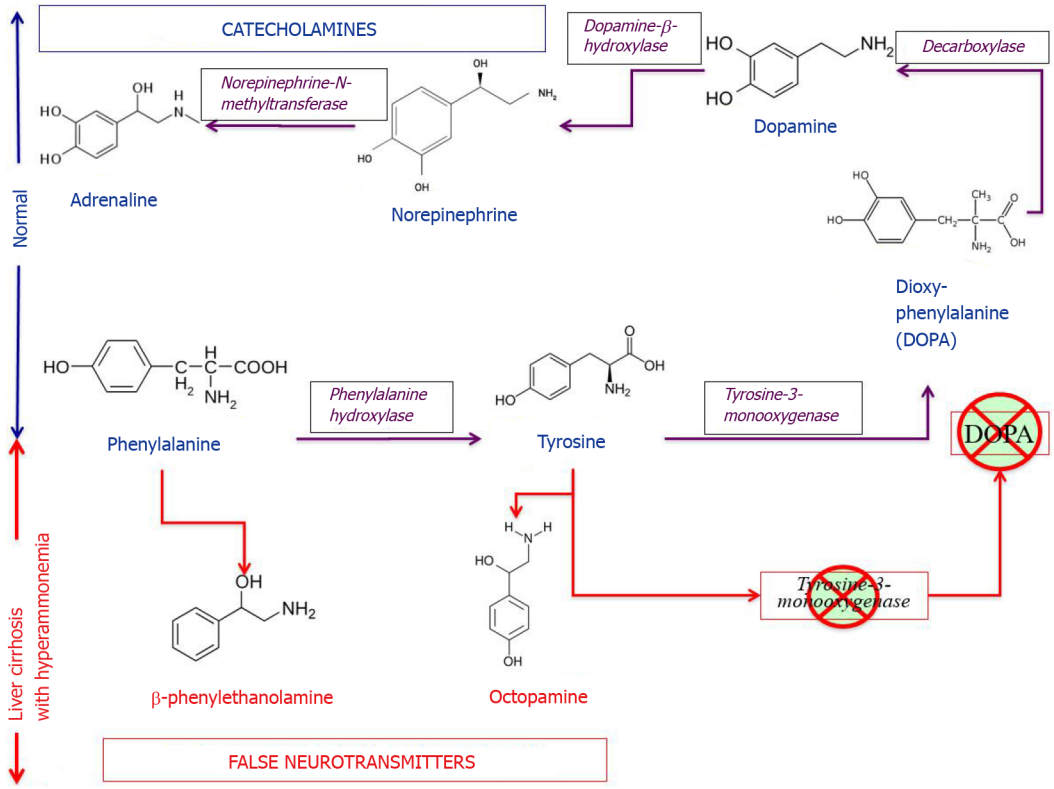

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Figure 5 Synthesis of false neurotransmitters in hyperammonemia.

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

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

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

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

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

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

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

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

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

CONCLUSION

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

ACKNOWLEDGEMENTS

The authors are grateful to Tatiana Igorevna Karlovich and Alexander Igorevich Burmistrov for discussions and technical assistance in preparing the review for publication.

FOOTNOTES

Author contributions: Reshetnyak VI and Maev IV have equally contributed to the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final

version.

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

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S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

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World Journal of Meta-Analysis

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

World J Meta-Anal 2022 June 28; 10(3): 99-121

DOI: 10.13105/wjma.v10.i3.99

ISSN 2308-3840 (online)

REVIEW

Viral hepatitis: A narrative review of hepatitis A–E

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Balaban YH, Turkey; Mogahed EA, Egypt
A-Editor: Zhu JQ, China

Received: February 16, 2022
Peer-review started: February 16, 2022
First decision: April 13, 2022
Revised: April 27, 2022
Accepted: June 24, 2022
Article in press: June 24, 2022
Published online: June 28, 2022

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Abstract

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

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

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

Citation: Ahmed Z, Shetty A, Victor DW, Kodali S. Viral hepatitis: A narrative review of hepatitis A–E. *World J Meta-Anal* 2022; 10(3): 99-121
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/99.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.99

INTRODUCTION

Hepatitis A

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

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

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

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

Hepatitis B

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

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

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

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

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

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

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

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

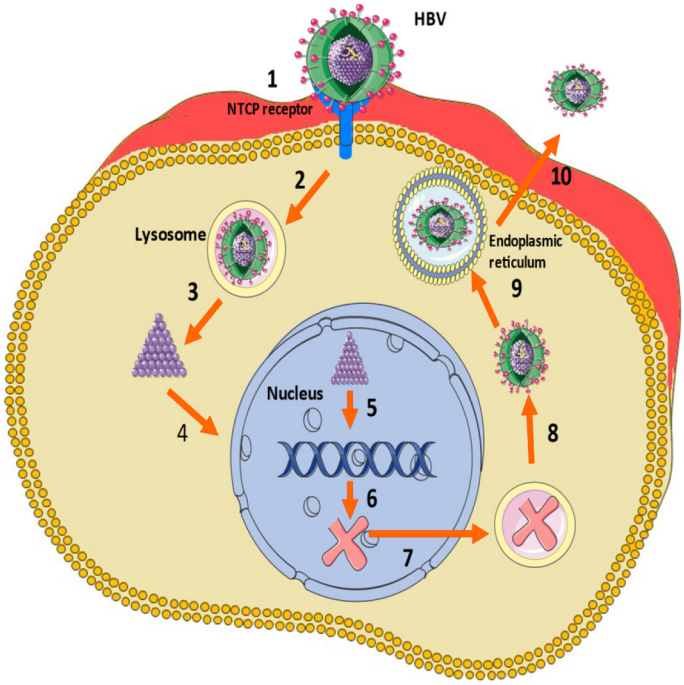
Functional cure is defined as loss of HbsAg with gain of anti-HbS. True cure is defined as elimination of HBsAg and closed covalent circular DNA (cccDNA)[45].

BARRIERS TO CURE

Clearance of hepatitis B and host immune response

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

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



DOI: 10.13105/wjma.v10.i3.99

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

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

HBV vaccine and linkage of care

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

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

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

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

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

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

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

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

HEPATITIS C

Epidemiology

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

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

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

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

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

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

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

Awareness and screening programs

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

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

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

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

Table 2 Drugs in pipeline for hepatitis B virus

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

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

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

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

Table 3 DAA therapy in pediatric population

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

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

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

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

Table 4 DAA therapy for chronic hepatitis C virus

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

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

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

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

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

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

HEPATITIS D

Epidemiology

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

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

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

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

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

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

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

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

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

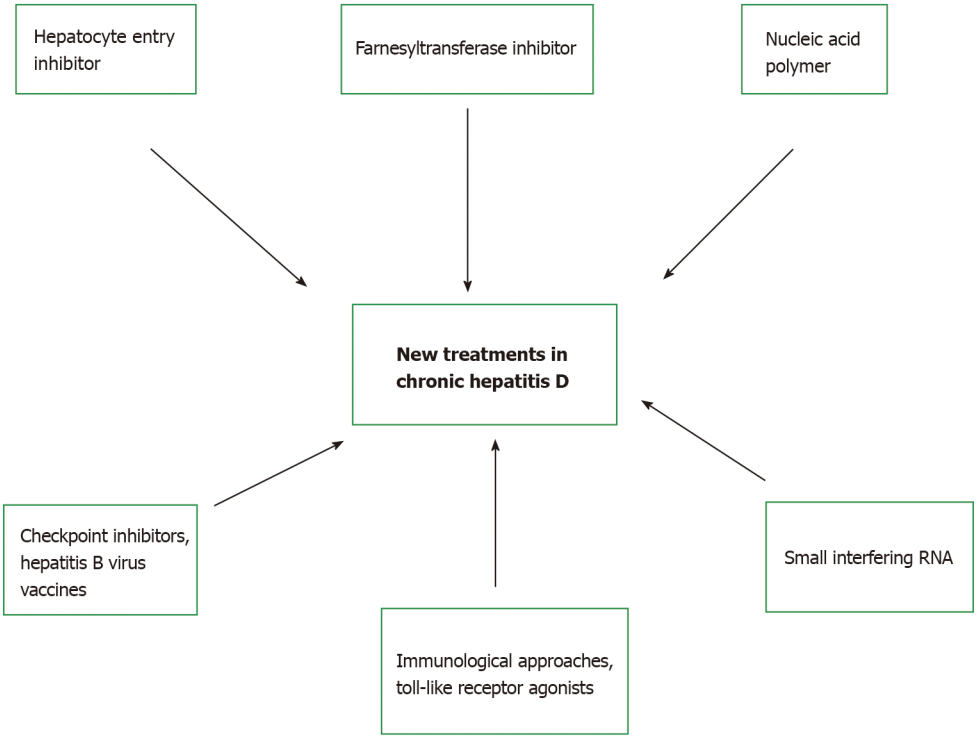
Additional approaches: siRNAs have shown early promise in this field. In a phase IIa clinical trial that showed that a single injection of siRNA ARC-520d decreased HbsAg levels in HbeAg negative CHB patients in a dose-dependent fashion[152]. A multi-dose extension study of up to 12 doses, with once monthly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

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

Table 5 Novel drug treatments for chronic hepatitis D virus

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

IFN: Interferon.



DOI: 10.13105/wjma.v10.i3.99

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

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

HEPATITIS E

Epidemiology

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

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

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

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

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

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

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

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

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

CONCLUSION

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

FOOTNOTES

Author contributions: Ahmed Z, Shetty A, and Kodali S contributed equally to this work; Ahmed Z, Shetty A, Victor DW and Kodali S designed the research study; Ahmed Z Kodali S performed the research; Ahmed Z, Shetty A, Victor DW and Kodali S wrote the manuscript; all authors have read and approve the final manuscript.

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

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S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Liu JH

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World Journal of Meta-Analysis

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World J Meta-Anal 2022 June 28; 10(3): 122-129

DOI: 10.13105/wjma.v10.i3.122

ISSN 2308-3840 (online)

MINIREVIEWS

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

Marta Aleksandra Przybysz, Rafał Stankiewicz

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Kim KH, South Korea; Spadaccini M, Italy
A-Editor: Wang JL, United States

Received: March 15, 2022
Peer-review started: March 15, 2022
First decision: April 13, 2022
Revised: May 11, 2022
Accepted: June 24, 2022
Article in press: June 24, 2022
Published online: June 28, 2022

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Abstract

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

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

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

Citation: Przybysz MA, Stankiewicz R. Rare post-endoscopic retrograde cholangiopancreatography complications: Can we avoid them? *World J Meta-Anal* 2022; 10(3): 122-129
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/122.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.122

INTRODUCTION

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

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

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

SPLENIC INJURY

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

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

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

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

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

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

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

HEPATIC INJURY

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

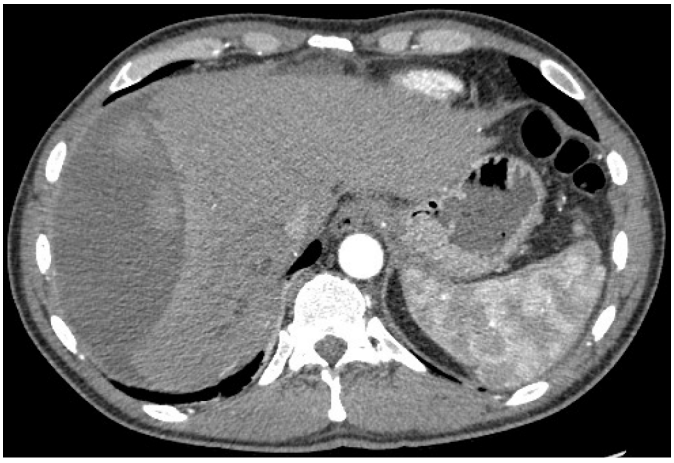
Subcapsular hepatic hematoma as a post-ERCP complication was first presented in 2000 by Ortega *et al*[20]. ERCP was performed on an 81-year-old man due to choledocholithiasis. Following the procedure, the patient presented abdominal pain and a computed tomography (CT) scan revealed a hepatic hematoma.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

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

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

PERFORATION

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



DOI: 10.13105/wjma.v10.i3.122

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

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

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

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

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

STENT RELATED COMPLICATIONS

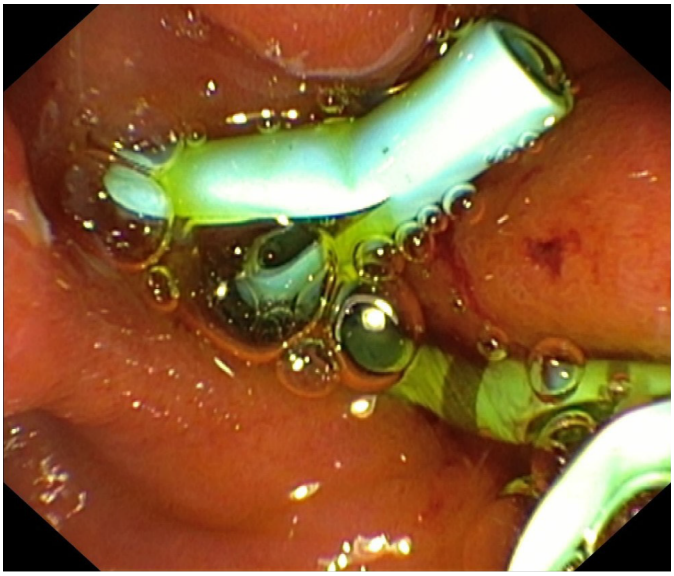
Occlusion is one of the most common complications resulting from inserting plastic or metal biliary and pancreatic stents during the procedure of ERCP. In cases of malignant strictures, this rather late negative outcome is a result of the progression of the primary disease[36]. The group of rare complications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

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

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

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

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



DOI: 10.13105/wjma.v10.i3.122

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

resulting in respiratory arrest and heart failure.

BASKET IMPACTION

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

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

CONCLUSION

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

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

FOOTNOTES

Author contributions: Przybysz MA conceptualized the study, did the literature search, wrote the paper, and approved the final version of the article; Stankiewicz R conceptualized the study, did the literature search, critically reviewed the paper, and approved the final version of the article.

Conflict-of-interest statement: All the authors declare that there are no conflicts of interest regarding this manuscript.

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

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World J Meta-Anal 2022 June 28; 10(3): 130-142

DOI: 10.13105/wjma.v10.i3.130

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

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

Peter Nicholas Lee, Katharine Jane Coombs, Janette Susan Hamling

Specialty type: Statistics and probability

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

Peer-review model: Single blind

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

P-Reviewer: Aggarwal P, India; Seid AA, Ethiopia
A-Editor: Zhu JQ; China

Received: February 10, 2022
Peer-review started: February 10, 2022
First decision: April 13, 2022
Revised: April 25, 2022
Accepted: May 28, 2022
Article in press: May 28, 2022
Published online: June 28, 2022

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Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

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

CONCLUSION

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

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

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

Citation: Lee PN, Coombs KJ, Hamling JS. Review with meta-analysis relating North American, European and Japanese snus or smokeless tobacco use to major smoking-related diseases. *World J Meta-Anal* 2022; 10(3): 130-142

URL: https://www.wjgnet.com/2308-3840/full/v10/i3/130.htm

DOI: https://dx.doi.org/10.13105/wjma.v10.i3.130

INTRODUCTION

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

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

MATERIALS AND METHODS

Study inclusion and exclusion criteria

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

Literature searches

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

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

Meta-analyses

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

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

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

RESULTS

Literature searches

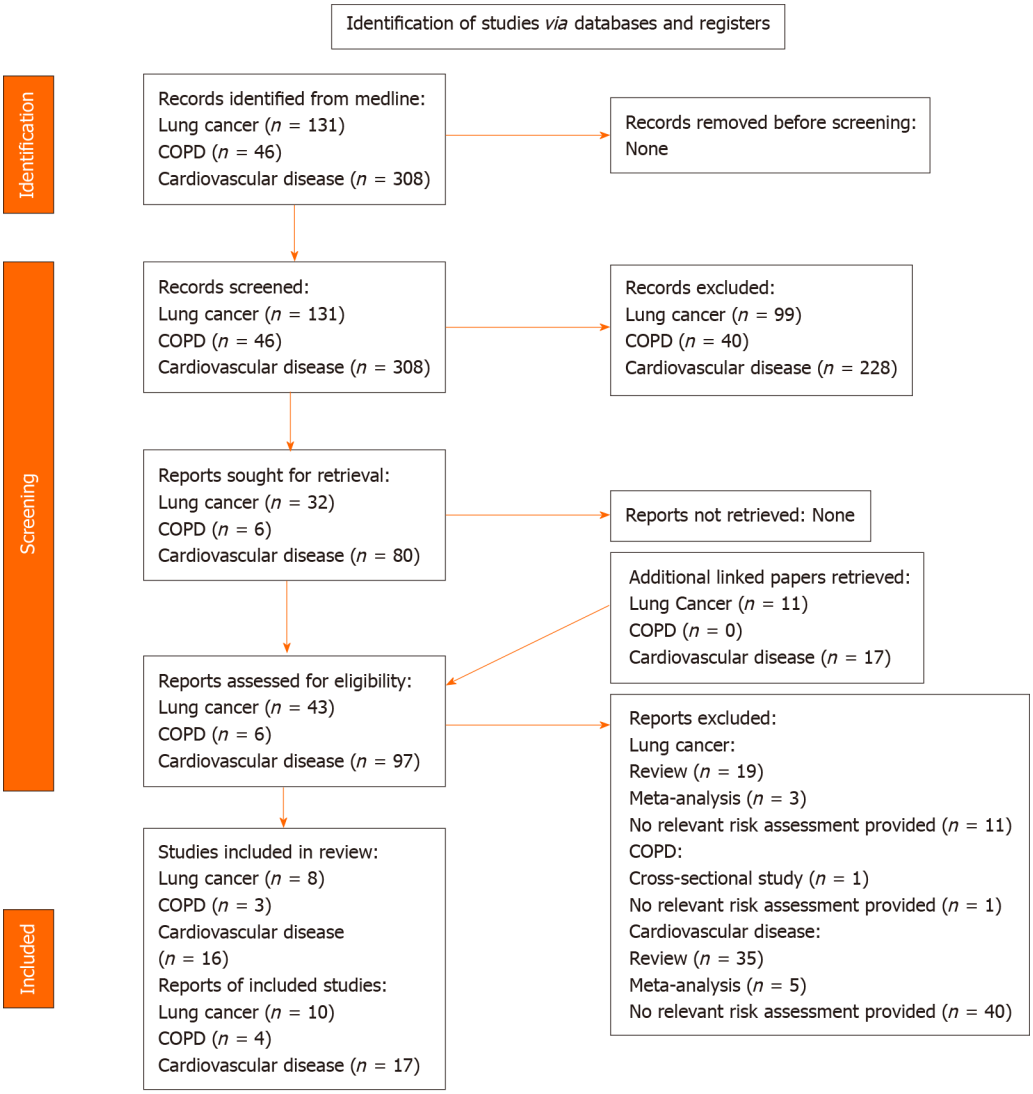
The results of the searches are given in detail in Additional File 1 and are summarized below and in Figure 1.

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

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

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

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



DOI: 10.13105/wjma.v10.i3.130

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

ST use in the US

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

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

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

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

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

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

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

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

varying list of other factors, including sex where relevant.

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

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

Snus use in Scandinavia

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

ACKNOWLEDGEMENTS

We thank Yvonne Cooper for typing the various drafts of the paper and obtaining the relevant references.

FOOTNOTES

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

Conflict-of-interest statement: The authors have carried out consultancy work for many tobacco organizations.

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

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World J Meta-Anal 2022 June 28; 10(3): 143-161

DOI: 10.13105/wjma.v10.i3.143

ISSN 2308-3840 (online)

META-ANALYSIS

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

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Specialty type: Orthopedics

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Belluzzi E, Italy; Haque N, Bangladesh; Yang YZ, China; Zhang W, China; Zhu L, China

Received: December 18, 2021
Peer-review started: December 18, 2021
First decision: March 13, 2022
Revised: March 23, 2022
Accepted: June 21, 2022
Article in press: June 21, 2022
Published online: June 28, 2022

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Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

CONCLUSION

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

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

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

Citation: Muthu S, Jeyaraman N, Patel K, Chellamuthu G, Viswanathan VK, Jeyaraman M, Khanna M. Evidence analysis on the utilization of platelet-rich plasma as an adjuvant in the repair of rotator cuff tears. *World J Meta-Anal* 2022; 10(3): 143-161

URL: https://www.wjgnet.com/2308-3840/full/v10/i3/143.htm

DOI: https://dx.doi.org/10.13105/wjma.v10.i3.143

INTRODUCTION

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

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

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

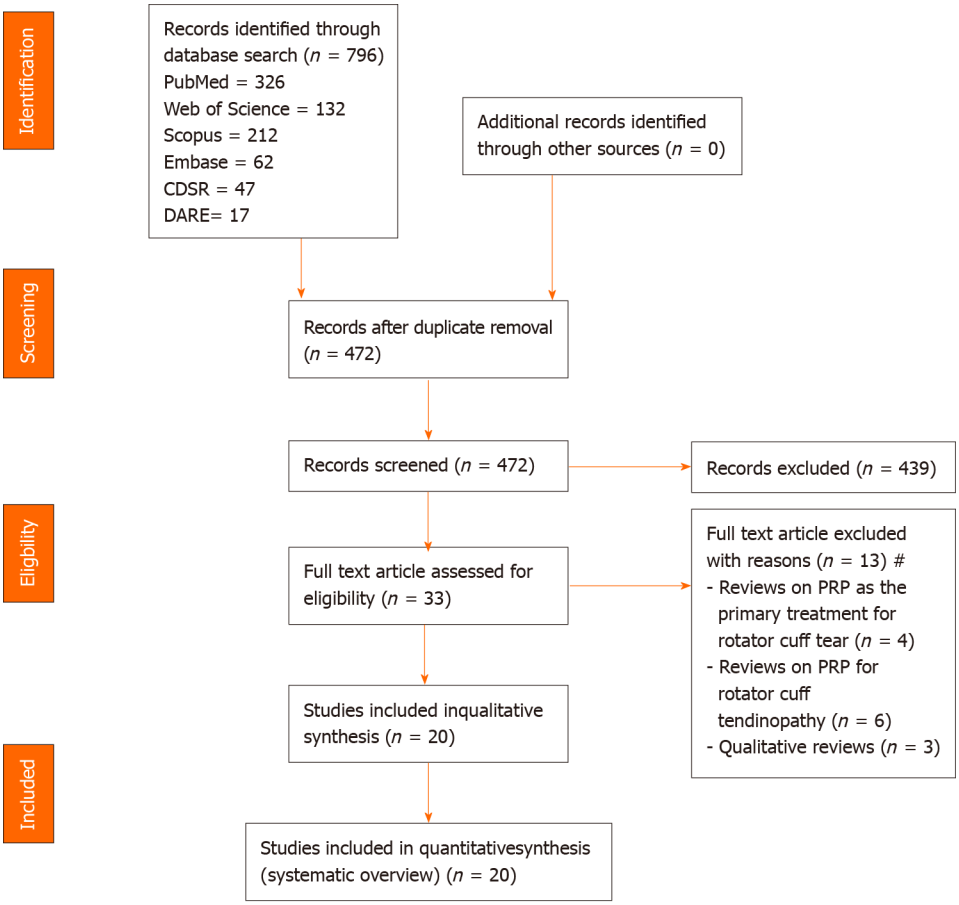
The overall purpose of the current study was to perform a detailed systematic review of the existing meta-analyses evaluating the role of PRP in patients undergoing rotator cuff repair; and to specifically provide answers to the following research questions, namely: (1) To evaluate the effect of this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

MATERIALS AND METHODS

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

Search strategy

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



DOI: 10.13105/wjma.v10.i3.143

Figure 1 PRISMA flow diagram of the included studies.

Inclusion criteria

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

Exclusion criteria

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

Data extraction

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

Assessment of quality of study methodology

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

Heterogeneity assessment

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

Application of Jadad decision algorithm

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

RESULTS

Search results

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

Search methodology of the meta-analyses

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

Methodological quality

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

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

Assessment of heterogeneity

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

Table 1 Characteristics of the included studies

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

Results of Jadad decision algorithm

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

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

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

Table 2 Search methodology used by each study

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

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

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

Major conclusions from the individual studies

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

Table 3 Methodological information of each study

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

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

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

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

Table 4 AMSTAR scores and AMSTAR 2 grading for included studies

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

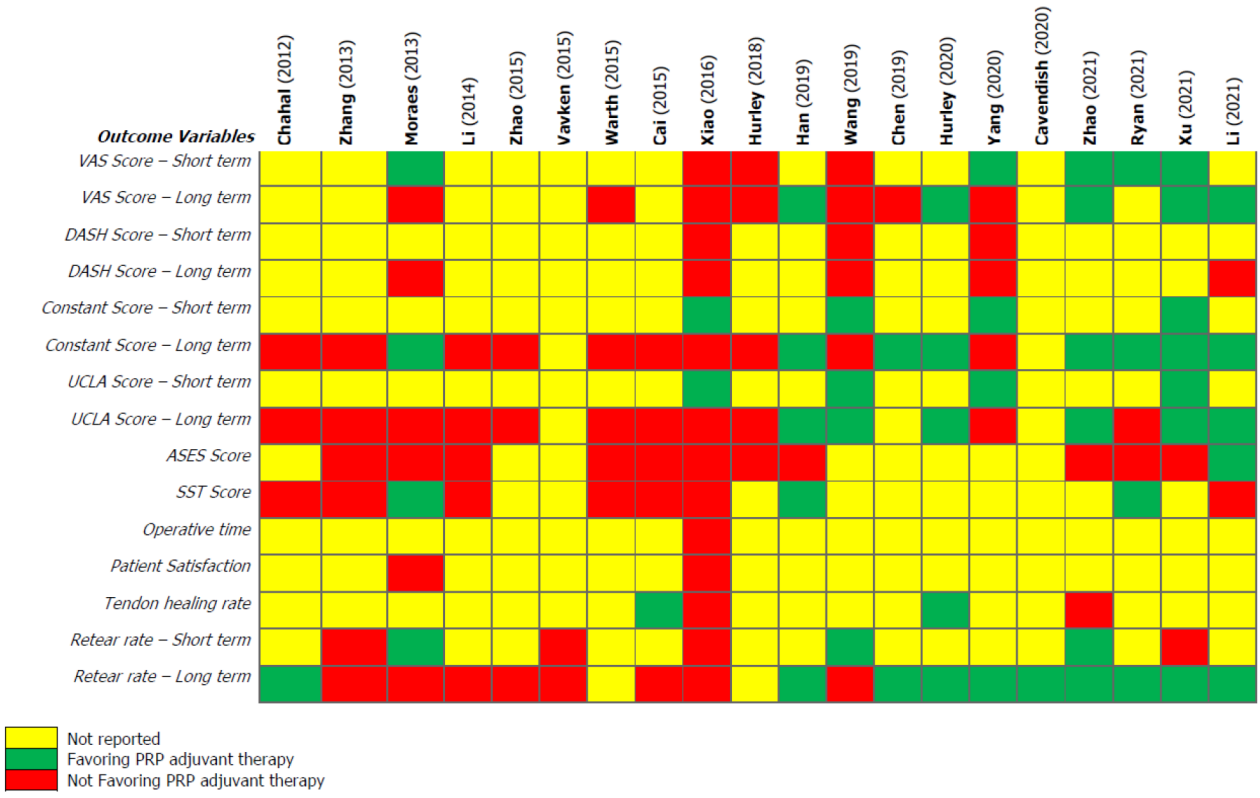
Warth *et al*[35] (2014) conducted a meta-regression analysis to evaluate the effect of 6 different co-variates (level of studies included, tear size, single- *vs* double-row repairs, types of PRP preparation, manual *vs* commercially available PRP preparations; and method of application of PRP) on overall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

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

Recent meta-analyses and their observations

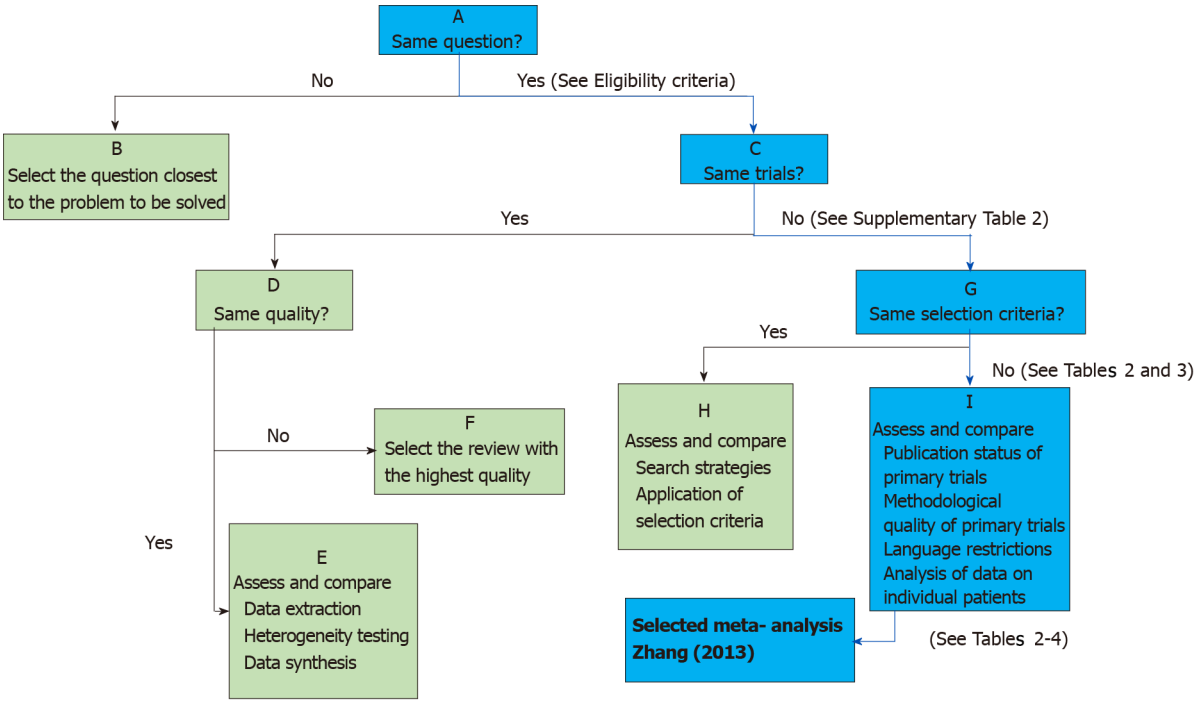
Between 2020 and 2021, 7 new meta-analyses have been published on this topic. Owing to the availability of better quality, larger-scale RCTs over the recent years, these recent meta-analyses have been able to put forth stronger recommendations regarding the administration of PRPs. Cavendish *et al*[43]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

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



DOI: 10.13105/wjma.v10.i3.143

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



DOI: 10.13105/wjma.v10.i3.143

Figure 3 Flowchart of Jadad decision algorithm.

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

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

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

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

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

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

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

Directions for future

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

Limitations

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

future research on this subject.

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

Author contributions: Muthu S conducted the research along with Viswanathan VK, Jeyaraman N, Patel K, Chellamuthu G, Jeyaraman M and Khanna M helped in the conduction of the study; All authors have read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have a conflict of interest over the subject presented.

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

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S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

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World Journal of Meta-Analysis

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

World J Meta-Anal 2022 June 28; 10(3): 162-176

DOI: 10.13105/wjma.v10.i3.162

ISSN 2308-3840 (online)

META-ANALYSIS

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

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Specialty type: Orthopedics

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Chrcanovic BR, Sweden; Jing F, China; Tsang HW, China; Yan T, China

Received: February 4, 2022
Peer-review started: February 4, 2022
First decision: April 19, 2022
Revised: May 2, 2022
Accepted: June 22, 2022
Article in press: June 22, 2022
Published online: June 28, 2022

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Abstract

BACKGROUND

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

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

AIM

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

METHODS

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

RESULTS

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

CONCLUSION

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

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

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

Citation: Muthu S, Mogulesh C, Viswanathan VK, Jeyaraman N, Pai SN, Jeyaraman M, Khanna M. Is cellular therapy beneficial in management of rotator cuff tears? Meta-analysis of comparative clinical studies. *World J Meta-Anal* 2022; 10(3): 162-176

URL: https://www.wjgnet.com/2308-3840/full/v10/i3/162.htm

DOI: https://dx.doi.org/10.13105/wjma.v10.i3.162

INTRODUCTION

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

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

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

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

MATERIALS AND METHODS

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

Search strategy

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

Inclusion criteria

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

Population: Patients with RC tears.

Intervention: MSC-based biological therapy.

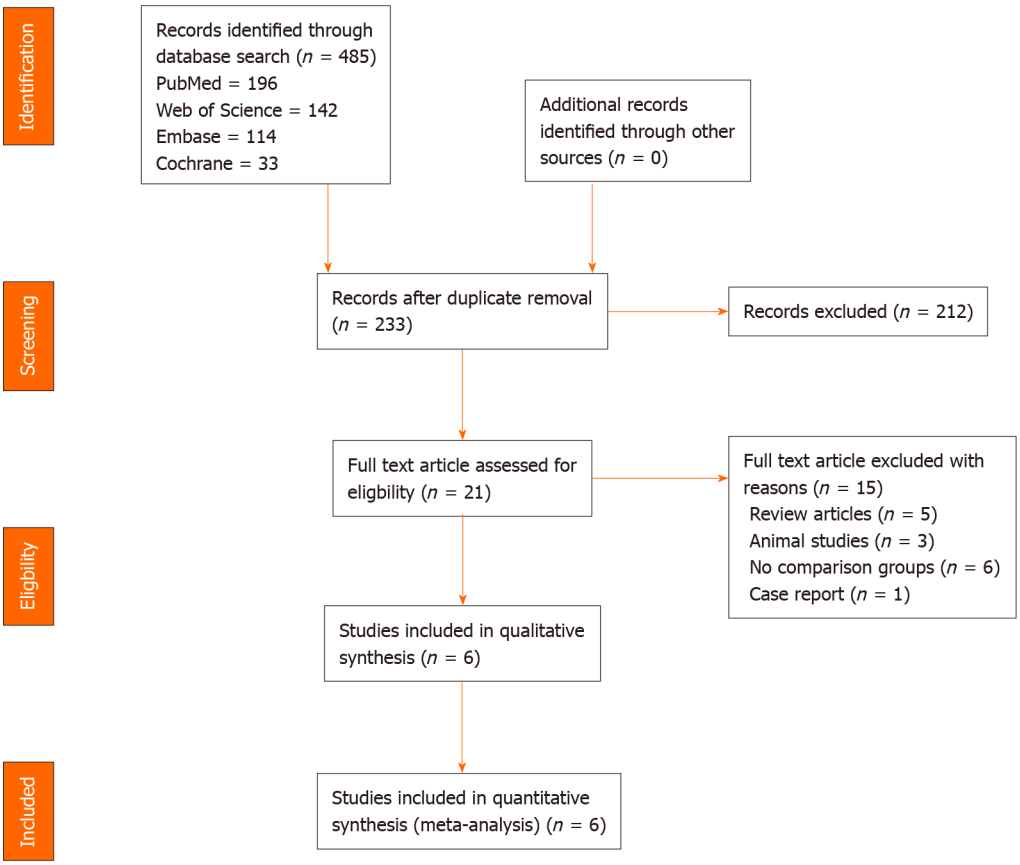
Comparator: Placebo.

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

Study design: Comparative clinical studies (CCSs).

Exclusion criteria

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



DOI: 10.13105/wjma.v10.i3.162

Figure 1 PRISMA flow diagram of the included studies.

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

Data extraction

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

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

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

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

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

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

Risk of bias and quality assessment

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

Statistical analysis

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

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

RESULTS

Search results

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

Quality assessment

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

Efficacy outcomes

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

ASES score

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

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

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

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

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

Constant score

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

Radiological healing

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

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

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

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

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

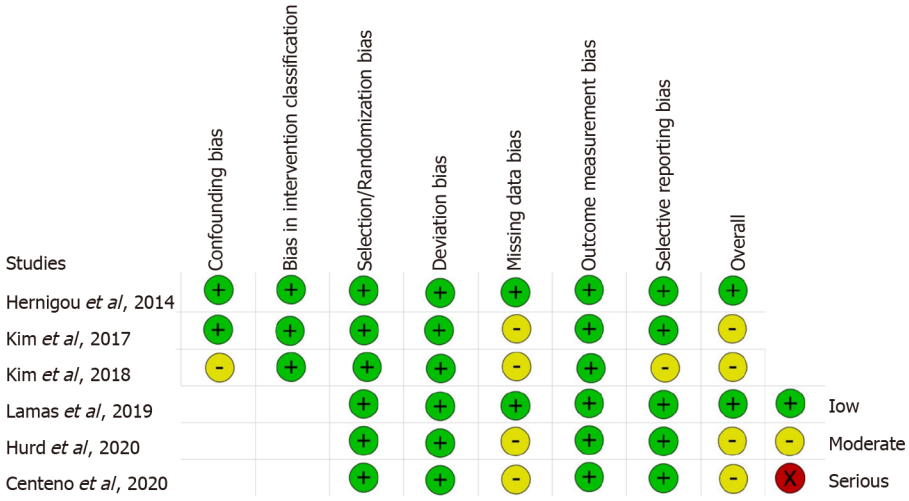
healing was noted in long term.

Retear rate

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

Adverse events

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



DOI: 10.13105/wjma.v10.i3.162

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

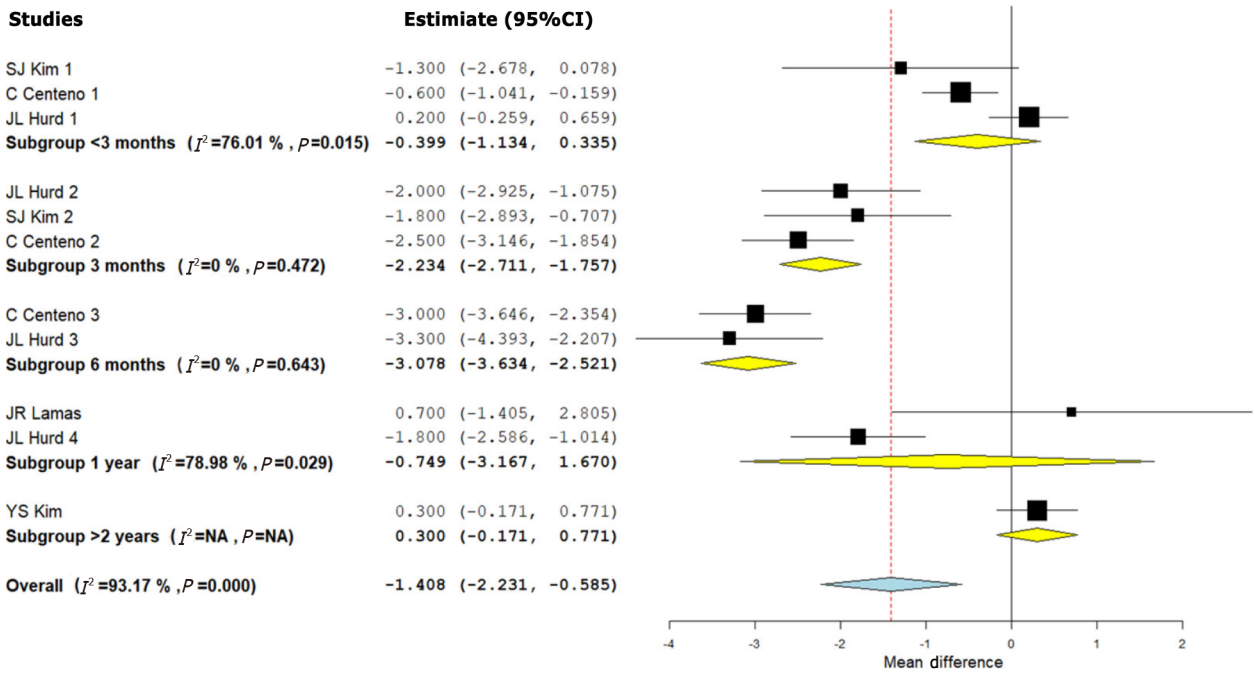


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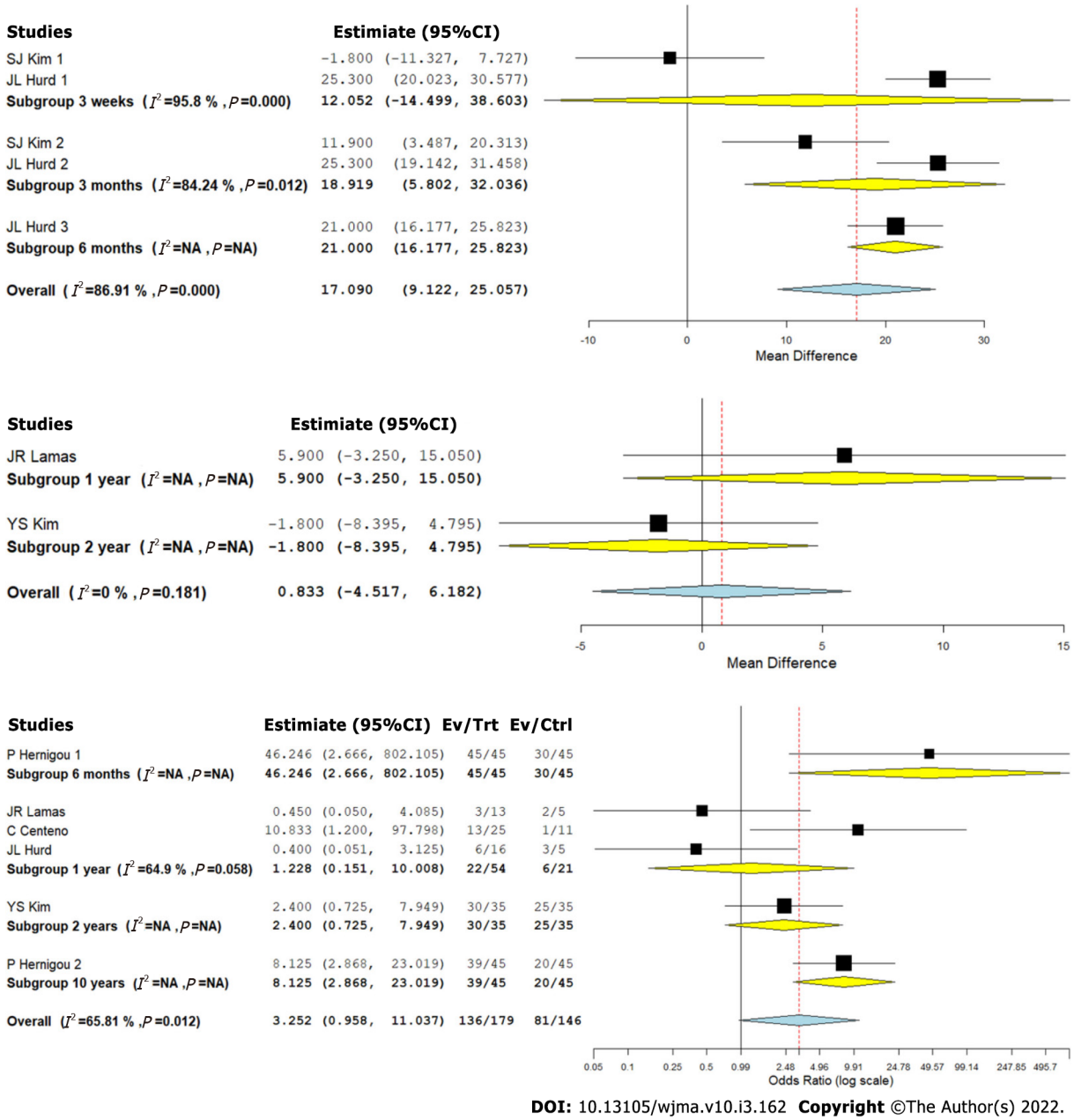
Figure 3 Forest plot of the included studies analyzing the Visual Analog Scale score outcomes at varied time points compared to their controls.

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

Sensitivity analysis

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



DOI: 10.13105/wjma.v10.i3.162

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

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

Publications bias

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

DISCUSSION

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

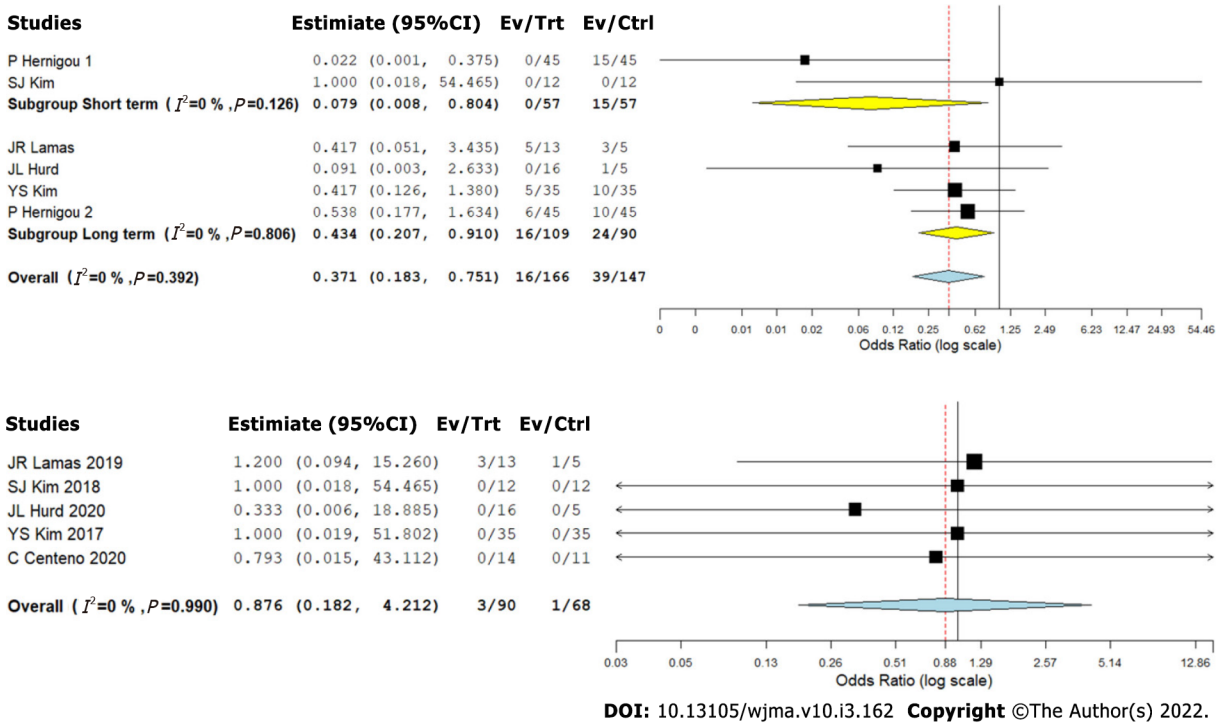


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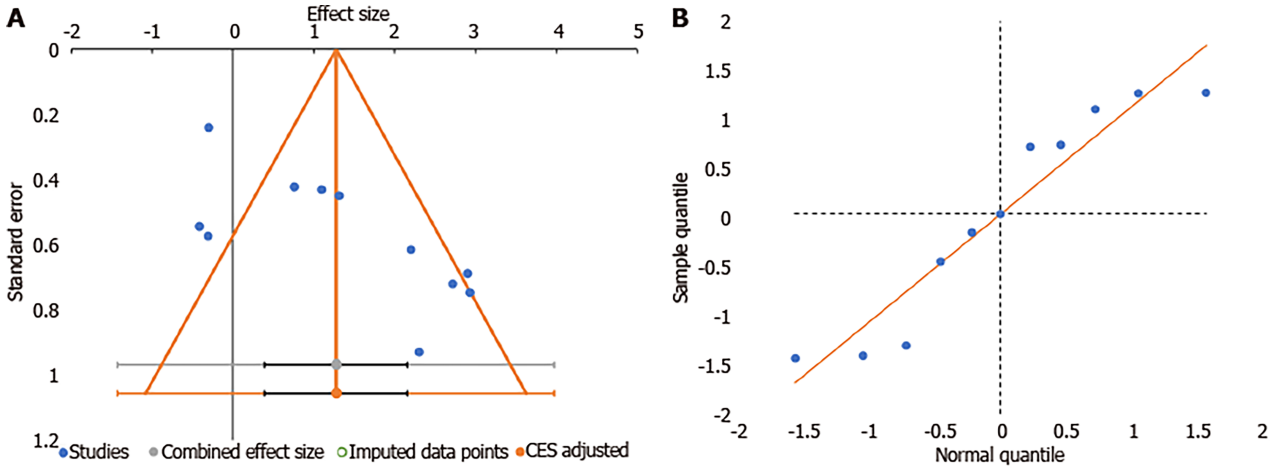
Figure 5 Forest plot of the included studies analyzing the complications at varied time points compared to their controls. A: Retear rate; B: Adverse events.



DOI: 10.13105/wjma.v10.i3.162

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

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

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

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

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

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

Influence of MSC therapy on pain severity and functional outcome scores

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

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

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

Influence of MSC therapy on radiological healing

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

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

Influence of MSC therapy on retear rates

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

Safety of MSC therapy

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

Limitations

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

CONCLUSION

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

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

Author contributions: Muthu S conducted the research along with Viswanathan VK; Jeyaraman N, Patel K, Chellamuthu G, Jeyaraman M, and Khanna M helped in the conduction of the study; all authors have read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have a conflict of interest over the subject presented.

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

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S-Editor: Liu JH

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

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World Journal of Meta-Analysis

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World J Meta-Anal 2022 June 28; 10(3): 177-185

DOI: 10.13105/wjma.v10.i3.177

ISSN 2308-3840 (online)

META-ANALYSIS

Clinical outcomes of the omicron variant compared with previous SARS-CoV-2 variants; meta-analysis of current reports

Mohsen Karbalaei, Masoud Keikha

Specialty type: Infectious diseases

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cure E, Turkey; Lelisho ME, Ethiopia

Received: March 24, 2022
Peer-review started: March 24, 2022
First decision: April 28, 2022
Revised: May 15, 2022
Accepted: June 24, 2022
Article in press: June 24, 2022
Published online: June 28, 2022

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Abstract

BACKGROUND

Omicron (B.1.1.529) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern; however, there is no comprehensive analysis regarding clinical features, disease severity, or clinical outcomes of this variant.

AIM

To compare the clinical characteristics of infection with omicron and previous variants of SARS-CoV-2.

METHODS

We searched major international databases consisting ISI Web of Science, PubMed, Scopus, MedRxiv, and *Reference Citation Analysis* to collect the potential relevant documents. Finally, clinical features, *e.g.*, death rate, intensive care unit (ICU) admission, length of hospitalization, and mechanical ventilation, of infection with SARS-CoV-2 omicron variant compared with previous variants were assessed using odds ratio and 95% confidence intervals by Comprehensive Meta-Analysis software version 2.2.

RESULTS

A total of 12 articles met our criteria. These investigated the clinical outcomes of infection with omicron variant compared with other variants such as alpha, beta and delta. Our results suggested that ICU admission, need for mechanical ventilation, and death rate were significantly lower for omicron than previous variants. In addition, the average length of hospitalization during the omicron wave was significantly shorter than for other variants.

CONCLUSION

The infectivity of omicron variant was higher than for previous variants due to

several mutations, particularly in the spike protein. However, disease severity was mild to moderate compared previous variants.

Key Words: SARS-CoV-2; COVID-19; Omicron; Infectious disease

Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron (B.1.1.529) is a variant of concern that was first identified on 24 November 2021 as a new global threat. However, due to the lack of comprehensive statistical analysis, clinical characteristics and disease outcomes of infection with omicron variant have remained unknown. Hence, the comparison of clinical profile between cases infected with this new variant and previous variants will lead to the establishment of a strategy regarding appropriate management and global control of this variant.

Citation: Karbalaei M, Keikha M. Clinical outcomes of the omicron variant compared with previous SARS-CoV-2 variants; meta-analysis of current reports. *World J Meta-Anal* 2022; 10(3): 177-185
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/177.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.177

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic that first emerged from Wuhan, China in December 2019. According to the World Health Organization (WHO), so far > 378 million cases, as well as 5.67 million deaths have occurred due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[1]. On 24 November 2021, the Network for Genomics Surveillance in South Africa (NGS-SA) reported a new variant of this virus from Gauteng Province, named omicron (B.1.1.529); the new variant was confirmed by WHO on 25 November 2021[2,3].

The omicron variant rapidly replaced the previous variants in South Africa and spread to other countries, so it quickly became a dominant variant. In the USA, approximately 95% of all new cases of COVID-19 were diagnosed as being caused by the omicron variant by January 2022[4,5].

The genome of this variant contains 26–32 mutations in the spike gene as well as 45–52 amino acid substitutions. these mutations are associated with increases in viral characteristics such as transmissibility, immune escape, and S gene target failure (SGTF). SGTF is due to the 69 to 70 deletion in the S gene of B.1.1.7[6-8]. Early studies have shown the inefficacy of current vaccines (vaccination schemes and booster doses) and the higher rate of re-infection with the omicron variant[9,10]. Based on animal model findings, the severity of symptoms as well as the viral load of the omicron variant were lower compared to the previously reported variants of SARS-CoV-2[11,12]. Clinical reports from Scotland, England, Canada, and the USA have also confirmed animal experiments[13-16]. However, the fourth global wave of COVID-19 caused by the omicron variant was not associated with increased hospitalization or death in comparison with previous SARS-CoV-2 variants[17].

Understanding the clinical characteristics, susceptibility factors, and immune response against the new SARS-CoV-2 variants could be useful strategies in managing these viruses and development of novel treatment options. In this study, we evaluated the clinical severity of SARS-CoV-2 omicron variant compared with previous variants.

MATERIALS AND METHODS

We searched global databases such as ISI Web of Science, PubMed, Scopus, MedRxiv, and Reference Citation Analysis (https://www.referencecitationanalysis.com/) using MeSH keywords such as "Omicron", "COVID-19", "SARS-CoV-2", "Disease severity", "Variant of concern", "ICU", "Intensive care unit", and "fourth wave". We retrieved all potential studies related to the clinical severity of SARS-CoV-2 omicron variant regardless of language and publication date. All eligible documents were carefully screened; required data including mean age, immunization status, mortality rate, intensive care unit (ICU) admission, length of hospitalization, and mechanical ventilation are summarized in Table 1. We also reviewed the bibliography of documents to avoid missing relevant articles. Finally, the severity of COVID-19 caused by omicron compared with previous SARS-CoV-2 variants was evaluated using odds ratio (OR) and 95% confidence interval (CI). We used a random-effect size due to the presence of significant heterogeneity (I^2 index and Cochrane *P* value test). Data were pooled using

Table 1 Characteristics of included studies

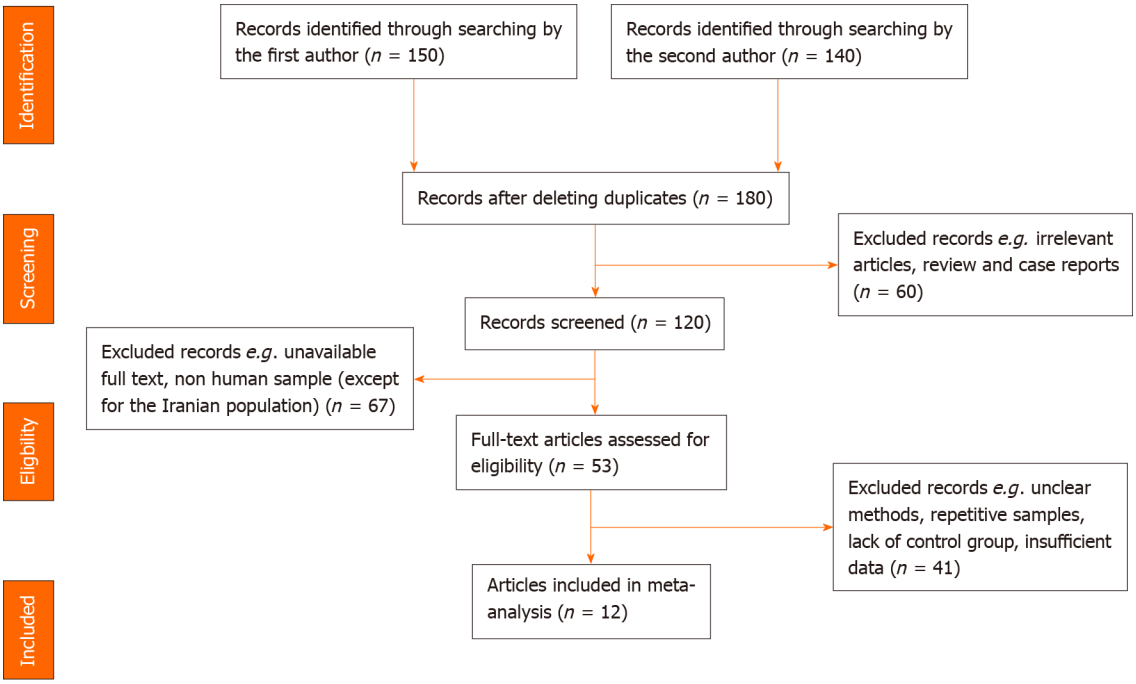
First author	Country	Mean age		Immunization		Death rate		ICU admission		Length of stay		Ventilation		Number of cases		Ref.
		Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	Omicron	Previous variants	
Abdullah	South Africa	39	49.8	NA	NA	4.5%	21.3%	1%	4.3%	4	8.8	NA	NA	466	3962	[18]
Cloete	South Africa	4.2	NA	NA	NA	4	NA	7	NA	3.2	NA	7	NA	6287	NA	[19]
Christensen	USA	44.3	50.0	2497	101	38	170	NA	NA	3.2	5.1	49	144	4468	3149	[20]
Davies	South Africa	NA	NA	HR:0.41, 95%CI: 0.29-0.59		HR: 0.27, 95%CI: 0.19-0.38		NA	NA	NA	NA	NA	NA	5144	11609	[21]
Goga	South Africa	33	55	NA	NA	NA	NA	3%	16%	3	6	0.2%	8%	17650	22888	[22]
Lewnard	USA	NA	NA	6,981	784	1	12	4	20	5.5	15.8	0	11	52297	16982	[23]
Iuliano	USA	NA	NA	NA	NA	1854	1924	24776	24774	3	5	358	503	48238	25873	[24]
Maslo	South Africa	36	53	235	NA	27	520	180	1104	3	8	16	431	971	2628	[25]
Santos	Portugal	37.1	43.4	295	201	0	26	0	17	3.7	8.6	NA	NA	6581	9397	[26]
Torjesen	UK	NA	NA	NA	NA	NA	NA	9.9%	14%	1.7	6.6	2%	5.8%	NA	NA	[27]
Wang	USA	36.4	36.1	2.4%	3.1%	23	30	0.26%	0.78%	NA	NA	0.07%	0.43%	14054	563884	[28]
Wang	USA	1.49	1.73	NA	NA	NA	NA	0.14%	0.43%	NA	NA	0.33%	1.15%	7201	63203	[29]

ICU: Intensive care unit; NA: Not available; HR: Hazard ratio; CI: Confidence interval.

Comprehensive Meta-Analysis software version 2.2 (Biostat, Englewood, NJ, USA).

RESULTS

A total of 12 studies investigated the clinical outcomes of infection with SARS-CoV-2 omicron variant compared with other variants such as alpha, beta and delta (Figure 1). Eligible studies were performed in South Africa, USA, Portugal and UK from 2021 to 2022[18-29]. We pooled the data of 887 132 cases with positive PCR test for SARS-CoV-2, including 163 457 cases positive for omicron variant, as well as 723 675 cases positive for other variants.



DOI: 10.13105/wjma.v10.i3.177

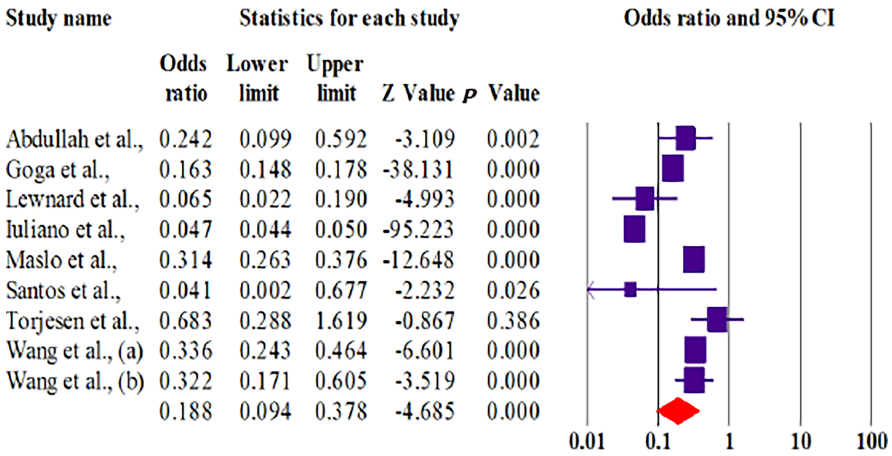
Figure 1 Flowchart of literature search and study selection process.

The mean age of patients infected with omicron variant was 28.93 ± 15 years. The frequency of events such as ICU admission, need for mechanical ventilation, and death rate for omicron variant was 0.8% (95% CI: 0.2%–3.7%; I^2: 99.89; P = 0.01; Egger's P = 0.01; Begg's P = 0.29), 0.2% (95% CI: 0.1%–0.5%; I^2: 95.75; P = 0.01; Egger's P = 0.16; Begg's P = 0.26), and 0.4% (95% CI: 0.1%–1.0%; I^2: 98.47; P = 0.01; Egger's P = 0.01; Begg's P = 0.45), respectively. The average length of hospitalization for omicron was significantly less than for other variants (3.36 ± 1 d *vs*. 7.98 ± 3 d; P < 0.05). The incidence of omicron infection among fully vaccinated individuals was 12.9% (95% CI: 5%–27%; I^2: 99.89; P = 0.01; Egger's P = 0.22; Begg's P = 0.40). the current findings revealed that the severity of infections caused by omicron was less than for previous infections caused by alpha, beta, and delta variants. The current findings are consistent with similar reports[30,31]. In comparing the fourth wave of COVID-19 caused by the omicron variant with previous waves, it should be said that the mean age for patients infected with omicron was ~13 years (28.93 ± 15 years), which was less than that for other variants (41.29 ± 17 years). There was a significant reduction in ICU admission (OR: 0.18; 95% CI: 0.094–0.37; P = 0.01; I^2: 99.05; P = 0.01; Egger's P = 0.2; Begg's P value: 0.07) (Figure 2). Our results suggested a significant reduction in the need for mechanical ventilation (OR: 0.135; 95% CI: 0.05–0.31; P = 0.01; I^2: 97.24; P = 0.01; Egger's P = 0.12; Begg's P = 0.26) among omicron cases (Figure 3). The mortality rate also declined among patients infected with omicron variant (OR: 0.17; 95% CI: 0.06–0.46; P = 0.01; I^2: 98.32; P = 0.01; Egger's P = 0.44; Begg's P = 0.71) compared with previous variants (Figure 4).

DISCUSSION

We found that the severity of COVID-19 caused by the SARS-CoV-2 omicron variant was significantly less than for previous variants; however, there was significant heterogeneity that could be due to differences in several factors such as study design, geographical region, time for assessment of clinical outcomes, and diverse conditions of included cases; publication bias was also significant. Recently, Zhao *et al*[32], showed that the omicron variant is less dependent on the TMPRSS2-mediated entry pathway, which leads to less-efficient replication and decreased viral load within the lungs. In addition, the omicron variant is more susceptible to interferons than other variants are, especially the delta variant [33]. Similar evidence could be a reasonable explanation for the lower severity of COVID-19 with the omicron variant, as confirmed by numerous observational studies[15].

The omicron variant nucleotide sequence has several mutations, especially 32 single substitutions in the spike protein that cause resistance to neutralizing antibodies, as well as inefficiency of current vaccines[34-36]. We revealed that omicron variant causes less severity of COVID-19 than previous variants; however, heterogeneity and publication bias were significant in our estimations (Figure 5). Further studies need to confirm the present findings.



DOI: 10.13105/wjma.v10.i3.177

Figure 2 Forest plot of the meta-analysis on intensive care unit admission for patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

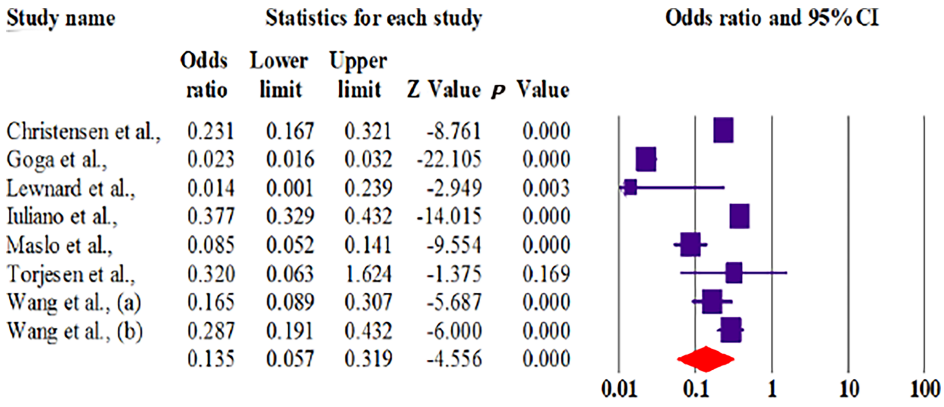


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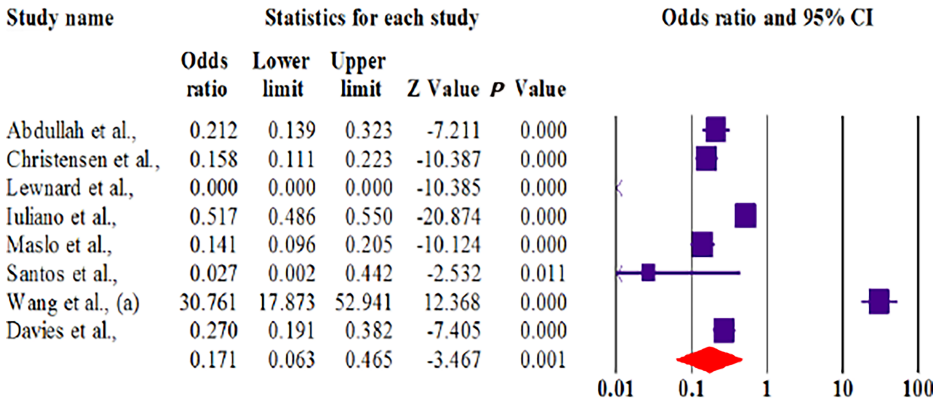
Figure 3 Forest plot of the meta-analysis for need for mechanical ventilation in patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

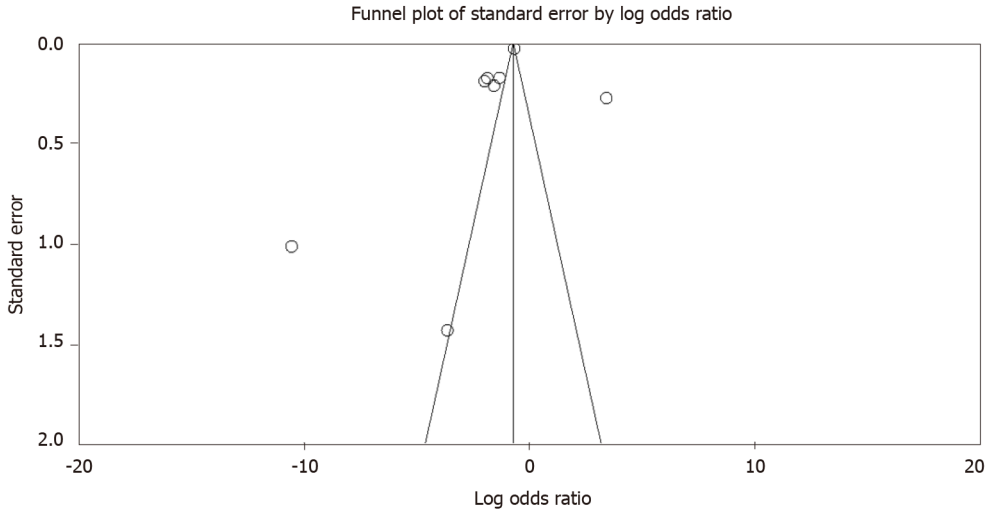


DOI: 10.13105/wjma.v10.i3.177

Figure 4 Forest plot of meta-analysis of risk of mortality in patients infected with severe acute respiratory syndrome coronavirus 2 omicron variant.

CONCLUSION

A new global increase in COVID-19 has been accompanied by the emergence of the SARS-CoV-2 omicron variant that is associated with less disease severity, as well as fewer ICU admissions, shorter



DOI: 10.13105/wjma.v10.i3.177

Figure 5 Funnel plot of meta-analysis of disease severity of patients intfected with severe acute respiratory syndrome coronavirus 2 omicron variant compared with previous variants.

hospitalization, and lower mortality rate. Nonetheless, there is limited information about the effect of omicron on children, pregnant women, and immunodeficient individuals. Overall, omicron has been considered as the most contagious SARS-CoV-2 variant that affects children and young adults more than other groups. Continuation of the current situation can have deadly consequences for these age groups.

ARTICLE HIGHLIGHTS

Research background

Omicron (B.1.1.529) is a new variant of concern of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, there is no comprehensive analysis regarding clinical features, disease severity, and clinical outcomes of infection with this variant.

Research motivation

There is insufficient evidence regarding clinical characteristics, standard therapeutic regimen, and efficacy of currently available vaccines against the omicron variant.

Research objectives

This study was a comprehensive review and statistical analysis to compare the clinical characteristics of infection with the omicron and previous variants.

Research methods

We searched major international databases consisting ISI Web of Science, PubMed, Scopus, and MedRxiv to collect the potential relevant documents. Finally, clinical features, *e.g.*, death rate, intensive care unit (ICU) admission, length of hospitalization, and need for mechanical ventilation of patients infected with omicron variant compared with previous variants, were assessed.

Research results

Twelve articles met our criteria. These studies investigated the clinical outcomes of infection with SARS-CoV-2 omicron variant compared with other variants such as alpha, beta and delta. Our results suggested that ICU admission, need for mechanical ventilation, and death rate were significantly lower for omicron than previous variants. In addition, the average length of hospitalization during the omicron wave was significantly shorter than for other variants.

Research conclusions

The infectivity of the omicron variant was much higher than for previous variants due to the presence of several mutations, particularly in the spike protein. However, disease severity was mild to moderate disease compared with previous variants.

Research perspectives

We revealed that the disease severity of infection with omicron was lower than for previous variants. However, this variant was more contagious. Nevertheless, further investigation with larger samples is needed to confirm the present findings.

FOOTNOTES

Author contributions: Keikha M contribute in design of study, study conceptual, literature search, writhing the draft; Karbalaei M revision the draft and manuscript editing; all authors agree with publish in this journal.

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

PRISMA 2009 Checklist statement: This study was conducted according to PRISMA 2009 Checklist statement.

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S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Liu JH

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World Journal of Meta-Analysis

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World J Meta-Anal 2022 June 28; 10(3): 186-194

DOI: 10.13105/wjma.v10.i3.186

ISSN 2308-3840 (online)

META-ANALYSIS

Difference in incidence of developing hepatocellular carcinoma between hepatitis B virus-and hepatitis C virus-infected patients

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ciotti M, Italy; Talal A, United States

Received: April 13, 2022
Peer-review started: April 13, 2022
First decision: May 31, 2022
Revised: June 14, 2022
Accepted: June 27, 2022
Article in press: June 27, 2022
Published online: June 28, 2022

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Abstract

BACKGROUND

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. The reason why this difference in the incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We report the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

AIM

To investigate this, we surveyed the hazard ratio of inflammation for HCC development which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

METHODS
The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC identifying 8924 HBV-and 7376 HCV- infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV- infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

RESULTS
In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77] and that in the 8 studies of HCV-infected patients was 5.51 [3.08-9.83]. The HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. HR in HCV-infected patients was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

CONCLUSION
The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT between HBV and HCV infections.

Key Words: Hazard ratio of alanine aminotransferase; Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Elevated alanine aminotransferase

Core Tip: It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers. In HBV infection, alanine aminotransferase (ALT) is the second highest risk factor, and in HCV infection, ALT is the highest risk factor, for HCC development. The hazard ratio (HR) for developing HCC in the inflammatory state (serum ALT levels exceeded the normal range) was compared between HBV and HCV patients. In the 14 studies of HBV patients, the average HR was 2.74 as compared with 5.51 in the 8 studies of HCV patients (P = 0.0391). The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT for HCC development between HBV and HCV infections.

Citation: Tarao K, Nozaki A, Komatsu H, Ideno N, Komatsu T, Ikeda T, Taguri M, Maeda S. Difference in incidence of developing hepatocellular carcinoma between hepatitis B virus-and hepatitis C virus-infected patients. *World J Meta-Anal* 2022; 10(3): 186-194
URL: https://www.wjgnet.com/2308-3840/full/v10/i3/186.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i3.186

INTRODUCTION

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers[1].

However, the reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We have been considering this for many years, and finally arrived at the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

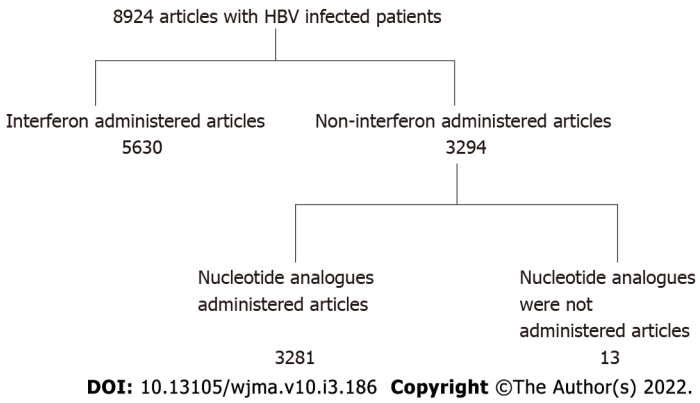


Figure 1 Flow diagram of articles with hepatitis B virus infected patients. HBV: Hepatitis B virus.

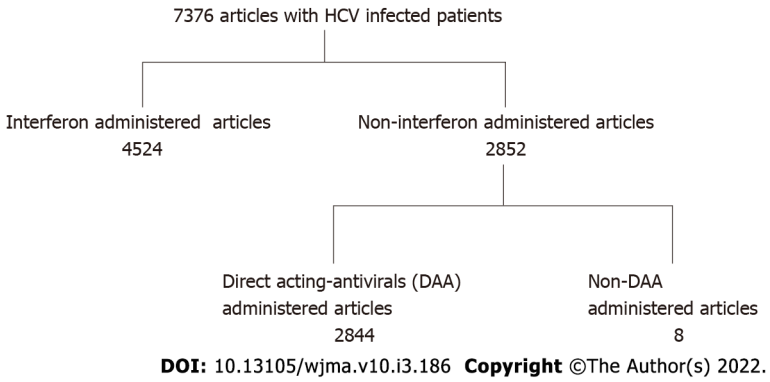


Figure 2 Flow diagram of articles with hepatitis C virus infected patients. HCV: Hepatitis C virus; DAA: Direct acting antivirals.

To investigate this, we surveyed the hazard ratio (HR) of inflammation which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

Why ALT, not AST was adopted in this study was as follows: We previously demonstrated[2] the strong association between sustained high serum ALT levels (≥ 80 international units (INU) annual average) and the development of HCC in patients with HCV-LC (Child Stage A) by long-term observation lasting about 7 years, (Cancer 1999; 86: 589-595). In this series of the study, we also investigated the association between sustained high serum AST levels (≥ 80 INU) and development, but the association was not so strong as ALT. Moreover, many studies have demonstrated a close association between severe inflammation as estimated by higher serum ALT level and initiation of HCC development (Veldt *et al*[3]; Miyakawa *et al*[4]).

MATERIALS AND METHODS

Search strategy

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC in HBV or HCV infected patients. There were 8924 studies involving HBV patients, and 7376 studies of HCV patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those who were administered nucleos(t)ide analogues were excluded, and HCV patients administered direct acting antivirals were also excluded. We also excluded articles which include co-existing liver disease such as alcoholic liver diseases and/or fatty liver diseases. Then, studies which dealt with the HR of HCC regarding inflammation (serum elevated ALT levels) were selected. Finally, there were 13 studies of HBV-infected patients[5-17], and 8 studies of HCV-infected patients[13,18-24] (Figures 1 and 2). In these selected papers, the HR of patients in a non-inflammatory state (serum ALT levels within normal range) was set as 1. We then calculated the HR in patients in an inflammatory state (serum ALT levels were above normal range).

Furthermore, for the purpose of comparing elevated ALT levels between hepatitis B and C patients, we examined the actual ALT levels cited in patients with chronic hepatitis B and hepatitis C included in this series (Tables 1 and 2) .

Table 1 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis B

Ref.	Actual elevated ALT levels
Kim *et al*[5]	Above normal levels
Du *et al*[6]	Above normal levels
Choi *et al*[7]	Above normal levels
Wen *et al*[8]	≥ 25 IU/L
Hann *et al*[11]	Elevated
Chen *et al*[12]	≥ 45 IU/L
Kumada *et al*[13]	Absence of persistently normal ALT levels
Chen *et al*[14]	Above normal levels
Ishiguro *et al*[15]	≥ 30 IU/L
Ando *et al*[16]	≥ 23 IU/L
Yamada *et al*[17]	≥ 40 IU/L

ALT: Alanine aminotransferase.

Table 2 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis C

Ref.	Actual elevated ALT levels
Ishiguro *et al*[15]	≥ 30 IU/L
Chen *et al*[18]	≥ 45 IU/L
Sun *et al*[19]	Elevated
Tanaka *et al*[20]	Elevated
Kumada *et al*[21]	> 20 IU/L
Ito *et al*[22]	> 35 IU/L
Suruki *et al*[23]	> 35 IU/L
Lee *et al*[24]	Always ≥ 45 IU/L

ALT: Alanine aminotransferase.

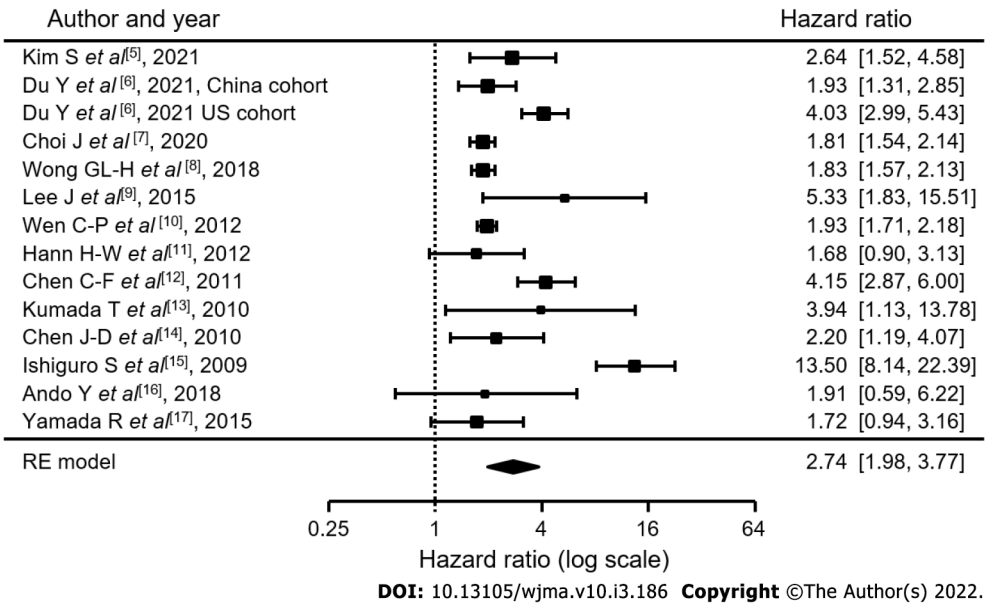
Statistical analysis

To compare HR of ALT for HCC between HBV and HCV patients, we calculated the weighted mean of HR for each type using the random effect model (Ref.: Dersimonian R, Laird N. Meta-analysis in Clinical trials. Controlled Clinic Trials 1986; 7: 177-188). To assess whether the mean HR among HBV patients was lower than that among HCV patients, we calculated the *P* value using a *Z* test. All reported p- values correspond to two-sided tests, and those $P < 0.05$ were considered significant. All analyses were performed using R (version 4.1.2) and R Studio (version 1.4) software.

RESULTS

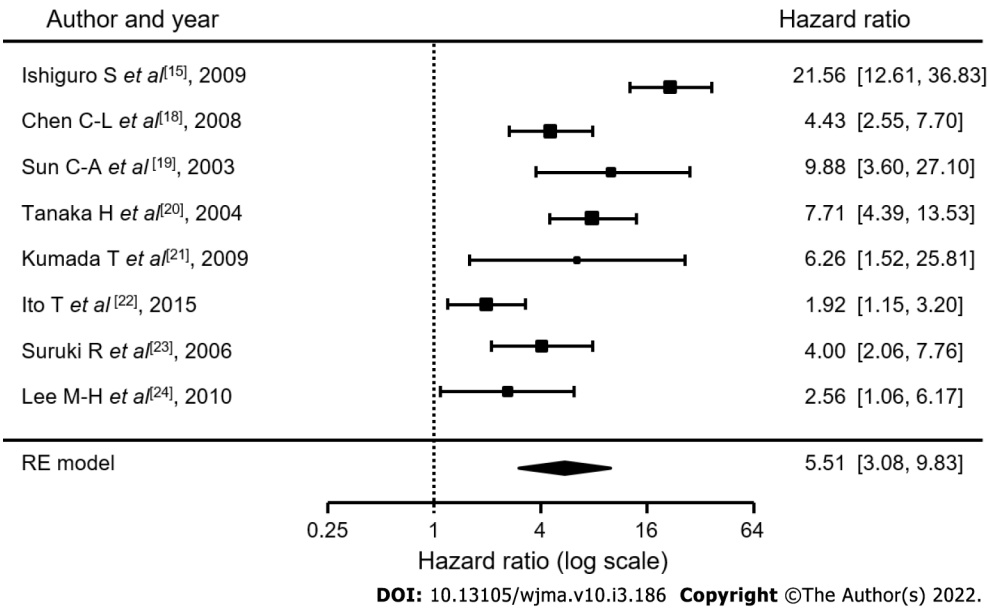
In the 14 studies of HBV patients[5-17], the average HR of elevated ALT for developing HCC was 2.74 [1.98-3.77] (Figure 3), and that in 8 studies of HCV-infected patients[12,15-21] was 5.51 [3.08-9.83] (Figure 4). It was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. The HR in HCV-infected patients was significantly ($P = 0.0391$) higher than that in HBV-infected patients.

In hepatitis B patients, the abnormal range adopted was 28-45 IU/L (Table 1), and in hepatitis C patients, it was 20-50 IU/L (Table 2). It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.



DOI: 10.13105/wjma.v10.i3.186

Figure 3 In hepatitis B virus patients, a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.



DOI: 10.13105/wjma.v10.i3.186

Figure 4 In hepatitis C virus patients, Hazard ratios of patients in a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.

DISCUSSION

There are many risk factors for developing HCC: Sex, age, ALT, α-fetoprotein, presence of cirrhosis, habitual alcohol consumption, tabaco, and diabetes mellitus are typically cited, and HBV-DNA[1,3,6-8, 10] and the HBV genotype[9] are added for chronic HBV infection. The HCV genotype is also cited for HCV infection[21]. To study the impact of ALT on HCC development in chronic hepatitis B and chronic hepatitis C virus infections, we initially surveyed risk factors for HCC that are strongly associated with its development.

As shown in Table 3, the HR for developing HCC for each item in patients with chronic hepatitis B virus infection was 2.52 for sex, 3.15 for age, 2.212 for HBV-DNA, 3.37 for ALT, and 6.42 for presence of cirrhosis. Except for the presence of cirrhosis, ALT shows the highest risk ratio for HCC development.

As shown in Table 4, in patients with chronic hepatitis C virus infection, it was 5.486 for age and 5.877 for ALT. The value for ALT was higher than that for age. In HBV infection, ALT is the second-highest

Table 3 Hazard ratio for developing hepatocellular carcinoma for each item in various reports of patients with chronic hepatitis B virus infection

Ref.	Sex	Age	HBV-DNA	ALT	AFP	Presence of cirrhosis	HBV genotype	Alcohol use	Tabaco	DM
Kim *et al*[5]	2.782	1.080	0.986	2.641		2.955		2.105		2.00
Du *et al*[6]	2.94	3.30		2.55		2.45				
Choi *et al*[7]	1.67	1.05	1.02	1.54	1.21	1.54				
Wen *et al*[10]	1.93	5.34		1.93						
Hann *et al*[11]				1.21						2.60
Chen *et al*[12]			3.12	5.75		7.961	2.05 (Type C)			
Kumada *et al*[13]	6.011		5.125	3.939	6.779	18.033				
Chen *et al*[14]	1.2	2.0	1.6	1.7				2.3	1.9	
Ishiguro *et al*[15]				10.5	2.183					
Ando *et al*[16]	2.200	3.395	1.442	1.914	1.967					
Yamada *et al*[17]	1.44	5.867				5.59				
Average	2.52	3.15	2.212	3.37		6.42				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HBV: Hepatitis B virus.

Table 4 Hazard ratio for developing hepatocellular carcinoma in each item in various reports of patients with chronic hepatitis C virus infection

Ref.	Sex	Age	ALT	AFP	Presence of cirrhosis	DM	HCV-genotype
Ishiguro *et al*[15]		11.4	10.5				
Chen *et al*[18]	1.65	5.83	4.43			3.46	
Sun *et al*[19]		6.5	7.7				
Tanaka *et al*[20]	2.63	4.47	6.23				
Kumada *et al*[21]		2.42	6.263		10.003		
Ito *et al*[22]	1.448	2.187	1.916	6.5			
Suruki *et al*[23]							
Lee *et al*[24]							2.8 (HCV-1)
Average		5.486	5.877				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HCV: Hepatitis C virus.

risk factor, and in HCV infection, ALT is the higher risk factor.

In support of our findings, Benvegnù *et al*[25] demonstrated that patients with HCV infection with persistently elevated or fluctuating ALT levels during the observation period demonstrated a significantly higher rate of HCC development compared with patients in whom ALT remained or became normal during follow-up. This observation confirms that the activity of liver disease, which is characterized by inflammation, necrosis, and regeneration, plays an important role in promoting HCC development and suggests that medical interventions that limit disease activity may prevent or delay neoplastic transformation and tumor growth.

Furthermore, we demonstrated that the average HR of ALT for HCC development in HCV patients is about twice that in HBV patients ($P < 0.05$).

CONCLUSION

In conclusion, the difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

ARTICLE HIGHLIGHTS

Research background

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers.

Research motivation

The reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unknown. We considered the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

Research objectives

To investigate this, we surveyed the hazard ratio of inflammation for HCC development, which was identified by serum alanine aminotransferase levels between patients with HBV and HCV infections.

Research methods

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC, identifying 8924 HBV-and7376 HCV-infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV-infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

Research results

In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77], and that in the 8 studies on HCV-infected patients was 5.51 [3.08-9.83]. HR in HCV-infected patients was about twice that in HBV-infected patient, and was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

Research conclusions

The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

Research perspectives

In this study, it was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. So, we must optimally suppress inflammation in patients with HCV-associated liver diseases to prevent HCC development.

FOOTNOTES

Author contributions: Tarao K summarized the data and wrote the paper; Nozaki A, Komatsu H, Ideno N, Komatsu T, Ikeda T, Maeda S were involved in the interpretation of data, and the development and critical revision of the manuscript for important intellectual content; Taguri M conducted statistical analysis.

Conflict-of-interest statement: All the authors declare no conflicts of interest associated with this manuscript.

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

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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