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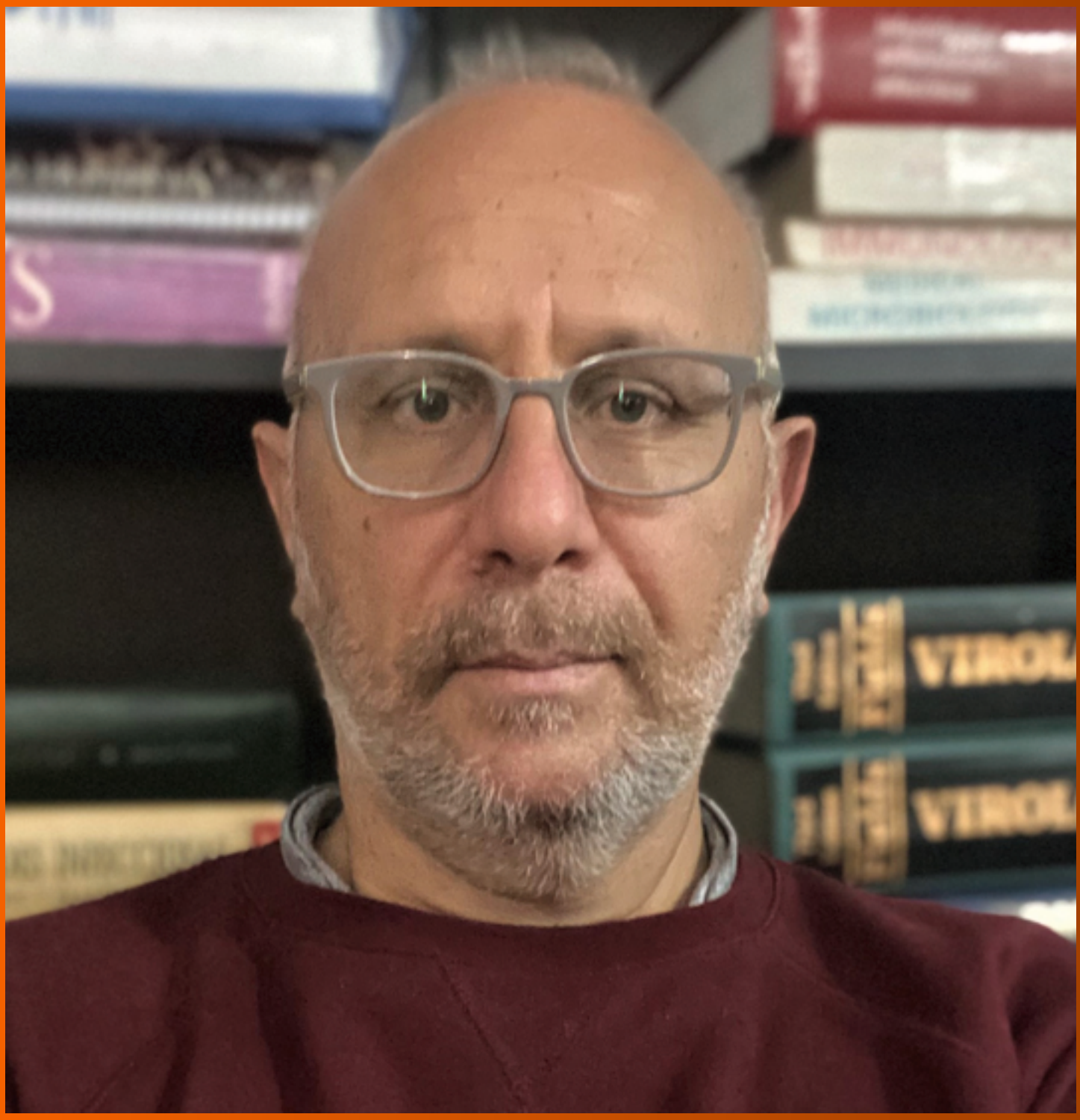

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Editorial Board Member of *World Journal of Hepatology*, Jorge Quarleri, PhD, Adjunct Professor of Microbiology, Research Scientist, Institute of Biomedical Research on Retrovirus and Aids, School of Medicine, University of Buenos Aires (UBA)-National Scientific and Technical Research Council (CONICET), Buenos Aires C1121ABG, Argentina. quarleri@fmed.uba.ar

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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EDITORIAL

Current state of medical tourism involving liver transplantation-the risk of infections and potential complications

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Abstract

Liver transplant has been shown to significantly improve mortality and quality of life in various liver diseases such as acute liver failure, end-stage liver disease, and liver cancer. While the organ transplant demand is continuing to rise, the organ donation supply remains unmatched. The organ shortage, high cost, and long waiting lists have stimulated a desire for routes that may be unethical. This process which is named transplant tourism is the term used to describe traveling to another country to purchase an organ for transplant. Liver transplant tourism has been associated with post-transplant complications and higher mortality compared to a domestic liver transplant. Improper pre-and post-transplant infectious screening, inadequate opportunistic infection prophylaxis, and loss to follow-up were noted in patients who travel abroad for a liver transplant. It is crucial to understand the risk of transplant tourism to prevent morbidity and mortality.

Key Words: Commercial transplant; Liver transplant; Organ tourism; Transplant tourism

Core Tip: Liver transplant tourism can be associated with higher post-operative

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infections, biliary complications, and mortality compared to a domestic liver transplant. Pre-transplant education about the risk of liver transplant tourism and post-transplant management is essential to improve the patients' outcomes.

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INTRODUCTION

Liver disease and the role of transplantation

Acute liver failure, a rare and rapid deterioration of liver function in patients without pre-existing liver disease, is commonly caused by drug-related hepatotoxicity and viral hepatitis[1,2]. Without the transplant, mortality ranges from 26.7%-80%[3,4]. Chronic liver disease is frequently caused by non-alcoholic steatohepatitis, alcoholic and viral hepatitis, leading to cirrhosis and impaired function[5]. The immense morbidity and mortality of end-stage liver disease place a significant healthcare burden causing the liver transplant–its only 'cure'–the second most common transplanted organ globally[6-9].

Liver transplant has been shown to improve mortality and quality of life in various liver diseases such as acute liver failure, end-stage liver disease, liver cancer, liver disease with hepatopulmonary syndrome, and Porto-pulmonary hypertension[10,11]. Moreover, patients with metabolic disorders such as alpha 1-antitrypsin deficiency, familial amyloidosis, glycogen storage disease, hemochromatosis, and Wilson disease are also considered liver transplant candidates[11].

According to the United States Department of Health and Human Services, about 180000 liver transplantations were performed until 2020. While the organ transplant demand is continuing to rise, the supply remains unmatched. In 2018, the number of new registrants for the liver transplant waitlist in the United States was 11844, while 8250 liver transplants were performed[12]. The European Union has also stated a similar predicament with a severe donor shortage. This problem has been a constant stimulus for alternative–not so legal–pathways to obtain organ transplants.

TRANSPLANT TOURISM

According to World Health Organization, transplant tourism is the term used to describe traveling to another country to purchase an organ for transplant[13]. Travel for transplantation was defined by the 2018 edition of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism as the movement of the person across jurisdictional borders for transplant purposes and considered transplant tourism if it is related to trafficking humans for organ removal intention or trafficking in human organs, or if the resources dedicated to providing transplants to non-resident patients undermine the country's ability to supply transplant for people in its own country [14]. Transplant tourism can be divided into four models (Figure 1). First, the donor and recipient who are from the same country travel to another country for transplantation. Second, the donor travels to the country where the recipient resides. Third, the recipient travels to the country that the donor resides. Forth, the donor and recipient from different countries travel to the third country for transplantation[15]. Transplant tourism is a rampant phenomenon that needs more undivided attention. It accounts for approximately 10%-20.6% of global transplantation[16,17].

According to a national United States survey, many foreign transplants included young and male gender Asians with non-resident alien status[18]. Most of the countries that patients traveled to for transplant tourism were China, the Philippines, or India[18]. An interesting study from Syria pointed out the effects of a law passed in 2003 which legalized the use of organs from deceased donors, benefited patients, and increased commercialization as the poor used it as a means for monetary gain[19]. The

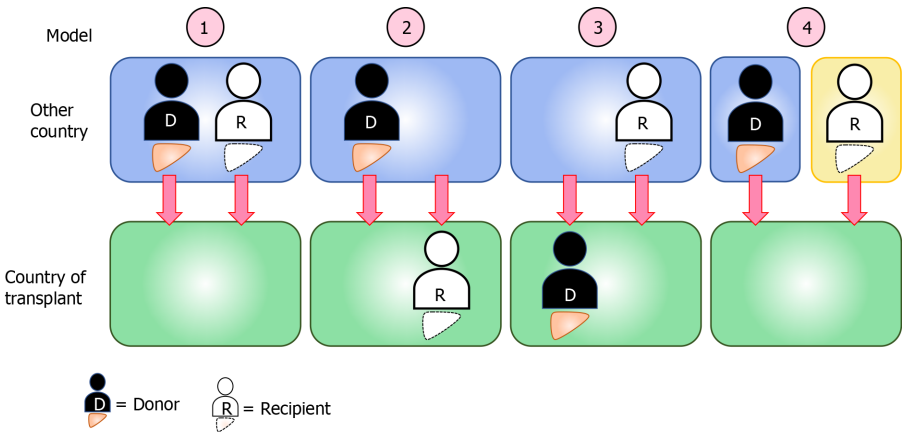

Figure 1 Transplant tourism models. 1: Donor and recipient from the same country travel to another country for transplantation; 2: Donor travels to the country where the recipient resides; 3: Recipient travels to the country that the donor resides; 4: Donor and recipient from different countries travel to the third country for transplantation.

formulation of law cannot be completed without enacting the regulation. The exploitation of the poorer population who give up organs for monetary benefit cannot be ignored. Although reports on tourism related to transplant have continued to decrease after great interest in the initial decade at the start of the 21st century, the lack of data is obvious as there is zero probability of anything remotely illegal to be documented. There is a great paucity of data involving liver transplantation pursued through illegal means and international travel for medical tourism for organ procurement. Most of the current data available is on renal transplantation. There has been a report of end-stage liver disease patients who traveled from Saudi Arabia and Egypt to China for liver transplantation due to lower associated financial burden and shorter waiting time[20]. From 2000 to 2016, a total of 1229 Korean patients traveled overseas for liver transplants based on the Korean Network for Organ Sharing. Of these, 98% of the patients underwent liver transplants in China[21]. In Taiwan, 5%-24.5% of patients who underwent liver transplants came from abroad[22,23].

From 2013 to 2016, 2806 patients who were non-United States citizens/non-United States residents registered for an organ transplant in the United States[24]. Of these patients, 1149 patients were foreigners who traveled to the United States for transplantation purposes. Deceased donor liver transplants were conducted in more than 5% of non-United States citizen/non-United States resident patients[24]. Liver transplant tourism is not limited to adult patients and can also be found in the pediatric population. In a study from Taiwan, pediatric cases comprised 79% of all foreign living donor liver transplant cases[22]. Liver transplant tourism can be costly. The price of liver transplants ranges from $40000 to $300000 which is higher than kidney transplants[17].

OUTCOME

The transmission of infectious diseases is one of the problems related to liver transplant tourism (Table 1) that can occur due to the lack of proper evaluation and management before and after the transplant for both donor and recipient[25]. Donor risks have been studied in detail and associated morbidity and mortality have been established. The people who remain vulnerable to trafficking, putting themselves at increased risks of surgical complications, infections, and increased mortality with 'less intensive' and 'poorly regulated' protocols need to be protected. Most of the time, this certain group of people appears vulnerable due to the existing inequities in health care. The financial drain resulting from this is bound to impact subsequent health care post-transplant, which carries significant importance. There have been reports of a lack of screening for even general pathogens like hepatitis-causing viruses. Thus, it compromises the general principles and practices which are crucial for such a sensitive procedure.

According to questionnaires from severe United Kingdom liver transplant centers, the top destinations for patients who traveled abroad for liver transplant were China, Egypt, India, followed by South Africa, France, and the United States[26]. This report

Table 1 Problems related to liver transplant tourism compared to domestic transplant[20,25,26]

	Previous reported problems related to liver transplant tourism
1	Higher surgical procedure complications
2	Inadequate pre-operative infection screening, prophylaxis documentation and higher post-operative infections rate
3	Higher mortality

showed that patients underwent liver transplants without or with unknown screening for hepatitis B and C viruses in some places. Unknown screening is also noted for carbapenemase-producing Enterobacteriaceae, cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. The majority of intraoperative and post-transplant prophylaxis in these patients is even unknown[26]. Indigenous infections such as malaria, Zika, rabies may be able to transmit through commercial transplant. Compared to domestic transplants in Saudi Arabia, overseas transplants in China showed a higher rate of sepsis (9.5% *vs* 0.83%) and acquired hepatitis B infection (5.4% *vs* 0%) following transplantation[20]. Surgical procedure complications can be difficult to manage by the new surgeon who did not perform the transplant for the patient in the first place. Compared to domestic transplantation, patients who received transplants abroad in China had significantly higher biliary complications (32.4% *vs* 11.7%) and significantly higher post-transplant interventions[20].

An eleven-year retrospective study from Taiwan demonstrated significant discrepancies between domestic and foreign liver transplants and their outcomes, with the latter faring worse mainly attributed to malignancy and liver disease. Survival rates within the 1st, 5th, and 10th year of the Taiwanese patients who received liver transplants domestically *vs* abroad were 89.2%, 79.5%, 75.2% *vs* 79.8%, 62.3%, and 49.9%, respectively[23]. An unfavorable outcome of transplant tourism was also noted in China. One- and three-year survival rates of liver transplants were 83% and 62% for Saudi and Egyptian patients who received a liver transplant in China while 92% and 84% were reported for domestic transplants in Saudi Arabia[20]. In the United States, post-liver transplant outcomes of non-United States citizen/non-United States resident were comparable to those of a United States citizen/United States resident, except the former group which had an increased risk of being lost to follow-up[27]. The significant influx of Taiwanese people to China appeared to decrease after the Human Organ Transplant Act was passed in 2007. This followed suit by Taiwan in 2015 when they passed amendments to the act by punishing organ brokers, and those patients received illegal transplants[23].

CLINICAL IMPLICATIONS

This article provided an overview of liver transplant tourism and outcomes.

CONCLUSION

Liver transplant has been shown to improve mortality in various advanced liver diseases. However, due to the shortage of organ donations, patients may seek liver transplant tourism. To prevent liver transplant tourism and its ongoing complications, it is crucial to educate patients regarding the risks of transplant tourism, the importance of proper screening, transplant center follows ups and liver transplant tourism morbidity and mortality. While efforts have been made at innumerable national and international platforms, more aggressive implementations to raise the awareness of organ donations are needed to overcome the rise in liver transplant tourism.

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OPINION REVIEW

Hepatitis E virus in professionally exposed: A reason for concern?

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Abstract

The zoonotic risk of hepatitis E virus (HEV) is well established. The HEV seroprevalence rates vary according to geographical region, assays used, and study cohorts. HEV infection is still underdiagnosed, implying the need to evaluate the disease's burden in the general population and specific risk groups, such as professionally exposed. Close contact with various animal reservoirs such as pigs, rabbits, sheep, dogs, wild boars, and deer has been associated with higher anti-HEV seroprevalence as a part of occupational exposure. While exact transmission routes remain to be determined, some general preventive measures such as proper hand hygiene, the usage of personal protective equipment, and the thermal processing of food before consumption should be followed. A "One-Health" multisectoral approach should be implemented to achieve optimal health and well-being outcomes, recognizing the interconnections between humans, animals, plants, and their shared environment, in which a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered as a possible public health measure. This opinion review comprehensively addresses the HEV burden of professional exposure for butchers, slaughterhouse workers, veterinarians, farmers, hunters, and forestry workers delineates the current limits of protective work measures, and tackles future directions.

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Key Words: Hepatitis E virus; Zoonotic infection; Occupational disease; Veterinarians; Farmers; Butchers; Slaughterhouse workers; Forestry workers; Hunters

Core Tip: The zoonotic risk of hepatitis E virus (HEV) is well established. Close contact with various animal reservoirs such as pigs, rabbits, sheep, dogs, wild boars, and deer has been associated with higher anti-HEV seroprevalence as a part of occupational exposure. However, precise HEV transmission routes yet need to be determined. This opinion review addresses the HEV burden of professional exposure, delineates the current limits of protective work measures, and tackles future directions.

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INTRODUCTION

The global burden of hepatitis E virus (HEV) is high, with an estimated 20 million new HEV infection events yearly, 3.3 million symptomatic cases, and 44,000 deaths[1]. HEV RNA genotypes 1 and 2, found only in humans, primarily cause waterborne epidemics in resource-poor regions. Infections are usually self-limiting and not associated with progression to chronic disease. In high-income countries, zoonotic HEV genotypes 3, 4, and 7 circulate in various animal species, and human infections are usually asymptomatic, cause sporadic, or clustered cases of hepatitis[2,3]. In immunocompromised individuals, chronic HEV infection can progress to cirrhosis[3,4].

Besides contaminated water, transmission routes include consuming insufficiently cooked meat and meat products from infected animals (*e.g.*, pork liver), transfusions of infected blood derivatives, solid-organ transplants, and vertical transmission[1,3].

In the last two decades, there has been an increase in autochthonous infections related to the transmission of zoonotic genotypes HEV-3 and HEV-4[5]. Seroprevalence rates in the general population of industrialized countries vary from < 5% to > 50%. Higher rates are observed in the southwest region of France, Poland, and Netherlands, moderate seroprevalence rates from 10% to 30% in the United States, United Kingdom, Belgium, and Germany, and the lowest in Canada, Ireland, Australia, and New Zealand[3,6].

In 1995, the first HEV animal strain was found in sera and stool of swine in Nepal's Kathmandu Valley[7]. Since then, different reservoirs (infected pigs, rabbits, wild boars, and deer) and various zoonotic transmission routes[5] have been associated with professional exposures of those in close contact with the reported HEV reservoirs. Detected HEV sequences in pigs, rabbits, and humans are tightly related[8]; however, it is still unclear whether HEV strains from other animals can cross the species barrier and infect humans. Recently described HEV-7, distributed in dromedary camels from the Middle East[9,10], has been detected in a transplant recipient who consumed camel milk and meat[4]. In addition, a Chinese study showed that viral RNA of HEV-4 could be excreted by cow milk[11], implicating possible HEV transmission through milk or milk products.

Accordingly, professionally exposed workers such as butchers, slaughterhouse workers, veterinarians, farmers, hunters, and forestry workers are considered a risk group for HEV infections. This article addresses the burden of professional exposure to HEV, determines the current situation, delineates the limits, and tackles the future directions.

HEV IN VETERINARIANS AND FARMERS

Among domestic animals, pigs are considered the main reservoir of zoonotic HEV-3 and -4 in industrialized countries. High seroprevalence of HEV IgG antibodies was

detected in pigs in many countries, which implicate a high risk of zoonotic transmission to professionally exposed workers, such as veterinarians and farmers. Indeed, the occupational risk is well known and confirmed by numerous studies and several meta-analyses (Table 1) that investigated the association between direct contact with animals and HEV seroprevalence.

However, when interpreting serological studies, it is important to bear in mind that there are considerable variations in sensitivity and/or specificity between different HEV antibody assays. Thus, it is difficult to compare prevalence estimates using different assays[12], and the lack of a gold standard hampers the interpretability of serological studies[13].

The United States data confirmed that swine veterinarians were 1.51 times more likely to be anti-HEV positive than blood donors[14]. Similarly, studies from Norway and Austria show that swine veterinarians are twice as likely to be HEV seropositive than other veterinarians[15,16]. Other studies from France[17], Germany[18], and Israel[19] support high HEV professional exposure in pig farm workers. In Portugal, in addition to pig farmers, higher HEV seroprevalence was also found in sheep farmers and cheesemakers (29.3%) compared to the general population (16.1%)[20]. In east Africa, Rwandan farmers have higher HEV seroprevalence compared to other professions, with the highest being in high-density pig breeding regions[21].

Studies from China demonstrate high IgG seropositivity in veterinarians (26.7%-43.7%)[22-24] and farmers (34.8%-53.0%)[22-24]. In high-density, pig-farming areas in central China, HEV IgG seroprevalence in swine farm workers rises to 48.35% and increases with age and working years, with all the isolates belong to HEV-4d[25]. Except in swine and sheep farmers, higher seroprevalence was observed in deer (40.2%) and mink farmers (31.8%)[22].

However, despite high HEV seroprevalence rates and zoonotic potential, the awareness of HEV is still inadequate in farmers and veterinarians, who report the lack of knowledge and low perception of the HEV's importance for implementing on-farm risk mitigation strategies[26].

Recent studies additionally highlight risk in small animal practitioners due to high HEV seroprevalence in pet animals. Seroprevalence in dogs in the Netherlands and Germany was 18.52% and 56.6%, respectively[27,28]. The same Dutch study showed that 14.89% of cats had HEV antibodies. Nevertheless, the results of a German study show that pet ownership is inversely associated with infection[29]. On the on the hand, American data indicate that having a pet in the home increases odds of HEV seropositivity [odds ratio (OR), 1.19 (95% Confidence interval (CI), 1.01–1.40)][30]. These results are in line with the observation that veterinarians and farm staff exposed to dogs in the southwest of China have significantly higher seroprevalence than the general population[23]. In Finland, veterinarians have almost two times higher HEV seroprevalence (10.2%) than non-veterinarians (5.8%), and surprisingly, among veterinarians, the highest HEV seroprevalence (17.8%) was detected among small animal practitioners[31]. Similar results were confirmed in Estonia, where all antibody-positive veterinarians were small animal practitioners[32]. A high HEV seroprevalence in pet animals highlighted that in addition to generally known occupational exposure in pig farm workers (farmers and veterinarians), small animal practitioners could also be professionally exposed to HEV. High HEV seroprevalence in pet animals raises the question of their role in the HEV epidemiology as a potential risk of HEV transmission from pets to their owners, which needs to be further investigated.

HEV IN BUTCHERS AND SLAUGHTERHOUSE WORKERS

In geographically distinct locations, studies on swine related occupational exposure report a higher HEV seroprevalence in butchers and slaughterhouse workers compared to the general population; for Germany (41.7% *vs* 15.5%)[18], Portugal (29.7% *vs* 19.9%)[33], Republic of Moldova (14.3% *vs* 0)[34], India (75% *vs* 10.71%)[35], and Burkina Faso (76% *vs* 47.8%)[36]. However, the general population in these studies should be interpreted with caution, *e.g.*, a control group of freshman students who drank only filtered water may be misleading[35].

The results of several meta-analyses substantiate higher HEV risk in swine-related professions. A meta-analysis on 28 studies from mainland China showed that those professionally exposed (swine farmers, slaughters, swine vendors, and veterinarians) have a 2.63-fold higher risk for HEV IgG seropositivity than the general population [24]. Additionally, a recent meta-analysis on 32 studies on swine-related occupations (swine farmers, butchers, meat processors, port retailers, and veterinarians) from 16

Table 1 Occupation-related key points from meta-analyses on hepatitis E virus infection

Meta-analysis: Region/Period/No of studies	HEV IgG seroprevalence: occupational/general population	Occupation-related key points
16 countries; 1999-2018; 32 studies[37]	32.85%/21.70%	The anti-HEV IgG PR for all swine workers was 1.52 (95%CI: 1.38-1.76); butchers 1.75 (95%CI: 1.31–2.35), swine farmers 1.51 (95%CI: 1.32–1.74), meat processors 1.46 (95%CI: 1.13–1.89), veterinarians 1.36 (95%CI: 1.15–1.61) and pork retailers 1.19 (95%CI: 1.09–1.29) compared to the general population; The anti-HEV IgG PR for swine workers in Asia was 1.49 (95%CI: 1.35-1.64) and in Europe 1.93 (95%CI: 1.49-2.50)
Mainland China; 2004-2018; 28 studies[24]	47.4%/27.3%	Anti-HEV IgG positivity: Swine vendors (77.0%), producers (56.0%), swine farmers (53.0%), slaughters (51.7%) and veterinarians (43.7%); The OR for HEV IgG seropositivity in swine occupational population was 2.63 (95%CI: 1.87–3.70) compared to the general population
Europe; 2003-2015; 73 studies[51]	17%/28% using WT	Seroprevalence rates depend on the serologic assays used; increased with age, were unrelated to gender, varied within countries; Individuals in contact with swine/wild animals had higher seroprevalence rates than the general population, irrespective of assay used ($P < 0.0001$)
Global, non-endemic HEV countries; 1994-2018; 163 studies[52]	Not calculated	The OR for HEV seropositivity for occupational contact with pigs was 1.95 and for the employment in forestry population 2.49 compared to the general population; Recreational hunting was a non-significant predictor for HEV seropositivity; Contact with pigs (not categorized as occupational), cats or horses was non-significantly associated, contact with dogs was significantly associated with increased odds of HEV IgG seropositivity; The consumption of meat (uncooked liver sausage, rabbit and game meat, liver or organ meats, bacon or ham, and pork) was a significant predictor of HEV IgG seropositivity (median OR = 1.44, range (1.12-2.77)

CI: Confidence interval; HEV: Hepatitis E virus; OR: Odds ratio; PR: Prevalence ratio; WT: Wantai test.

different countries demonstrated that swine workers are 1.52-fold more likely to be HEV IgG seropositive than the general population. Interestingly, the association with the HEV exposure, the prevalence ratio (PR) is higher in Europe (PR = 1.93, 95%CI 1.49-2.50) than in Asia (PR = 1.49, 95%CI 1.35-1.64)[37] (Table 1).

Furthermore, the data show that rabbit slaughterhouse workers have a 6.9-fold increased risk for HEV compared to the general population and that their seropositivity also increases with working years[38].

The precise HEV transmission route among occupationally exposed workers remains to be determined. However, it is possible that increased risk of infection during slaughtering results from manipulation of raw HEV-rich organs and tissues (*i.e.* liver and bile) without direct consumption[18]. In addition, well-known risk factors for anti-HEV IgG seropositivity are the frequency and duration of contact with animals [33,39].

Over the past decades, it has become clear that a collaborative and multisectoral approach across boundaries of animal, human, and environmental health (a One-Health approach) is needed to develop control and achieve optimal health outcomes in a setting of zoonotic diseases. The use of protective equipment and vaccination (when possible) should be an integral part of the prevention of zoonotic infections. The HEV studies on protective equipment in butchers and slaughterhouse workers are scarce with conflicting results. An Indian study showed that slaughterhouse workers are routinely in contact with swine without adequate protective equipment[35]. A South Korean study demonstrated that anti-HEV IgG positive slaughterhouse workers use protective equipment (vinyl gloves, aprons, boots, and disposable protective suits) more often than anti-HEV IgG negative workers, suggesting that the equipment does not prevent the HEV infection or that the equipment is not appropriately used[40]. Although the clinical course of HEV infection in most cases is subclinical, in middle-aged and older men workers with underlying liver disease, the risk of HEV infection should be especially minimalized given the frequency of complications in this population group[41]. The authors propose that for workers at continued risk of exposure, strict hygiene measures, personal protective equipment, and a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered. However, the first and only HEV vaccine produced and licensed in China is not approved for widespread use, even though it shows a good tolerance and the efficacy of 86.8% on the extended follow-up[42,43]. Despite these results, the efficacy in different genotypes of the virus and safety in chronic liver disease and other vulnerable populations remains unclear[43].

HEV IN FORESTRY WORKERS AND HUNTERS

In Europe, hunting and forestry work, particularly woodcutting, are associated with increased HEV seropositivity[17,44-47]. It is a well-known fact that the HEV seroprevalence increases with age, duration, and animal-related activity frequency. This general trend is also confirmed for the forestry workers and hunters[47,48].

However, some studies do not support previous data. Studies from central Germany and Northern Italy showed no differences in anti-HEV IgG antibodies in hunters[49] and forestry workers compared to the general population[50].

A meta-analysis on HEV seroprevalence in Europe conducted on 73 studies shows that individuals in contact with swine/wild animals have significantly higher seroprevalence rates than the general population. It is important to notice that they vary according to geographical region, assays employed, and study cohorts[51].

As wild boars and deer represent important HEV reservoirs, HEV transmission route in hunters may occur during skinning and disemboweling of an infected animal or through contact with its blood or feces[49]. Studies show that hand hygiene immediately after disembowelment reduces the HEV infection risk[48] and that the regular use of protective gloves is associated with an 88% lower HEV seroprevalence [49]. Additionally, a study from Southern France found that wearing work boots by forestry workers is associated with significantly lower HEV seroprevalence (46% without *vs* 28% with boots). Interestingly, no differences were detected for wearing gloves (39% without *vs* 34% with gloves)[17]. Despite conflicting evidence, the authors believe the use of personal protection minimizes the risk of infection.

In conclusion, most of the published studies showed that the risk of HEV infection is higher in forestry workers and hunters than in the general population. However, some studies did not identify hunting activity as an important risk factor for the HEV seropositivity. Close and frequent contact with HEV-infected animals, especially wild boars, represents important risk factors, where the use of personal protection minimizes the risk of infection.

CONCLUSION

Given the high seroprevalence rates observed in swine workers, veterinarians, farmers and hunters, contacts with infected animal reservoirs (mainly pigs, wild boars, deer) have been recognized as risk factors for the transmission of HEV. The list of new animal reservoirs is ever-expanding as new HEV strains are continuously being found in a broad range of hosts. Although the precise HEV transmission route in occupationally exposed workers remains to be determined, occupational exposure plays a significant role.

HEV infection is still an underdiagnosed disease due to the lack of routine diagnosis and surveillance protocols, limiting the knowledge of the data about the HEV burden. Thus, there is a need for a realistic evaluation of HEV disease's burden in humans in general and in specific risk groups, such as professionally exposed.

A better understanding of HEV transmission routes from the infected animals to workers might help develop more specific preventive measures for specific occupational groups that have shown to be associated with the higher risk of acquiring HEV. Until other evidence is found, several protective measures to decrease the risk in occupationally exposed groups should be respected: the proper hand hygiene following contact with animals known to be HEV reservoir, the usage of recommended personal protective equipment, and the proper thermal processing of food before consumption. Although HEV infection is not an economically important pig disease, developing a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered a possible public health measure. Epidemiologically important pet animals should also be further investigated as a potential additional risk factor for small animal practice veterinarians and pet animal owners.

Further testing of different populations including the general population and professionally exposed persons as well as animals are needed to better understand the epidemiology of hepatitis E.

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REVIEW

Clinical algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis

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Abstract

Portal hypertension (PH), a common complication of liver cirrhosis, results in development of esophageal varices. When esophageal varices rupture, they cause significant upper gastrointestinal bleeding with mortality rates up to 20% despite state-of-the-art treatment. Thus, prophylactic measures are of utmost importance to improve outcomes of patients with PH. Several high-quality studies have demonstrated that non-selective beta blockers (NSBBs) or endoscopic band ligation (EBL) are effective for primary prophylaxis of variceal bleeding. In secondary prophylaxis, a combination of NSBB + EBL should be routinely used. Once esophageal varices develop and variceal bleeding occurs, standardized treatment algorithms should be followed to minimize bleeding-associated mortality. Special attention should be paid to avoidance of overtransfusion, early initiation of vasoconstrictive therapy, prophylactic antibiotics and early endoscopic therapy. Pre-emptive transjugular intrahepatic portosystemic shunt should be used in all Child C10-C13 patients experiencing variceal bleeding, and potentially in Child B patients with active bleeding at endoscopy. The use of

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carvedilol, safety of NSBBs in advanced cirrhosis (*i.e.* with refractory ascites) and assessment of hepatic venous pressure gradient response to NSBB is discussed. In the present review, we give an overview on the rationale behind the latest guidelines and summarize key papers that have led to significant advances in the field.

Key Words: Portal hypertension; Endoscopy; Non-selective betablockers; Transjugular intrahepatic portosystemic shunt

Core Tip: Variceal bleeding is a severe, and often deadly, complication of portal hypertension. Screening for varices, effective bleeding prophylaxis and standardized management of bleeding is critical to improve clinical outcomes. While carvedilol seems to be the treatment of choice for primary prophylaxis in compensated cirrhosis, the use of hepatic venous pressure gradient measurements and safety of non-selective betablockers in advanced cirrhosis with refractory ascites is controversial. The pre-emptive use of transjugular intrahepatic portosystemic shunt within 72 h after variceal bleeding prevents rebleeding and mortality in Child C10-C13 patients.

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INTRODUCTION

Chronic liver diseases cause recurrent liver damage and can result in the development of liver fibrosis and, ultimately, liver cirrhosis[1]. Fibrosis and cirrhosis lead to gradually increased intrahepatic vascular resistance, splanchnic vasodilatation and increased portal blood flow, which subsequently results in increased portal pressure and the development of collaterals[2]. To allow risk stratification, evidence-based guidelines have been developed to grade portal hypertension severity, and the term clinically significant portal hypertension (CSPH) has been defined to indicate a high risk of complications[3]. CSPH is defined as a hepatic venous pressure gradient (HVPG), an invasive surrogate parameter of portal venous pressure, of ≥ 10 mmHg[4]. This definition is based on studies demonstrating that esophageal varices (EV) develop above the 10 mmHg HVPG threshold, subsequently increasing the risk of bleeding[5]. In cross sectional studies, between 40%-60% of patients with liver cirrhosis show EV, highlighting the clinical importance of this condition[6,7]. Variceal bleeding is, next to liver failure, hepatocellular carcinoma, infections and the hepatorenal syndrome, one of the main causes of mortality in patients with CSPH and adequate diagnosis as well as treatment is of utmost importance, given that variceal bleeding episodes are still associated with a high mortality rate of up to 20%[8-12]. Thus, to avoid unnecessary fatal outcomes, variceal bleeding and re-bleeding must be prevented, ideally by (primary or secondary) prophylactic treatment of portal hypertension *per se*. Therefore, this review focusses on clinical algorithms and summarizes the available evidence on prevention and treatment of variceal bleeding.

PREVENTION OF ESOPHAGEAL VARICEAL BLEEDING

Screening for gastroesophageal varices in patients with portal hypertension

In patients with cirrhosis but without EVs at baseline, the incidence of developing EV rises from 5% after one year to 28% after three years, independently of liver function or compensated/decompensated liver cirrhosis[13]. In a cross-sectional study of 494 patients of which 48% had decompensated liver cirrhosis, 38% of patients had EV at the time of screening[14]. Thus, EV are common in patients with advanced chronic

liver disease, and it was shown that patients with EV suffer from significantly higher mortality rates and decompensating events than patients without[14]. Of note, however, bleeding risk is correlated with HVPG values, and patients with a HVPG of ≥ 12 mmHg are at significantly higher bleeding risk than patients with < 12 mmHg, despite the diagnostic CSPH cutoff value of 10 mmHg[15,16]. Although HVPG is considered the gold standard, measurement requires specific expertise and equipment, comes at relatively high cost and is invasive. Thus, it is not considered as standard of care and not available to most centers[17]. As an alternative, transient elastography (TE) has been established as a well-validated cheap, non-invasive tool to measure liver stiffness, as fibrosis/cirrhosis severity and portal pressure directly correlate[18,19]. TE allows to classify patients with liver cirrhosis, defined as a liver stiffness measurement value > 15 kPa and can be used as screening tool[3,20]. Efforts to establish clear cutoff values have been made[21], and evidence indicates that patients with TE values < 20 kPa and platelet count > 150 G/L are unlikely to have varices (< 5%)[22]. These values can be used to avoid screening gastroscopies for EV, and the next TE screening for EV can be postponed for another year[22]. Screening gastroscopy is, however, required in patients with diagnosed liver cirrhosis who do not meet these mentioned criteria[3,17,22] and allows to identify "high risk" varices, which are referred to as "varices needing treatment" (VNT) in recent guidelines[22]. VNT are varices of large size (> 5 mm diameter) or small varices (< 5 mm diameter) with red spot signs/red wale markings, as both of them are at high risk of bleeding[22]. When VNT are detected, treatment with non-selective betablockers (NSBB) or endoscopic band ligation (EBL) should be initiated for primary prophylaxis of variceal bleeding[3,17,22].

While evidence is clear on these VNTs, current guidelines are less validated whether endoscopic screening is indicated for small varices[23]. Augustin *et al*[24] found that following the current Baveno VI criteria spared more screening endoscopies with a minimal risk of missing VNT, but when guidelines are followed strictly, small varices would be missed in a significant number of patients. Thus, treatment decisions in these cases should be made on a case-to-case basis until further evidence is available.

Preprimary and primary prophylaxis for patients with small esophageal varices

When patients with high risk EV are identified, treatment should aim to prevent variceal bleeding as primary prophylaxis. Current guidelines recommend either NSBB or EBL for prevention of first EV bleeding in patients with medium to large varices, while they do not specifically recommend treatment for small varices due to above mentioned lack of decisive studies[3,17].

While available evidence uniformly demonstrated that NSBB therapy effectively prevents first, as well as recurrent, EV bleeding and reduces mortality when EV are diagnosed[25,26], it is under debate whether NSBB should be prescribed without signs of EV. One large randomized multicenter study assigned patients with CSPH without EV to timolol or placebo and found that although HVPG was lower in timolol-treated patients, the subsequent development of EV or variceal bleeding rate did not differ between timolol or placebo treated patients[27]. Although the HVPG-response to NSBB differs in patients with or without CSPH, the results were relatively unexpected [27].

Little high-quality evidence is available regarding treatment of patients with small and low risk varices in primary prophylaxis[22,28]. It seems as if some trials were underpowered to see sufficient effects of NSBB on the incidence of first variceal bleeding in patients with small varices[23] while others demonstrated that NSBB effectively prevented the progression from small to large varices, especially in patients assigned to carvedilol[29,30]. The recently published PREDESCI trial showed that NSBB were associated with a decreased risk of decompensation [hazard ratio: 0.51 (95%CI: 0.26-0.97), P = 0.041] in patients with CSPH and low risk varices, potentially resulting in longer decompensation-free survival[31]. Taken together, the conflicting evidence led the authors of the current international guidelines to not recommend NSBB treatment for patients with no EV or for prevention of varix progression. However, some experts still recommend using NSBB in patients with cirrhosis as soon as CSPH is evident (*e.g.* by HVPG ≥ 10 mmHg or by any size of varices) to prevent clinical decompensation.

Beta blocker therapy for primary prophylaxis in patients with medium and large esophageal varices

Prescribing NSBB for primary prophylaxis is less expensive, has no procedural risk, does not require repetition of esophageal gastroscopy after initiation of NSBB for prevention of variceal bleeding and saves time for gastroenterologists[3,17]. Therefore,

NSBB are sometimes favorable compared to EBL, with dosing intensities summarized in Table 1. Beside the positive effect of NSBB on variceal bleeding (absolute risk reduction of up to -16%, NNT = 6), several studies have also demonstrated benefits that are likely mediated by their additional non-hemodynamic effects[32-35]. With regards to beta blocker selection, some trials showed a better or comparable efficacy in primary prophylaxis of carvedilol in comparison to other NSBBs, probably as carvedilol has additional anti-α-1-adrenergic activity and does therefore result in a more potent decrease of portal pressure[36-38]. Thus, carvedilol is recommended as first line therapy in some national guidelines[3,39-41]. However, carvedilol for the sole indication of portal hypertension should not be prescribed in doses above 12.5 mg per day, as higher doses (> 12.5 mg/d) do not lead to further reductions of portal pressure [36,37]. Importantly, carvedilol may be prescribed when NSBB have already failed, as our group could show that in 58% of patients who did not respond to propranolol, carvedilol still resulted in a significant HVPG response (defined as reduction of HVPG of more than 20% or reduction to a HVPG value < 12 mmHg)[36].

Despite the easy handling of NSBB or carvedilol, up to 15% of patients require a dose reduction or discontinuation due to common and severe side effects such as hypotension, shortness of breath and/or fatigue[42], and 15% to 25% of patients have absolute or relative contraindications for NSBB initiation[35,42]. In addition, there is a great abundance of studies comparing NSBB to EBL in primary prophylaxis, and there is no clear outcome benefit for one or the other. In a Cochrane analysis from 2012, patients who underwent EBL as primary prophylaxis showed reduced variceal bleeding rates compared to patients using NSBB alone, while bleeding did not impact on mortality[43]. Another meta-analysis demonstrated that there was no difference in bleeding rates when high-quality studies were assessed[44]. In contrast to these meta-analyses, one large multicenter study showed better efficacy of carvedilol for primary prophylaxis compared to EBL alone[41], and another meta-analysis of 32 randomized controlled trials and a total number of 3362 patients with large varices in primary prophylaxis found that NSBB monotherapy was associated with a decrease of all-cause mortality, decrease risk of first variceal bleeding and a better safety profile compare to patients treated with EBL[45]. Overall, bleeding rates in primary prophylaxis greatly vary between studies and no reproducible differences between the overall effectiveness, especially the overall- or bleeding-related mortality, could be established so far[46-49]. To address certain limitations of previous studies, another large randomized controlled open-label multicenter study, CALIBRE, is currently recruiting patients with liver cirrhosis and medium to large EV, and will investigate the effect of carvedilol or EBL on the incidence of variceal bleeding within 1 year of treatment initiation[50], potentially impacting on treatment regimes in the future.

NSBB in patients with complicated ascites and/or spontaneous bacterial peritonitis

Due to vasodilating effects, sympathetic activation, increased left ventricle systolic function and, therefore, impairment of renal perfusion, several studies questioned the safety of NSBB and carvedilol in patients with decompensated cirrhosis[51-59]. This is in line with evidence that NSBBs were associated with higher mortality in patients with refractory ascites[51,60,61]. However, these findings were not uniformly confirmed and some studies report no impact on outcome[62-64]. As a result of this conflicting evidence, current guidelines suggest to monitor blood pressure, serum sodium levels and kidney function in patients with decompensated cirrhosis[3,17,22], but do not state that NSBB are contraindicated[17,22]. Nevertheless, high doses of NSBB (*e.g.* propranolol > 160 mg/day) should be avoided as they seem to be associated with worse outcome[65]. In addition, there is limited evidence supporting a switching strategy from carvedilol to propranolol in patients with ascites and/or renal impairment[56]. Thus, carvedilol should not be used in patient with severe ascites[3].

Similar conflicting results were reported for NSBB use in patients with spontaneous bacterial peritonitis (SBP) and/or acute kidney injury[56]. In one retrospective study, NSBB use was associated with a higher risk for the development of a hepatorenal syndrome in patients with newly diagnosed SBP, resulting in impaired survival[59]. However, a more recent study suggests that NSBB maintenance during an SBP-episode is not associated with increased mortality as long as there is no severe arterial hypotension, highlighting the importance of the guideline's recommendations to monitor blood pressure[66].

EBL for patients in primary prophylaxis with medium or large esophageal varices

EBL has a very low procedural risk and is the most effective endoscopic choice for EV [3,17,22,67,68]. When EBL is chosen for primary prophylaxis, it should be repeated every two to four weeks until varices are completely eradicated (small "remnant"

Table 1 Recommended use of non-selective betablockers in patients with primary and secondary prophylaxis [adapted from the Austrian (Billroth III), European (Baveno VI) and American (Guidance by the AASLD 2017) guidelines][3,17,22]

Beta blocker	Initial dose	Goal	Treatment duration	Further guidance
Propranolol	20–40 mg twice daily	Maximum dosage of 160 mg/day; Or until the resting heart rate of 55–60 beats/min; Maximum dosage of 80 mg/day in patients with ascites	Indefinite	Adapt every 2-3 d until optimal dose is reached; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125 mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed
Carvedilol	6.25 mg once daily	Maximum dosage of 12.5 mg/day	Indefinite	Adapt dose after 3 d and increase to 6.25 mg twice daily; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed; Potential switch from carvedilol to propranolol in case of new onset of ascites
Nadolol	20-40 mg once daily	Maximum dosage of 160 mg/day; Or until the resting heart rate of 55–60 beats/min; Maximum dosage of 80 mg/day in patients with ascites	Indefinite	Adapt every 2-3 d until optimal dose is reached; Discontinue during spontaneous bacterial peritonitis, hyponatremia (Na < 125mmol/L) or acute kidney injury; Systolic blood pressure should not decrease below 90 mmHg; EGD for further variceal screening is not needed

EGD: Esophagogastroduodenoscopy

varices can be tolerated) and endoscopy should subsequently be repeated after six and twelve months[3]. If EV reappear, the treatment algorithm has to be restarted in the same intervals[3]. Compared to NSBB, EBL for primary prophylaxis has a lower overall rate of adverse events, but if adverse events occur they are more severe and life-threatening (*e.g.* EBL-related ulcer bleeding)[47,49,69]. Procedure related bleeding as a potential complication after EBL has been described to occur in 2%-6% of interventions[68,70-72]. In addition to potential esophageal injuries, EBL induces/accelerates the development of gastric collaterals[73] as it does not affect the underlying cause of increased portal pressure and thus has no disease-modifying effects. In summary, however, both treatments, namely NSBB or EBL, are effective and physicians should choose individually which primary prophylaxis is used, based on patients' concomitant risk factors and local availability. As a brief overview, we have summarized the recommended clinical algorithms in Figure 1.

ACUTE ESOPHAGEAL VARICEAL BLEEDING

Management of acute variceal bleeding

When EV are not detected in time, or if primary prophylaxis fails and acute variceal bleeding cannot be prevented, a determined and rapid treatment initiation as well as intensive care are required to optimize outcome. Despite improved mortality rates in the past decades, bleeding-related mortality remains as high as 15%-20%[9,10,12,74]. Patients presenting with acute variceal bleeding are classified as "decompensated cirrhosis", irrespective of fibrosis severity[5,17]. Despite this classification, 5 year mortality rates are affected by the underlying fibrosis severity as complications such as ascites and/or hepatic encephalopathy also impact on overall survival[14]. Fluid resuscitation, pharmacological treatment and endoscopy/EBL are the three main pillars for acute variceal bleeding treatment (see Figure 2)[3,17,22].

Initial fluid resuscitation to counteract hemorrhagic shock is the first important step in patients with acute variceal bleeding, and packed red blood cell (PRBC) transfusions are indicated when hemoglobin levels are below 7 to 8 g/dL, as too liberal administration of PRBCs has been shown to impair outcome[3,75]. In the randomized controlled study by Villanueva *et al*[75], patients with "liberal" use of PRBC transfusion showed significantly increased mortality rates compared to patients in which PRBCs were only transfused at a threshold of 7 g/dL, maintaining hemoglobin levels of 7-9 g/dL. Thus, the threshold of 7 g/dL is still recommended by current guidelines [3,17,22].

In contrast to PRBCs, transfusion of platelets, the use of fresh frozen plasma or administration of recombinant factor VIIa to correct platelet count or international normalized ratio (INR), respectively, did not demonstrate a clear benefit and is therefore not recommended[3,17,22,76,77].

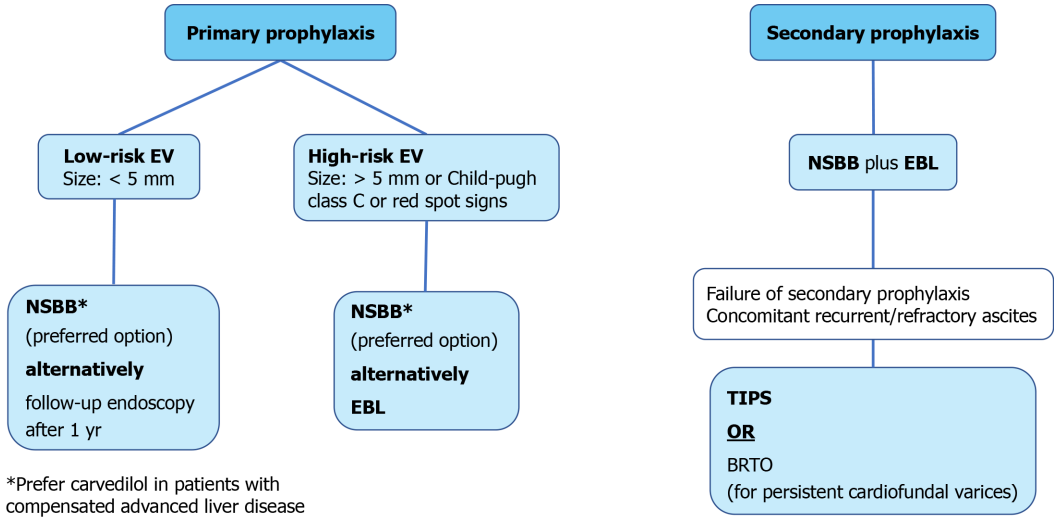

Figure 1 Clinical algorithms recommended for cirrhotic patients in primary prophylaxis and secondary prophylaxis (adapted from the Austrian Billroth-III guidelines)[3]. EV: Esophageal varices; NSBB: Non-selective betablocker; EBL: Endoscopic band ligation; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon occluded retrograde transvenous variceal obliteration.

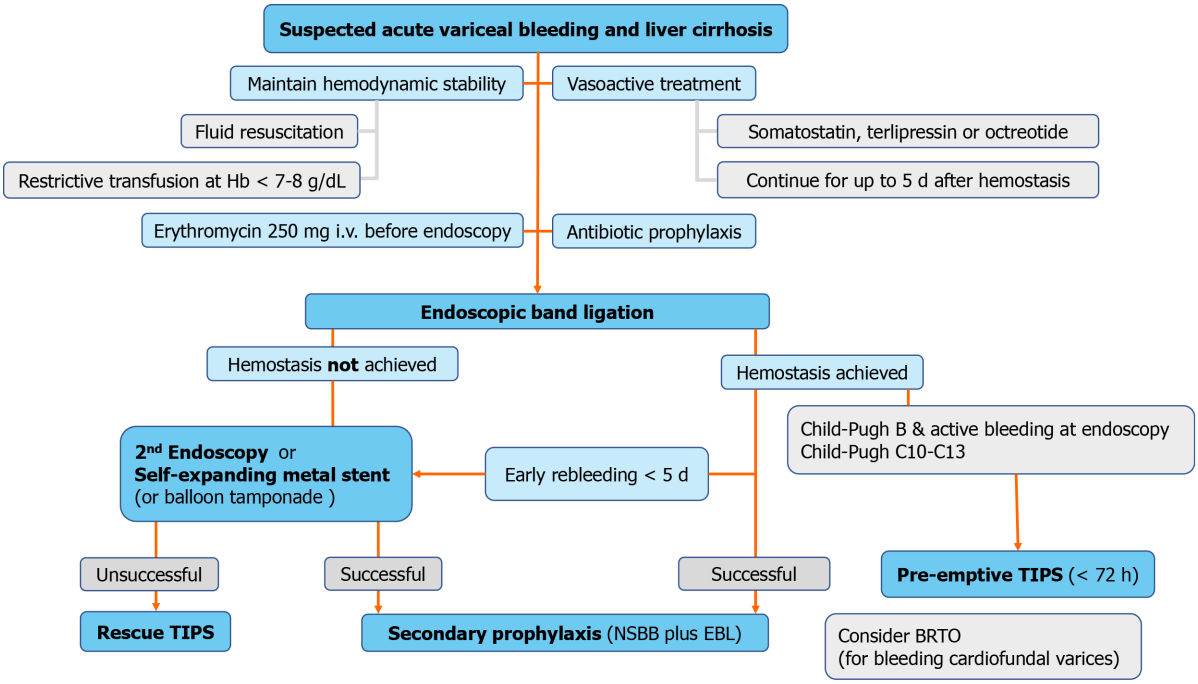

Figure 2 Clinical algorithm for treatment of patients with acute variceal bleeding (adapted from the Austrian Billroth-III guidelines)[3]. TIPS: Transjugular portosystemic shunt; i.v: Intravenous; NSBB: Non selective betablocker; EBL: Endoscopic band ligation; BRTO: Balloon occluded retrograde transvenous variceal obliteration.

To counteract active bleeding, vasoactive drugs (vasopressin, terlipressin, somatostatin or octreotide, dosing regimens summarized in Table 2) have been shown to reduce portal pressure by reducing portal systemic collateral blood flow, portal blood flow and intravariceal pressure *via* systemic and splanchnic vasoconstriction[17,78,79]. Thus, they are recommended for use in patients with acute variceal bleeding, while none of the vasoactive treatments has been shown to be superior to the others in terms of bleeding control and impact on mortality[3,17,22,80,81]. Of note, however, terlipressin has been associated with hyponatremia, especially in patients with preserved liver function and sodium levels should therefore be monitored, although these systemic sodium alterations did not translate to any outcome difference[80].

In addition to fluid resuscitation and administration of vasoactive drugs, antibiotic treatment is indicated as patients with acute variceal bleeding suffer from a significant risk of infection[82]. Thus, intravenous broad spectrum antibiotics (*e.g.* ceftriaxone at a

Table 2 Recommended vasoactive agents for management of acute variceal bleeding [adapted from the Austrian (Billroth III), European (Baveno VI) and American (Guidance by the AASLD 2017) guidelines][3,17,22]

Regimen	Dosing	Duration of regimen	Further guidance
Somatostatin	Bolus of 500 μg, followed by 500 μg/h *via* continuous infusion (6 mg/50 mL, infusion rate of 4.2 mL/h)	2-5 d	Bolus can be repeated in case of uncontrolled bleeding
Terlipressin	Bolus of 2mg every 4 h for the first 24-48 h, followed by giving bolus of 1mg every 4 h; Or continuous infusion 2 mg/d; maximum 12 mg/d	2-5 d	Be caution in patients with coronary artery disease, peripheral arterial occlusive disease hyponatremia (< 125 mmol/L), cardiac arrhythmia and severe asthma or chronic occlusive pulmonary disease
Octreotide (somatostatin analogue)	Bolus of 50 μg, followed by 50 μg *via* continuous infusion	2-5 d	Bolus can be repeated in case of uncontrolled bleeding

dose of 1g every 24 h with a duration for 7 d or less) should be administered before endoscopic therapy is initiated[3,17,22]. In addition, erythromycin should be administered ideally 30-120 min before endoscopy to improve sight during the procedure *via* facilitation of gastric emptying[3,17,22,83].

Finally, EBL is the gold standard of endoscopic treatment after hemodynamic stabilization and should ideally be performed within the first six to twelve hours of admission when EV bleeding is suspected or detected[3,17,22,84,85]. Performing endoscopists should be adequately trained, and EBL has been proven to be the best available treatment in terms of rebleeding, further development of esophageal strictures, and associated mortality[86].

Recently, however, data suggests that instead of vasoactive drugs and endoscopic therapy, preemptive implantation of a transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressure can be effective. An international multicenter observational study compared pre-emptive TIPS to endoscopy plus vasoactive drugs in patients with Child-Pugh C or Child Pugh B cirrhosis with active bleeding at the time of endoscopy[87]. The authors found that pre-emptive TIPS implantation, compared to standard of care with medication and endoscopic treatment, significantly reduced treatment failure and rebleeding in Child-Pugh C, and Child-Pugh B patients with active bleeding. This translated into a significantly lower mortality rate in Child-Pugh C patients, while mortality in Child-Pugh B patients with active bleeding were low in both, EBL/medication and TIPS, groups and did not improve by pre-emptive TIPS implantation[87]. Thus, pre-emptive TIPS implantation emerges as a valid option in patients with high risk of rebleeding, especially in Child-Pugh C patients.

Therapy-refractory variceal bleeding

These favorable results are in line with findings in patients with therapy refractory acute variceal bleeding in which rescue-TIPS implantation is the best choice when standard treatment fails[3,17,22]. Rescue-TIPS, *e.g.* TIPS implantation after EBL failure to control bleeding, achieves bleeding control in 90%-100% and results in very low rebleeding rates of approximately 15%[88]. However, despite the available encouraging results, use of TIPS in acute settings is limited by technical challenges and availability[89,90]. Therefore, balloon tamponade (Sengstaken tube and Linton-Nachlas tube) is the most commonly used treatment for uncontrolled bleeding in real-world settings. By compressing bleeding varices, it controls EV bleeding in up to 90%, but half of the patients suffer from rebleeding events after deflation of balloon tamponade[91-95]. Furthermore, it is associated with often life-threatening complications in 60% of patients, such as perforation, esophageal ulceration and aspiration pneumonia[91-94,96,97]. Additionally, balloon tamponade can only be left *in situ* for 24-48 h due to the high risk of pressure-induced necrosis[98].

As these high complication rates are considered unacceptable in modern medicine, a self-expanding metal stent (SEMS), SX-ELLA Stent Danis, has been developed to improve procedure related complication rates. It can easily be deployed without endoscopic guidance and can be left *in situ* for up to seven days. Several studies showed successful bleeding control in 70%-100% of patients[99-101] with lower complication rates than balloon tamponade, although this did not improve mortality rates[102,103]. Current guidelines nevertheless recommend the use of SEMS because of its better safety profile[3,17,22].

On the basis of these poor outcome data, balloon tamponade and SEMS are usually only used as a bridging to further definitive therapy, such as TIPS implantation. Despite this large body of favorable evidence, however, we recently reported a lack of systematic use of TIPS implantation after SEMS in acute variceal bleeding[101]. This is in line with recently published real-life data from France which showed that approximately 1/3 of patients with variceal bleeding fulfilled the criteria for early TIPS, but only 7% underwent subsequent early TIPS implantation[90]. This knowledge gap on TIPS indication criteria was also evident in our recently published survey in which only 20% of the respondents could report TIPS criteria correctly[104]. Therefore, knowledge on early TIPS implantation must be improved among all specialists.

Furthermore, in case of additional cardiofundal variceal bleeding and/or ongoing variceal bleeding after TIPS implantation, balloon occluded retrograde transvenous variceal obliteration (BRTO) should be considered[3,105-107]. A recently published meta-analysis showed improved outcome in terms of rebleeding, mortality and hepatic encephalopathy in patients who also underwent BRTO as compared to patients who only underwent TIPS implantation[106].

PREVENTION OF ESOPHAGEAL VARICEAL REBLEEDING

Secondary prophylaxis of EV bleeding

Secondary prophylaxis is defined as the prevention of recurrent variceal bleeding. Patients who survive and recover from an episode of acute variceal bleeding are at high risk of rebleeding and death, which is 60% and 33% in the first year, respectively [17,108]. Older studies found that HVPG measurement at the time of the first bleeding episode can predict rebleeding risk, and a HVPG of ≥ 20 mmHg was associated with a significantly increased risk for rebleeding and death[109]. Despite several non-invasive scores (APRI, FIB-4, AST/ALT, King´s score) are available, their role as non-invasive predictors for the presence of esophageal varices in patients with cirrhosis is not established. Kraja *et al*[110] showed that the FIB-4 is a powerful predictor of EV (cut off value: 3.23; AUC: 0.66, 95%CI: 0.54-0.78) but a poor predictor for EV bleeding (AUC: 0.42, 95%CI: 0.28-0.56) and that all other non-invasive biomarkers were not useful. This is in line with several other available studies that showed great variation in accuracy in different populations and etiologies of liver cirrhosis[111-113]. Recently, Drolz *et al*[68] reported high bilirubin and larger size varices as risk factors for rebleeding within 30 d of prophylactic EBL, while reduced platelet counts, elevated INR, and decreased fibrinogen levels were associated with procedure-related bleeding in other studies [113-115]. Another study showed an adequate prediction value for predicting in-hospital rebleeding using Child-Turcotte-Pugh score (cut off > 7) and Clinical Rockall score (cut off > 2)[116], while the well-established MELD and MELD-Na scores showed good results for predicting in-hospital mortality[116]. Thus, non-invasive prognostic scoring systems cannot be recommended to predict risk for recurrent variceal bleeding but are useful tools to estimate overall mortality rates[116-118].

In terms of secondary prophylaxis to avoid rebleeding, monotherapy of NSBB or EBL are associated with higher mortality in secondary prophylaxis than combined NSBB + EBL therapy, which is in contrast to studies in the primary prophylaxis setting [35]. Thus, current guidelines recommend the combination of EBL + NSBBs[3,17,22, 119,120], while the combined treatment of NSBB and low-dose isosorbide mononitrate, a combination used in the past, is no longer recommended due to high rates of adverse events[3,17,22].

With regard to NSBB choice, propranolol is recommended at a daily dosage of 80–160 mg/day in most guidelines, with a maximum dosing of 80 mg/day in patients with ascites[3]. Similar to primary prophylaxis, some guidelines also recommend carvedilol, while others do not (yet) recommend its general use[17,22]. Guidelines that do recommend carvedilol suggest to use it at a concentration of 6.25–12.5 mg/day and only in patients without ascites[3]. Finally, with regards to EBL for secondary prophylaxis, endoscopy and banding intervals are equal to the intervals in primary prophylaxis (complete eradication, re-endoscopy after 6 and 12 mo).

Similarly, when first-line therapy with EBL + NSBB to prevent rebleeding fails, TIPS implantation is the best choice for further treatment[3,17,22], as it decreases portal pressure and therefore targets the underlying cause of EV bleeding. Of note, however, no significant benefit on survival rates was found despite the better outcomes in terms of rebleeding rates[15,126,122]. In patients with gastric varices and contraindications for TIPS implantation such as spontaneous episodes of hepatic encephalopathy, BRTO can be considered as treatment option in selected patients, as it may even decrease

portosystemic shunting through the collaterals that are scheduled for occlusion[3]. Furthermore, surgical shunts, devascularization, splenectomy or (partial) splenic embolization may be considered if first-line treatments fail[3].

CONCLUSION

The continuous efforts of hepatologists and gastroenterologists around the world, as well as initiatives of international collaborations to generate high-quality evidence has translated to improved survival in patients with EV bleeding in the last decades. Thus, we have summarized recent advances and highlighted the rationale for specific treatments now recommended by several national and international guidelines.

In primary prophylaxis, NSBB or EBL are equal in outcomes and are therefore both recommended as monotherapies to prevent a first variceal bleeding event[3,17,22]. However, carvedilol – due to its higher potency to lower portal pressure[36] resulting in higher proportions of HVPG responders – may be the treatment of choice for primary prophylaxis in compensated cirrhosis. No clear recommendation for the use of betablockers can be made for patients with small varices (even with additional risk factors), as their efficacy in this setting remains unclear. Importantly, due to non-hemodynamic effects of NSBBs on intestinal permeability[34], systemic inflammation [124] and considering the results of the recent PREDESCI trial[31] showing reduced risk of decompensation and mortality, NSBB may already be recommended for small varices.

To monitor NSBB treatment response, invasive HVPG measurement is still considered as gold standard, but other non-invasive surrogates to monitor NSBB response to prevent variceal bleeding such as ultrasound-based elastography or transient elastography assessment of the spleen are currently under consideration as HVPG measurement is not widely available[125,126].

When acute variceal bleeding occurs, standardized treatment algorithms recommend conservative transfusion strategies, early initiation of vasoactive drugs, prophylactic antibiotics, and EBL[3,17,22]. More recently, the pre-emptive use of TIPS implantation in selected high-risk patients with variceal bleeding has been demonstrated to not only decrease rebleeding rates but also mortality[3,17,22,127,128].

Due to logistic challenges with the "time-critical" use of pre-emptive TIPS implantation, specialist should be familiar with this concept and infrastructure and networks need to be developed in order to improve the outcomes of patients with variceal bleeding.

In secondary prophylaxis, the combination of NSBB and EBL has proven to be superior to either monotherapy[3,17,22].

In conclusion, NSBBs remain the cornerstone of medical therapy of portal hypertension and are still used for pharmacological bleeding prophylaxis. EBL may also be used for primary prophylaxis, but its main role is in effective control of acute variceal bleeding and variceal eradication in secondary prophylaxis. Standardized concepts and the infrastructure for the general use of pre-emptive TIPS in selected patients with high-risk variceal bleeding need to be developed. This review should have provided clinicians with valuable concepts for the management of PH, including variceal screening, primary bleeding prophylaxis, management of acute variceal bleeding and finally effective secondary prevention of variceal rebleeding.

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REVIEW

Liver injury associated with drug intake during pregnancy

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Abstract

Drug use during pregnancy is not common. Drug-induced liver injury (DILI) is a potential complication that is rare but can adversely affect both the mother and the fetus. Although many drugs can directly cause hepatotoxicity, idiosyncratic liver injury is common in pregnancy. Underreporting of adverse drug reactions, lack of adequate literature regarding drug safety in pregnancy, and the inherent difficulty in diagnosing DILI during pregnancy make the management of this condition challenging. This review attempts to describe the existing literature regarding DILI in pregnancy, which is mainly in the form of case reports; several studies have looked at the safety of antithyroid drugs, antiretroviral drugs, and paracetamol, which have an indication for use in pregnancy; the relevant data from these studies with regard to DILI has been presented. In addition, the review describes the diagnosis of DILI, grading the disease severity, assessment of causality linking the drug to the adverse event, regulatory guidelines for evaluating the potential of drugs to cause liver injury, efforts to ensure better participation of women in clinical trials and studies in pregnant women population in particular, and the challenges involved in generating adequate research evidence. The establishment of DILI registries in various countries is an encouraging development; however, there is a need for promoting active, spontaneous reporting of adverse events during pregnancy to ensure rapid generation of evidence regarding the safety of a drug in pregnant women.

Key Words: Drug induced liver injury; Pregnant women; Liver failure; Adverse effects; Pregnancy outcome; Registries

Core Tip: Drug-induced liver injury is a rare but potentially life-threatening consequence of drug administration. Few drugs are indicated for use in pregnant

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women based on their lack of teratogenic risk; however, these can be hepatotoxic. This review collates information from case reports and other research studies to present the current knowledge regarding the hepatotoxic potential of drugs used in pregnancy. The challenges in diagnosis and methods for causality assessment are described. Attempts to generate evidence by formulating guidelines enabling the conduct of inclusive clinical trials involving women as well as reinforcing the pharmacovigilance activities by developing adverse event registries are described.

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INTRODUCTION

Liver injury is an uncommon but potentially life-threatening adverse consequence of drug administration. Although the marketing of a new drug entails substantial effort in ensuring drug safety, both in the pre- and post-marketing phase, the limited size of the population that can be formally monitored in a controlled setting of a clinical study makes detection of uncommon adverse events a challenging task. Drug-induced liver injury (DILI) remains one of the common post-marketing events leading to drug withdrawal or significant labelling changes[1]. An incidence of up to 24 cases per 100000 population has been reported; the exact incidence reported varies widely and is probably not a true reflection of the magnitude of the problem[2-4]. Moreover, the inter-drug risk is highly variable, with the risk of hepatotoxicity with azathioprine being 1 in 133[3] and for chlorpromazine being approximately 1 in 800 users compared with less than 10 per 100000 users for many other drugs[5]. Traditional and complementary medicines also contribute significantly to DILI burden to varying extent in different countries[6,7]. It is to be noted that drugs generally considered safe and used in pregnancy, such as cephalosporins, amoxicillin-clavulanate, ibuprofen, *etc*., are commonly implicated inciting drugs[8].

DILI is one of the least studied aspects of pregnancy. Although accurate estimates of liver disease incidence and prevalence during pregnancy are not available, a study conducted using a nationwide inpatient sample in the United States showed that the rate of liver disease among hospitalized pregnant women ranged from 0.3% for chronic and alcohol-related liver disease to 7.18% for liver disorders of pregnancy[9]; apart from the adverse health impact on the mother, cases of fetal liver injury and mortality have also been reported. In general, liver disease during pregnancy can be categorized into three types. First, liver diseases that are specific to pregnant women and tend to occur at a specific trimester. Second, diseases such as viral hepatitis which occur irrespective of the pregnancy status; third, pre-existing liver disease in a pregnant woman.

Most of the available literature regarding DILI in pregnancy is in the form of case reports. Though DILI has become the leading cause of acute liver failure in the United States and Europe[10] and acute liver injury is more likely to progress to acute liver failure in women[11], only a few studies concerning pregnant women are found. A study in the United Kingdom found that drugs accounted for 2.8% of the abnormal liver function tests in pregnant women[12]. Similarly, a study in Singapore reported that 2.1% pregnant women with abnormal LFT overall, and 3.4% women presenting in the third trimester, had DILI[13]. However, not all studies have been able to identify similar rates of DILI in pregnancy[14]. Difficulty in diagnosis or underreporting is likely to account for a significant number of such cases[12]; subclinical cases due to the use of over-the-counter and herbal medications are also likely to be missed, especially since spontaneous resolution occurs following the withdrawal of the inciting drug. Furthermore, under-reporting is all the more likely since the clinical presentation of liver injury may occur weeks to months following drug exposure.

DILI IN PREGNANCY

Drug intake during pregnancy, although requires careful discretion on the part of the physician as well as the expectant mother, is common[15,16]. Antimicrobials, antiemetics, and analgesics are the common categories of drugs used. The use of herbal medicines and dietary supplements, either inadvertently or based on personal and cultural beliefs of benefit, is common.

Liver injury due to drugs may be direct, idiosyncratic, or indirect[17]. The direct form is the commonest and has become the leading cause of acute liver failure in western countries[10]; it is related to the pharmacological properties of the drug, is dose-dependent, and can affect any individual. The idiosyncratic form is not predictable, is rare, has variable features, and affects susceptible individuals[18]. The indirect form occurs due to a drug exacerbating a pre-existing liver disease or inducing clinical manifestation of subclinical liver disease.

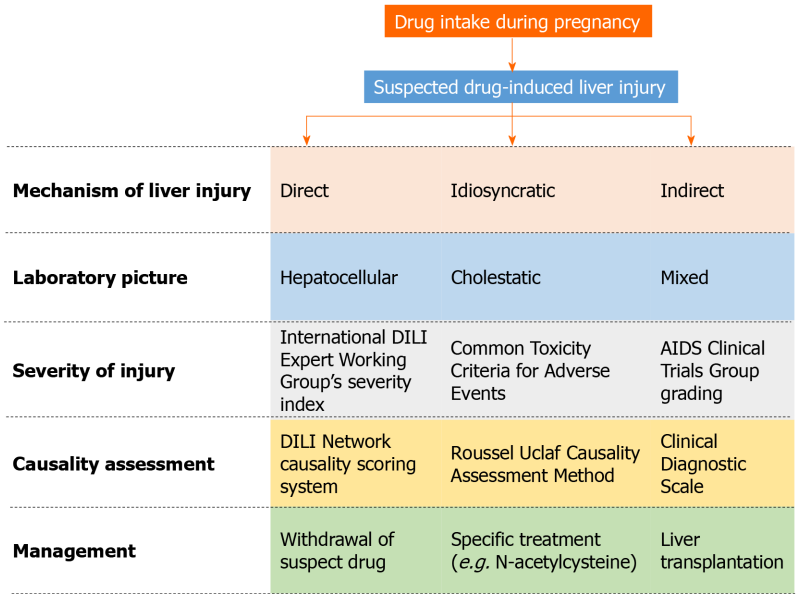
Drugs considered safe for use in pregnancy are known to cause idiosyncratic DILI. Co-morbidities like malnutrition, obesity, diabetes, and pre-existing liver disease may further intensify the risk of DILI during pregnancy[19]. Drug factors like the pharmacological class, dosage, and polypharmacy could also contribute[20]. Other factors that have a potential role in contributing to DILI causation include the circadian rhythm, presence of infection, intestinal microbiome, alcohol consumption, smoking status, environmental pollutants, and socioeconomic conditions[21]. The common medications reported in literature associated with DILI in pregnancy, such as paracetamol, alpha methyldopa, nevirapine, and propylthiouracil, are known for their safety and efficacy. Hence, an index of suspicion is important for the early detection of DILI in pregnancy.

Besides the above-mentioned factors, physiological changes that occur during pregnancy are also known to affect the pharmacokinetics of drugs. In particular, changes in the hepatic blood flow, microsomal enzyme activity levels, body fluid distribution, and serum albumin levels are important. There is a significant increase in the hepatic blood flow, mainly due to increased venous return[22]; this influences the metabolism of drugs with high hepatic extraction. Similarly, fall in serum albumin levels due to hemodilution can alter the pharmacokinetics of highly protein bound drugs, such as efavirenz[23]. An important change during pregnancy is in the hormonal milieu; this has significant effect on the hepatic metabolizing enzymes[24]. While the activity of a large number of cytochrome enzymes is increased, a decrease in activity is seen for CYP1A2 and CYP2C19[25]. The potential effect of such changes on the hepatotoxic potential of a drug would depend on whether it is the parent drug or its metabolite that causes the liver damage. In studies where specific drug use has a higher risk of hepatotoxicity in pregnant women compared with non-pregnant women, the mechanisms underlying the increased risk is unclear; for example, severe hepatotoxicity and temporary drug withdrawal during antitubercular therapy has been shown to be more frequent in pregnant women[26]. Similarly, nevirapine-induced hepatotoxicity is more frequent in pregnant women[27]. It is to be noted that in both the above examples, it is pregnancy, rather than the drug, which is a risk factor for hepatotoxicity, suggesting that the changes that occur during the pregnant state influence the likelihood of a drug to cause hepatic damage. However, it is to be noted that while there are several studies of changes in drug pharmacokinetics in pregnancy and several pharmacokinetic models have been developed to predict these[28], the actual clinical significance of these changes has not been adequately studied[29].

The management of DILI in pregnancy is similar to that in the non-pregnant population, in that the suspect drug is discontinued based on the clinical feasibility and risk-benefit assessment[30]. Although glucocorticoids have been used in severe cases, there is no adequate evidence to support their use; moreover, their use in pregnancy is associated with a higher risk of inducing diabetes[31]. Liver transplantation is also an option to be considered in severe cases.

DILI ASSESSMENT

Various algorithms, scales, and decision pathways have been proposed for the diagnosis, causality assessment, and grading of severity of DILI (Figure 1). The initial step is to suspect DILI; although an obvious case of liver injury may present with symptoms of hepatitis prompting an enquiry into the possible causes, a number of cases may go unaware initially unless alerted by an abnormal liver chemistry result. The challenge further is to determine whether liver injury is drug-induced, partic-



Mechanism of liver injury	Direct	Idiosyncratic	Indirect
Laboratory picture	Hepatocellular	Cholestatic	Mixed
Severity of injury	International DILI Expert Working Group's severity index	Common Toxicity Criteria for Adverse Events	AIDS Clinical Trials Group grading
Causality assessment	DILI Network causality scoring system	Roussel Uclaf Causality Assessment Method	Clinical Diagnostic Scale
Management	Withdrawal of suspect drug	Specific treatment (*e.g.* N-acetylcysteine)	Liver transplantation

Figure 1 Overview of drug-induced liver injury management including various grading scales and assessment methods. AIDS: Acquired immunodeficiency syndrome; DILI: Drug-induced liver injury.

ularly in the presence of pre-existing or new-onset liver disease. Although a correlation is not always present, DILI can be classified as hepatocellular, cholestatic, or mixed based on the initial liver enzyme levels at the time of clinical presentation [32]. The ratio of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) normalized to the upper limit of normal indicates the biochemical nature of the liver insult; a ratio ≥ 5 suggests hepatocellular injury, ≤ 2 suggests cholestatic injury, and 3-4 suggests a mixed pattern of injury. Aspartate aminotransferase values can be used to determine the liver injury pattern in the absence of availability of ALT data; gamma-glutamyl transferase is considered less reliable as an ALP substitute[33]. The biochemical tests may be supplemented with imaging and biopsy to determine the liver histology and rule out alternative causes of liver injury. Each hepatotoxic drug is more likely to be associated with a specific pattern of liver injury[34]; this may help in narrowing down the suspected medications or confirming DILI.

DILI rank is a database that consists of 1036 Food and Drug Administration-approved drugs that are divided into four classes based on their potential for causing DILI; most-DILI-concern drug, less-, no-, and ambiguous-DILI-concern drug[35]. Screening of this database will further help in associating a drug with an event. In terms of causality assessment, general assessment scales, such as the World Health Organization-Uppsala Monitoring Centre scale and Naranjo scale, lack validity and reproducibility; assessments based on expert opinion, such as the DILI Network (DILIN) Causality Scoring System, are limited by lack of availability of such expertise in usual clinical care[36]. A widely used tool specific for DILI is the Roussel Uclaf Causality Assessment Method (RUCAM). This scale by the Council for International Organizations of Medical Sciences, consisting of seven domains, includes weighted scoring of an event according to "the temporal relationship between exposure to a particular drug and the liver injury (both its onset and course), exclusion of alternative non-drug-related etiologies, exposure to other medications that could explain DILI, risk factors for the adverse hepatic reaction, evidence in the literature regarding DILI from the drug in question and response to re-exposure to the medication"[33]. However, it is relatively complex and involves workup to collect all the relevant data before arriving at a conclusion. Modifications have been done to the RUCAM scale to overcome some of its limitations; these include the Clinical Diagnostic Scale and Digestive Disease Week Japan 2004 Scale[37]; however, their performance is not significantly better than RUCAM which remains a useful tool, both in the context of clinical trials and routine assessment, to be used in DILI cases[38].

Determining the severity of DILI helps in provisioning appropriate care and prognostication. Severe DILI is one of the factors associated with mortality and chronic liver injury, although a majority of the cases will resolve completely[39]. Various DILI severity categorization schemes have been developed that take into consideration a combination of factors such as liver enzyme levels, bilirubin level, presence of

comorbid liver diseases, hospitalization, literature evidence, *etc.* For example, the DILIN prospective study proposed a five-point system for grading severity based on ALT, ALP, total bilirubin levels, need for hospitalization, signs of hepatic failure, and death or need for liver transplantation[39]. The International DILI Expert Working Group's severity index consisting of four severity classes is in principle similar to the DILIN scale but does not take into consideration hospitalization[32]. The Common Toxicity Criteria for Adverse Events, developed by the Cancer Therapy Evaluation Program of the National Cancer Institute of the National Institutes of Health, is a commonly used grading scale for adverse drug events. The scoring is based on the levels of liver enzymes and total bilirubin. However, this general purpose grading scale has not been shown to correlate with the clinical outcomes; it categorizes liver enzyme/bilirubin levels but does not evaluate DILI per se[40]. A similar grading that uses slightly different lab value limits is that developed by the Acquired Immune Deficiency Syndrome Clinical Trials Group[41].

DRUGS CAUSING DILI

The case reports describing DILI in pregnancy have been summarized in Table 1. Literature evidence in the form of prospective/retrospective, mostly observational, studies has been summarized in Table 2. Some of the commonly implicated drugs for liver injury in pregnancy are described below.

Paracetamol

Paracetamol is one of the most commonly used agents for fever/pain and is used in pregnancy as well. However, it has been known from previous studies that it can cross the placenta and, in higher than recommended doses, may even harm the fetal and maternal liver cells[42]. There are case reports of liver failure warranting the need for liver transplantation during or immediately after pregnancy[43-45]. The presenting symptoms have been severe abdominal pain, vomiting and signs of hepatotoxicity. The reasons for consumption of paracetamol have been for pain, self-medication, and in a couple of cases, even intentional poisoning has been reported[46,47]. Histology has shown acute fatty liver of pregnancy and toxin-induced injury consistent with paracetamoluse[43].

Fetal hepatocytes breakdown paracetamol into a variety of metabolites, some with a toxic activity that can directly damage the fetal hepatocytes. The antidote N-acetylcysteine has been seen to cross the placenta to combine with these metabolites [48]. Though the available data is sparse, it has been suggested that if *N*-acetylcysteine therapy, which is safe in pregnancy, is initiated early (within 16 h of paracetamol intake), the morbidity from paracetamol overdose can be significantly reduced[42]. Cases of intentional poisoning by ingestion of paracetamol have been reported. In both cases the fetal outcome was favorable, and both the patients recovered without sequelae[46,47] (Table 3).

Antithyroid drugs

Hyperthyroidism is a common endocrine disorder affecting 2% of females and 0.5% of males worldwide. Most of the times, anti-thyroid drugs are the mainstay of treatment. However, these drugs are also known to cause several side effects. Liver failure is a rare yet life-threatening adverse effect of these drugs[49]. In the case of the latter, post-mortem histology showed submassive necrosis[50]. Though hepatotoxicity is common, otherwise uneventful pregnancies with successful outcomes have been reported widely. In many such cases, propylthiouracil was changed to carbimazole leading to the resolution of the liver injury[51,52]. However, few severe cases of fulminant hepatitis that needed liver transplantation have also been reported[53-55]. Though fetal outcomes have been largely favorable, cases with adverse outcomes such as fetal growth restriction, oligohydramnios, frequent episodes of focal seizures, delayed developmental milestones, have been reported[53]. Transient thyrotoxicosis and signs of acute hepatic injury have also been reported[56,57].

Antiretroviral drugs

The role of nevirapine in causing hepatic damage more frequently in pregnancy is known, although conflicting results regarding the same have been reported[27,58,59]. The treatment duration is likely to play a significant role in the causation of hepatotoxicity. A shorter course of nevirapine for human immunodeficiency virus (HIV) prophylaxis is seen to be linked with fewer hepatotoxic reactions for non-HIV-infected

Table 1 Data available from case reports regarding drug-induced liver injury in pregnant women

Suspect drug	Pathological finding(s)	Outcome in mother	Outcome in child
Azithromycin[78]	Intrahepatic cholestasis	Recovery without sequelae	Birth by caesarean section
Chlorpromazine	Severe reduction in the number of bile ducts; marked cholestasis and pseudoxanthomatous transformation of ductular epithelia and hepatocytes in the region of the limiting plate; progressed to cirrhosis[85]; Ductopenia, long-standing cholestasis with pseudoxanthomatous transformation of hepatocytes and ductular epithelia[84]	Prolonged liver disease culminating in vanishing bile duct syndrome and cirrhosis [85]; Gradual resolution with non-active periportal and septal fibrosis[84]	Premature birth by cesarean section [84,85]
Combination antiretroviral therapy	Fulminant hepatitis[105]	Recovery without sequelae [70,105]; death[105]	Nonreassuring fetal testing; improved following drug withdrawal; normal delivery[70]
Human chorionic gonadotropin and follicle stimulating hormone for *in vitro* fertilization[87]	Cholestasis	Recovery without sequelae	Premature birth by cesarean section
Methyldopa	Cytolytic hepatitis and cholestasis, toxic hepatitis [106]; hepatitis[73,74,107,108]	Improved following drug withdrawal[72-74]	-
Nitrofurantoin[109]	Toxic liver damage	Recovery without sequelae	Normal
Paracetamol	Acute fatty liver of pregnancy and toxin-induced injury[43]; fulminant hepatitis[45]	Liver transplantation[43,45]	Fetal death[43]; intrauterine fetal demise with extensive pericerebral and intraventricular hemorrhage with extensive periventricular leukomalacia[45]; intracranial hemorrhage, fetal hepatotoxicity[110]; preterm birth[111]
Propylthiouracil	Liver necrosis[50,53,54,112]; widened portal triads, and lymphoplasmocytic infiltrate[50]; hepatitis[52]; portal hepatitis[112]; acute liver failure[55]	Liver transplantation[53,55]; recovered[52,54]; death[50]	Miscarriage[50,54]; Antenatal ischemic encephalopathy, delayed developmental milestones[53]; normal [52,55]; caesarian delivery[112]
Tetracycline[83]	Fatty liver	Death	-

individuals or pregnant HIV-infected women and the fetus. However, intake of nevirapine for ≥ 2 wk for prophylaxis has a higher risk of hepatotoxicity among non-HIV-infected individuals and HIV-infected pregnant women[60]. Various studies have also been conducted to study the relation between CD4 counts and the occurrence of nevirapine toxicity. It has been noted that initiating nevirapine-based antiretroviral regimens during pregnancy at higher pre-treatment counts (CD4 ≥ 250 cells/μL) increases toxicity risk and should be avoided. The severity of hepatotoxicity was also more[61-63]. However, there are conflicting reports regarding this aspect as well, as no correlation was observed between high CD4 counts and adverse events in some studies[64-67].

Hepatitis C coinfection has been implicated as a risk factor for hepatotoxicity in pregnant women on antiretroviral therapy as a higher risk of liver toxicity to combination antiretroviral therapy has been observed[68].

Overall, it has been largely observed that there is no direct association between antiretroviral therapy in pregnancy and harmful effects on the fetal liver or the hepatic parameters at birth. However, a detailed and regular follow-up would be recommended before ruling out the harmful effects of maternal ARV treatment[69]. Antiretroviral-induced hepatotoxicity presenting as non-reassuring fetal testing has been known, wherein a detailed assessment later revealed maternal metabolic acidosis and transaminitis[70].

Alpha methyldopa

Alpha methyldopa is one of the first-line drugs for hypertension during pregnancy due to its long-known safety profile. However, there have been reports of methyldopa-induced hepatitis cases in pregnancy[71-73], with a temporal relationship between drug exposure and serum liver enzyme elevations. Also, a rapid decrease of liver enzymes on withdrawal of the drug further supports this observation[72,74]. Postpartum methyldopa-induced hepatotoxicity, up to two months after delivery, has also been reported; despite a full recovery from the acute phase, a residual underlying hepatic fibrosis was reported[71].

Table 2 Studies other than case reports describing effect of drugs on maternal/fetal/neonatal liver function

Ref.	Study design	Study population	Suspected medication (s)	Study outcome
Snijdewind *et al*[68]	Retrospective, comparative	Pregnant women	Antiretroviral therapy and hepatitis C virus co-infection	Nevirapine use related to hepatotoxicity in pregnant as well as non-pregnant women; the risk is significantly associated with hepatitis C coinfection during pregnancy
Beck-Friis *et al*[26]	Retrospective, comparative	Pregnant *vs* non-pregnant	Antitubercular drug	Severe hepatotoxicity and temporary drug withdrawal more frequent in pregnant women compared to non-pregnant women
Mandelbrot *et al*[113]	Retrospective, comparative	Pregnant women	Atazanavir	Three women had abnormal liver enzyme levels; grade 3 bilirubin elevations in 5 patients; jaundice in 5 neonates requiring phototherapy.
Heaton *et al*[82]	Retrospective, case-control	General population including pregnant women	Doxycycline, tetracycline	Doxycycline potentially less hepatotoxic than tetracycline
McCormack *et al*[114]	Prospective, placebo-controlled	Pregnant women	Erythromycin estolate, clindamycin hydrochloride, placebo	Erythromycin estolate resulted in raised liver enzymes; use not advised in pregnancy
Tempelman *et al*[115]	Retrospective, comparative	Pregnant women	Highly active antiretroviral therapy	Nelfinavir or nevirapine containing regimens are safe and effective in pregnant women with HIV
Franks *et al*[77]	Retrospective	Women with isoniazid hepatitis	Isoniazid	A 2.5-fold increased risk of isoniazid hepatitis and 4-fold higher mortality rate in the prenatal clinic group compared to non-pregnant women.
Gupta *et al*[116]	Multicenter, double-blind, placebo-controlled, noninferiority trial	Women with HIV (efavirenz-based antiretroviral therapy) receiving isoniazid preventive therapy either during pregnancy or after delivery	Isoniazid	Risk of composite adverse pregnancy outcome was greater in those who initiated isoniazid preventive therapy during pregnancy than those during postpartum period; majority of liver enzyme elevations and symptomatic hepatitis occurred in postpartum period.
Sato *et al*[117]	Single-cohort interventional	Pregnant women with choriocarcinoma and high-risk gestational trophoblastic neoplasia	Methotrexate, etoposide, actinomycin D	Of the 23 patients who received methotrexate, etoposide and actinomycin D, treatment changed to etoposide and actinomycin D in 14 patients due to leukocytopenia, hepatotoxicity, and stomatitis.
Fang *et al*[118]	Single-cohort, prospective, interventional	Pregnant women	Nelfinavir	Of the 16 women studied, one developed serious adverse event of elevated AST; the drug was well tolerated in general.
Timmermans *et al*[59]	Retrospective, comparative	Pregnant and non-pregnant women	Nelfinavir, nevirapine	Nevirapine related hepatotoxicity more frequent in pregnant than in non-pregnant women.
Joy *et al*[119]	Single-cohort, retrospective, observational	Pregnancy women in third trimester	Nevirapine	Incidence of adverse events lower; study in larger cohorts recommended to determine the relationship between nevirapine hepatotoxicity and trimester use.
Natarajan *et al*[58]	Retrospective, comparative	Pregnant women	Nevirapine	Risk of nevirapine-associated toxicity not higher in pregnancy; CD4 counts not predictive of toxicity.
Kondo *et al*[65]	Retrospective, comparative study	Pregnant women	Nevirapine	Hepatotoxicity occurred in those with pre-treatment CD4 counts ≥ 250 cells/μL; no correlation between high CD4 counts and adverse events.
Phanuphak *et al*[66]	Retrospective, comparative	General population including pregnant women	Nevirapine	Pregnant women with high CD4 counts have higher rate of symptomatic hepatotoxicity.
Kondo *et al*[67]	Single-cohort, retrospective, observational	Pregnant women	Nevirapine	No correlation between high CD4 counts and adverse events; hepatotoxicity occurred only in pregnant women with CD4 counts > 250 cells/μL
Ouyang *et al*[120]	Prospective, comparative	Pregnant women	Nevirapine	No significant association between nevirapine use and liver enzyme elevation regardless of pregnancy status; pregnancy associated with increased hepatotoxicity.
Ouyang *et al*[27]	Retrospective, comparative	Pregnant women	Nevirapine	No increased risk of hepatotoxicity among HIV-infected pregnant women on nevirapine *versus* other drugs, including in those treatment naïve.
Peters *et al*[64]	Prospective,	Pregnant women	Nevirapine	Severe hepatotoxicity and rash higher with

	comparative			nevirapine than with nelfinavir; no association with CD4 counts.
Lyons *et al*[62]	Single-cohort, retrospective, observational	Pregnant women	Combination antiretroviral therapy	Women with more severe hepatotoxicity had higher pretreatment CD4 counts.
Jamisse *et al*[63]	Single-cohort, prospective, observational	Pregnant women	Nevirapine-containing combination antiretroviral therapy	Severe hepatotoxicity more common at higher CD4 counts in pregnancy.
Sheng *et al*[121]	Prospective, comparative	Pregnant women with high viral loads of hepatitis B virus	Nucleos(t)ide analogues	Telbivudine therapy was safe in pregnant women.
Zhang *et al*[122]	Disproportionality analysis	Pregnant women	Omeprazole, lansoprazole, amoxicillin	The risk of cholestasis associated with these drugs higher in pregnant women; re-assessment of safety recommended.
Cecchi *et al*[88]	Single-cohort, prospective, observational	Pregnant women	Organophosphate pesticides	Subclinical hepatotoxicity during the second trimester in spraying period.
Trakulsrichaia *et al*[123]	Single-cohort, retrospective, observational	Pregnant women	Paraquat poisoning	Hepatotoxicity more common in patients who died.
Andersen *et al*[57]	Single-cohort, observational	General population including pregnant women	Antithyroid drugs	Antithyroid drug-associated liver failure observed less frequently in pregnant women than in the general population.
Brunet *et al*[124]	Single-cohort, prospective, observational	Pregnant women	Saquinavir/ritonavir	Among the 58 women who received the drug, one developed severe grade 3 hepatotoxicity; in general, the drug was effective and safe.
Jharap *et al*[125]	Single-cohort, prospective, observational	Pregnant women	6-Thioguanine nucleotide, 6-methylmercaptopurine	Fetal exposure to 6-thioguanine but not to 6-methylmercaptopurine; 60% had anemia at birth; no major congenital abnormalities.

HIV: Human immunodeficiency virus.

Table 3 Case reports of drug poisoning/abuse and alternative medicine use resulting in liver injury during pregnancy

Suspect drug	Clinical finding(s)	Maternal outcome	Fetal outcome
Cocaine[126]	Hepatic rupture	Prolonged hospital stay	Emergency caesarian delivery
Paracetamol	Raised liver enzymes[46,47]; coagulopathy[46]	Recovery without sequelae[46,47]	Normal[47]; prematurity, respiratory distress, metabolic acidosis, full recovery[46]
Mushroom (Amanita species)[127]	Low prothrombin activity	Recovery without sequelae	Normal
Mountain germander (*Teucrium polium*)[128]	Raised liver enzymes	Recovery without sequelae	Normal

Antitubercular drugs

Studies in the past have reported that the risk of hepatotoxicity to antitubercular drugs is significantly higher in pregnancy. Temporary drug withdrawals due to elevated transaminase levels were more frequent for pregnant than non-pregnant women, and cases of fatal hepatotoxicity have also been reported. The reason for the increase however has not been elucidated[26].

Administering isoniazid to prevent tuberculosis constitutes isoniazid preventive therapy (IPT); the benefit of treating active tuberculosis in pregnancy plus providing isoniazid preventive therapy to minimize the risk of developing active tuberculosis in persons with HIV, has been seen. However, data regarding the benefit of IPT in pregnant women who are on antiretroviral therapy is sparse, owing to the fact that pregnant women have usually not been included in various trials of isoniazid preventive therapy[75,76].

Studies have reported increased isoniazid toxicity among pregnant women as well [77]. From the limited data on IPT available so far, a higher incidence of unfavorable pregnancy outcomes, such as stillbirth or spontaneous abortion, has been reported. Also, the risks associated with initiating IPT during the postpartum period were seen to be lower than that associated with initiating it during the course of pregnancy[75].

Antibiotics

Azithromycin-induced liver injury has been rarely reported in the general population. There is a report of azithromycin-induced intrahepatic cholestasis in a pregnant woman; on withdrawal of azithromycin, the liver enzyme levels returned to normal within 4 wk without any symptoms after treatment with silymarin and bifendate, which help reduce ALT level and protect the liver from further injury[78].

A unique case of drug-induced mononucleosis-like hepatic injury in a patient with systemic lupus erythematosus has been reported following the administration of multiple antibiotics. An allergic reaction to the administered drugs was implicated based on a positive lymphocyte stimulation test[79].

Tetracycline is another antibiotic that has been known since decades for its potential to cause hepatic adverse events[80]. Tetracycline-induced liver injury typically causes fatty infiltration of the liver. The presence of kidney dysfunction and pregnancy are some of the risk factors for hepatotoxicity to tetracycline[81,82]. Fatal hepatotoxicity to tetracycline, when given in pregnancy, has also been reported, and post mortem examination has shown major histological changes in the liver along with fatty degeneration of the renal tubular epithelial cells[83].

Miscellaneous drugs

Individual case reports implicating other drugs, herbal medicines, and dietary components (Table 3) have also been described. Cholestatic liver disease in a pregnant woman in the 33rd week of pregnancy who received chlorpromazine and chlorprothixene has been reported; no signs of liver damage were present in the newborn[84]. A case of a primary biliary cirrhosis-like syndrome that developed after 2 wk of chlorpromazine therapy has also been reported[85]. A case of intrahepatic cholestasis of pregnancy, worsening after dexamethasone administration has also been reported [86]; however, the authors concluded that it was more likely due to the progression of the primary disease rather than drug-induced. Cholestasis developing following *in vitro* fertilization and ovarian hyperstimulation syndrome is also known[87].

Reports of the effect of environmental xenobiotics on pregnancy have also been reported. A prospective study conducted in a rural area where organophosphates were intensively applied, found that the liver enzymes were raised in the spraying period, which could be indicative of subclinical hepatotoxicity. Though the offspring at birth were normal, a follow up would be required to assess the delayed effects of raised maternal cortisol during pregnancy[88].

REGULATORY GUIDELINES FOR CLINICAL EVALUATION OF DRUGS FOR DILI IN PREGNANCY

Clinical trials seldom study drug effects in pregnant women due to ethical and safety concerns, unless the drug is to be specifically used in pregnant women. In fact, even in the case of non-pregnant females, the inclusion of females in eligible clinical trials is significantly less than men despite the regulatory intent of ensuring adequate participation opportunities[89]. The findings of drug studies in the general population regarding the effect of hepatic function on the drug kinetics and dynamics, including the possible toxic effects of drugs on liver, are generally applicable to pregnant women; however, the physiological changes that occur during pregnancy need to be considered in determining how the drug effects are likely to be affected.

DILI is often rare; although good, the relative rarity of the event also makes its detection during the clinical trial phase difficult. For example, most known drug-hepatotoxicity events occur with an incidence of < 1 in 10000; hence, such events are seldom detected during a clinical trial. Keeping this issue in mind, regulatory guidelines emphasize the need to detect lesser grades of liver injury, which may not necessarily manifest clinically/symptomatologically, but are potential markers for occurrence of serious liver injury if used in the wider population[90]. Accordingly, drugs which not only cause elevation of liver enzymes but also impair bilirubin metabolism or affect clotting factor synthesis are likely to cause severe liver injury. In general, considering the occurrence of mild elevations in liver enzyme levels even in placebo/control groups, an isolated 3-fold elevation is considered the minimum threshold for concern[90].

The above-mentioned aspects are also applicable to drug use in pregnancy. Although drug use is to be discouraged during pregnancy to the extent possible, studies show that a large number of women do receive drugs for various reasons[91-

93]. Regulatory guidelines encourage that drugs to be used specifically in pregnancy or includes an indication for use in pregnant women for a general indication should be studied in the pregnant population[94-96]. These may be studies conducted exclusively among pregnant women or in the general population that does not exclude subjects who are pregnant. Such studies provide useful data regarding the potential safety of the drug in relation to liver function, although the limited sample size of such studies precludes arriving at definite conclusions. The safety update reports from drug manufacturers, based on drug use in the general population as well as the pregnancy exposure registries, may provide information regarding the hepatotoxic potential of a drug; the latter are not regulatory in nature but do provide vital information in this population. The increasing emphasis on pharmacovigilance activities in various countries is also expected to contribute to earlier identification of DILI in pregnancy. However, the reporting of adverse drug events in pregnant women has so far been low[97,98]; underreporting is the norm, and much needs to be done to improve reporting. Most of the DILI cases have been identified through published case reports, with some of these forming the basis for specific clinical studies in pregnant women, particularly for antiretroviral drug-associated hepatotoxicity. The regulatory mandated section of drug effects in pregnancy in the drug labels is a good source of information regarding drug safety specifically in pregnancy for prescribers[99].

CHALLENGES FOR EVIDENCE GENERATION

Besides the lack of adequate representation of females in clinical trials, assessment of the hepatotoxic potential of a drug in pregnant women has two important challenges. The first is a general challenge, not limited to pregnant women, of differentiating liver injury incited by drugs in contrast to that by liver disease; the challenge arises due to lack of any specific clinical or biochemical marker for drug-induced injury. Hence, clinical and medication intake history and knowledge regarding the pharmacology of the suspected medication to a large extent dictates the identification of the cause of injury. Large adverse event databases, which contain spontaneously reported adverse events from consumers and healthcare professionals, are excellent sources for determining a signal[100]; however, the lack of adequate recording of history/sequence of events in these spontaneous reports often precludes any definitive conclusions to be made. The second challenge is to differentiate DILI from intrahepatic cholestasis of pregnancy, which is not uncommon[101,102]. These challenges are compounded by the infrequent identification and reporting of such cases. Given the hurdles, spontaneous active reporting by health professionals and patients seems to be the most appropriate way for evidence generation, supplemented by the safety data from pre- and post-market approval clinical studies. Recognizing the inability to identify potential hepatotoxic drugs during clinical trials and the immediate post-marketing period, a number of regions/countries have started DILI registries to gather data regarding cases of potential DILI so that the data can be collectively evaluated to identify signals[103-105].

CONCLUSION

DILI is a real concern in pregnancy, although most of the cases have a favourable outcome and require only withdrawal of the drug. Advances in diagnostic modalities and access to liver transplantation have further improved the outcomes. Most of the DILI cases during pregnancy go unreported; there is a need to capture these incidents efficiently to ensure an informed decision can be made regarding drug use in pregnancy. The establishment of DILI registries in various countries is encouraging and will add significantly to this effort.

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MINIREVIEWS

Racial differences in prevalence and severity of non-alcoholic fatty liver disease

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Abstract

The aim of this review is to assess the evidence regarding racial differences in the prevalence and severity of nonalcoholic fatty liver disease (NAFLD). We reviewed the published literature that reported prevalence, severity, and genetic associations of NAFLD in different ethnic groups. The metabolic syndrome (MetS) has been associated with NAFLD, but each component of the MetS is present in various races in different percentages and their effect on NAFLD appears to be dissimilar. An elevated triglyceride (TG) level seems to have the strongest association with NAFLD. The latter is more prevalent in Hispanic patients; Blacks have lower TG levels and a lower NAFLD prevalence, compared to Caucasians or Hispanics. The severity of liver fibrosis is lower in some, but not all biopsy-based studies of Black patients. No study has evaluated the severity of liver disease controlling for the individual components of MetS, especially TG. Important racial differences in the prevalence of selected genetic polymorphisms, particularly PNPLA-3 and MBOAT7 have been documented, together with their effects on the prevalence of liver steatosis and fibrosis. Data on overall and liver mortality have found no significant differences according to race/ethnicity, with the possible exception of one paper reporting lower cirrhosis mortality in Black patients. We conclude that NAFLD is more prevalent in Hispanics and less in Blacks. This is supported by differences in key genetic polymorphisms associated with hepatic

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fat storage. However, there is presently insufficient evidence to firmly conclude that race, per se, plays a role in the development of liver fibrosis and its complications. Further studies, appropriately controlled for diet, exercise, and individual MetS parameters are needed.

Key Words: Race; Ethnicity; Nonalcoholic fatty liver disease; Fatty liver disease; Metabolic syndrome

Core Tip: Nonalcoholic fatty liver disease is one of the most common diagnoses made in a Gastroenterology practice. The prevalence and severity of nonalcoholic fatty liver disease in different ethnic groups need to be evaluated by controlling for the individual variables of the metabolic syndrome. This is because these variables are different in various ethnicities.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common diagnoses made in a gastroenterology practice. Several articles suggested differences in the prevalence and severity of liver disease according to patient race/ethnicity. If such differences were proven, this would have an important impact on resource allocation to decrease health disparities. Thus, it is imperative that the available literature be critically reviewed and existing knowledge gaps, if any, identified.

RACE AND NAFLD

Definitions

NAFLD is a condition marked by excess fat storage accounting for > 5% of the liver's volume in the absence of known alcohol abuse[1]. The latter is usually defined as the use of > 20 g alcohol/day for women and > 30 g/d for men[2], although lower limits have been used[3]. No study addressing race differences has verified absence of alcohol by testing hair for alcohol or using blood phosphatidylethanol levels[4,5]. The diagnosis is usually inferred by imaging studies, typically an ultrasound showing increased hepatic echogenicity[6,7]. Elevated alanine aminotransferase (ALT) in the absence of known competing causes has also been accepted as "suspected NAFLD" [7]. It is also crucial to differentiate primary *vs* secondary causes (medications, genetic or nutritional disorders); however only approximately 12% of studies excluded the latter[8].

We accepted the authors' race classification, which was typically based upon self-reporting. We recognize that race and ethnicity are "constructs that have no clearcut definition"[9]. It is important to keep in mind that Hispanics and Asians include significantly heterogeneous sub-populations[3,7,9].

Since Asians are underrepresented in most United States studies, this review will focus on Blacks (or African-Americans), Hispanics (or Latinos) and Whites (or Caucasians).

For the purpose of this paper, we will accept that the alcohol history is accurate, that a compatible ultrasound and/or elevated transaminases in the appropriate clinical setting are reasonable diagnostic tools, and that all reported cases are primary NAFLD.

Specific aim

To assess the strength of evidence suggesting that race-ethnicity in adults is associated with not only prevalence, but also with severity and prognosis of NAFLD.

Methods

We queried the PubMed English language database using the following keywords in the title or abstract: "fatty liver", "nonalcoholic fatty liver disease", "NAFLD", "liver or hepatic steatosis", "steatohepatitis" AND "race" or "ethnicity". We eliminated articles including alcoholic liver disease or HIV infected patients. We restricted this narrative review to adult populations.

Prevalence of NAFLD by race/ethnicity

The prevalence of NAFLD is reported to be highest in the Middle East (32%) and South America (31%), followed by Asia (27%), and Europe (23%)[10,11]. In Africa and India, the prevalence of NAFLD is approximately 9% of the population[12,13].

The most recent estimate places the United States prevalence of NAFLD at about 32%[14]. The United States is unique due to its mix of various races and ethnicities, while maintaining relative homogeneity in terms of geography and alimentary patterns. Therefore, it seems like an optimal population to study to uncover potential racial differences in disease.

A recent meta-analysis[8] shows that in population-based cohorts (*i.e.*, not high-risk patient groups such as diabetics) 23% of Hispanics have NAFLD, *vs* 14% of Caucasians, and 13% of African Americans. These percentages translate into a higher relative risk (RR) for Hispanics being diagnosed with NAFLD (RR = 1.5), and lower for African/Americans (RR = 0.7) compared to Whites[8]. If one focuses on patient subgroups that are at high risk for NAFLD, these differences become smaller (Hispanics RR = 1.2 and African-American RR = 0.8) but remain significant[8]. Interestingly, a NHANES based study[6], not included in the above meta-analysis, also found that Hispanics have a RR for NAFLD of 1.7 and African-American a RR of 0.8 compared to Whites: however when restricted to 'never drinkers', those differences are no longer significant, implying that small amounts of alcohol may have different effects on different races[6]. Thus, despite higher rates of HTN and insulin resistance, African-Americans have a lower prevalence of NAFLD[1,6,15-18].

There is relatively little written about Asian patients other that the prevalence may be about 25% in Asia[19], but may be lower in US-residing Asians, where NAFLD is noted in 20%[14]. A summary of the estimated prevalence of NAFLD in the United States is shown in Table 1.

Prevalence of the metabolic syndrome by race/ethnicity

Contributors to the rising worldwide prevalence of NAFLD include non-modifiable factors like genetics, but also modifiable variables such as diet and lifestyle choices[7,21,22]. Identifying, quantifying and controlling for these factors will be useful to establish whether some groups may be at higher risk, and therefore help allocate resources to mitigate those differences[23].

Diet and exercise has been found to be different in different ethnic groups. Asians have better diets (measured with an adapted healthy eating index) than Caucasians who in turn have better diet scores than Latinos and Blacks[21]. In Hawaii, however, intake of fruits and vegetables was lowest in Japanese-Americans compared to Filipinos or Native Hawaiians[22]. Yet, it is not clear whether a better diet score necessarily translates into a lower NAFLD risk[21,22]; and if so, by how much.

Similarly, exercise habits appear to be different, highest in Caucasians and lowest in Asians[9,22]. This is important because exercise decreases intrahepatic fat by MRI, even in the absence of weight loss[24]. Unfortunately, in articles focusing on NAFLD, these potentially important variables have not been adjusted for.

Metabolic syndrome (MetS) is accepted as the major association with NAFLD. MetS is defined by the presence of 3 or more out of 5 criteria: Increased fasting glucose, central obesity/waist circumference, low high-density lipoprotein (HDL), elevated triglycerides (TG), and elevated arterial pressure. Meeting this definition is associated with future development of diabetes type 2 (DM) and cardiovascular disease (CVD)[23]. There are differences in the prevalence of MetS according to race ethnicity, in non-institutionalized adult individuals living in the United States. A recent assessment shows that the prevalence of MetS was 35% in Whites, 30% in Blacks, followed by Hispanics (termed "Mexican Americans") (29%)[15]. No increased prevalence was noted in the Latino population surveyed[15]. A United States military study looked at the incidence of MetS (by ICD-10 codes), and found the highest was in Pacific-

Table 1 Estimated prevalence of nonalcoholic fatty liver disease in the general United States population (three main Race-ethnicities)

Ref.	Whites			Blacks			Hispanics		
	No.	Denom	Percentage	No.	Denom	Percentage	No.	Denom	Percentage
Rich *et al*[8]	24454	200510	0.12	3625	54790	0.07	5125	40591	0.13
Kallwitz *et al*[7]							1691	9342	0.18
Zou *et al*[14]	2229	4341	0.51	538	2833	0.19	1686	3886	0.43
Lim *et al*[20]	82	400	0.2	49	297	0.16	180	377	0.48
Foster *et al*[16]	189	1244	0.15	106	992	0.10	208	775	0.27
Total	26954	206495	0.13	4318	58912	0.07	8890	54971	0.16

Islanders, and the lowest in White personnel[25].

However, there are 3 important problems with MetS as a dichotomous variable. First, individual components of the MetS have a different distribution among races, elevated TG being more common in Latinos and White males and abnormal waist circumference in Blacks and White females[23]. In fact, the low TG levels in Blacks have been called "the TG paradox"[26]. Thus, African American patients have a higher body mass index (BMI) and similar prevalence of DM, yet they display a better lipid profile and therefore are less likely to have MetS compared to Hispanics (Table 2)[17]. The prevalence of DM is lowest in Whites (12%) and similar in Asians (19%), Blacks (20%) and Hispanics (22%)[18]. The latter group showed major heterogeneity, South American patients having less DM (12%) compared to other Latino groups[18].

Second, a diagnosis of MetS predicts the development of DM or CV disease differently in different races. For example, in patients with MetS, rates of incident DM are highest in Black males and females (17%) and lowest in white women (8%); whereas the rate of development of CVD is highest in White men (25%) and lowest in Black women (6%)[23]. Third, the association between individual MetS variables and NAFLD is not the same. In a recent study from China (Asian patients), NAFLD patients had higher levels of each of the 5 MetS parameters *vs* controls. However, when a multivariable analysis was run, adjusted for age and sex, the strongest association was with an elevated TG; the prevalence of NAFLD in the highest and lowest TG quartile was 50% *vs* 5 %[27]. Therefore a *z*-score, where the MetS is measured on a continuous scale (from -1 to +4) has been developed and shown to predict the development of diabetes and CVD better than the binary MetS[23]. When controlled for the z-score, Black individuals have double the rate of DM and higher rates of hypertension *vs* whites[16,23]. There are no data assessing the prevalence and severity of NAFLD, in patients matched by the *z*-score.

Fat distribution/obesity

Lean NAFLD (*i.e.*, with normal BMI) is found in as many as 5% of those with NAFLD in the United States[14] and this subgroup has a 65% chance of being metabolically abnormal, *i.e.*, fulfilling criteria for MetS[28]. On the other hand, overweight and obese NAFLD patients have a correspondingly higher chance of having MetS, 92% and 95%, respectively. Lean NAFLD seems more common in Asians *vs* other ethnic groups[14,20]. Elevated TG appears to be the commonality in patients with NAFLD, independent from BMI[17,27,28].

Patterns of visceral and liver fat depositions show ethnic differences and may contribute to the prevalence and severity of NAFLD. Total adiposity, measured by DEXA and MRI to account for visceral, liver and truncal fat was found to be highest in Japanese Americans and lowest in African Americans[17]. Interestingly, women had lower visceral fat area than men, except in the Japanese American group[20]. African-American adolescents have less visceral fat than either Hispanics or Whites[29].

A study using transient elastography and controlled attenuation parameter estimated hepatic steatosis and fibrosis in 2000 Korean patients. Obese (*i.e.*, BMI 25 or greater) but metabolically healthy (no MetS) individuals had greater liver steatosis and fibrosis than non-obese patients[30]. However, in the non-obese group, those with MetS, had higher steatosis estimates but similar fibrosis to those without MetS. BMI rather than MetS was the variable independently associated ($P < 0.001$) with both steatosis and fibrosis[30]. The Dallas heart study quantified visceral fat percentage by MRI in the general population: unfortunately, 3% to 8% of the individuals reported alcohol intake levels exceeding those used to define NAFLD[1]. The findings were that

Table 2 Prevalence of metabolic syndrome and its components in African Americans *vs* Hispanics[17]

	AA	H	*P* value
Percentage MetS	19	33	< 0.0001
% Diabetes	17	17	NS
Mean HDL	53	47	< 0.0001
Mean TG	107	160	< 0.0001
Mean BMI	31	29	0.008

AA: African Americans; H: Hispanics; MetS: Metabolic syndrome; HDL: High-density lipoprotein (mg%); TG: Triglyceride (mg%); BMI: Body mass index.

male Hispanic and White individuals had similar risk (42% to 45%) of having hepatic steatosis greater than 5.5 g TG per 100 g of liver tissue, much higher compared to Black males (23%). Women, both White and Black, had lower rates of abnormal hepatic steatosis (24%) compared to Latinas (45%). The fact that Blacks had higher HTN and Insulin resistance rates, but lower circulating TG levels, suggests racial and genetic differences in intrahepatic TG storage[1,16,20,31].

Genetics

Pathways of lipolysis or lipogenesis (MBOAT7, PNPLA3, TM6SF2,) are some of the genetic polymorphisms that have been linked to NAFLD prevalence and its severity [16,32-34].

In individuals of European descent, a T mutation in the MBOAT7 gene (rs641738) has been associated with severity of NAFLD in those with TT homozygosity[34]. Even the presence of one T polymorphism was associated with a small [odds ratio (OR) = 1.3] but significant risk of biopsy-proven F2, F3 or F4 fibrosis[34]. However, the association between the PNLPA3 G allele and F2-F4 was stronger (OR = 1.6)[34].

The PNPLA3 gene controls hepatic VLDL excretion, likely leading to hepatic TG accumulation; it may also sensitize the liver to environmental stressors, thus contributing to elevated transaminase levels in the presence of obesity[2]. The G allele mutation (rs738409), termed I148M (*vs* CC wild type) is a single-nucleotide polymorphism (SNP), which increases the risk of fat accumulation in the liver and thus NAFLD four-fold[17,32,33]. The G allele was found to be more frequent in Hispanics (40%) compared to Africans and Europeans (both 15%). In those with GG alleles, the risk of having NAFLD was similar in Asians and Caucasians (3-fold) and Hispanics (4-fold) but was much higher in Black patients (9-fold) compared to those with wild type genotype[35].

Within the United States population, the PNPLA3-G allele had a significant association with a non-invasive estimate of liver fibrosis, the FIB-4 score[7], but in one study this association was not clear (Table 3)[3]. The GG homozygosity has also been associated with a 5-fold increase in HCC risk[33]. A recent study from Sicily confirmed that the G allele (either heterozygous or homozygous) was associated with more advanced liver fibrosis[36]. In patients with stage 3 and 4 fibrosis, the G allele was associated with more liver decompensation, HCC and liver related death, despite a relatively small total number of patients followed (n = 471)[36]. Interestingly, 2/3 patients had the G allele and almost a quarter was homozygous GG[36].

In Hispanics with American ancestry (Mexican-, Central-, and South American), the frequency of PNPLA3-G is higher than in those of European or Afro-Caribbean background[3]. A small study in Hmong patients suggests that some Asian subpopulations have high rates of the G SNP and thus may have increased risk for NAFLD[37]. These findings underscore the existence of distinct and potentially relevant subpopulations within a traditional race/ethnicity group.

A minor allele (rs58542926) in transmembrane 6 superfamily member 2 (TM6SF2) was associated with hepatic TG content measured by magnetic resonance spectroscopy, in the Dallas Heart Study[1]. The C to T polymorphism decreases VLDL excretion, thus increasing TG concentration in the liver[33]. In addition, this TM6SF2 polymorphism was noted to increase the risk for hepatic fibrosis independent of age, obesity, diabetes, and PNPLA3 genotype[38]. On the other hand, the TM6SF2-T allele mutation E167K had similar low frequencies between Hispanics[3] and those from European ancestry and had a strong association with ALT levels[15].

Table 3 Percentage of patients with the *PNPLA3* G allele polymorphism and FIB-4 > 2.67[3]

	% PNPLA3-G allele	% Suspected NAFLD	% FIB-4 > 2.67
Mexican American	52	21	0.4
South American	51	20	0.3
Central American	48	23	0.9
Puerto-Rican	35	16	2.0
Cuban	28	16	1.8
Dominican	22	13	0.5

NAFLD: Nonalcoholic fatty liver disease.

NAFLD, liver fibrosis and liver complications

Several studies assessed metabolic factors associated with varying histopathological severity of NAFLD. There is agreement that the degree of steatosis is proportional to the number of elements of the MetS[7,16,20,32,39,40]. Additionally, one study showed that the MetS was associated with significantly greater risk of liver fibrosis stage 3 or 4 (33% *vs* 15% in those without MetS) and necroinflammation (61% *vs* 44%)[39]. The same study showed that in patients with NASH, 88% had MetS compared to 67% of those with simple fatty liver[39].

NAFLD is more prevalent in Hispanics[6,15,18,31], but the significance of this finding is debatable, as fibrosis is the only histological variable consistently associated with liver mortality[41]. While mortality in NAFLD patients is chiefly associated with cardiovascular events[42,43], it would be useful to tease out whether race independently affects the development of cirrhosis, and therefore liver mortality.

The fact that there is a relationship between elements of MetS and liver steatosis, inflammation and fibrosis[23,39] means that studies comparing liver disease severity between races must be controlled for the 5 MetS variables, keeping in mind that each may be more predictive in specific races.

The multi-ethnic cohort[44] looked at a United States population enriched with Asian minorities. The results showed that NAFLD was the most common cause of chronic liver disease in Japanese Americans (64% of those with liver disease) followed by Hawaiians (58%), Latinos (46%), Whites (41%) and Blacks (39%). When looking at the percentage of patients who had NAFLD-related cirrhosis (by ICD-9 codes) by race, the percentages were 4% (Japanese), 3.1% (Latinos), 1.7% (Whites) and 1.5% (Blacks)[44].

Dulai *et al*[42] reviewed 5 studies that assessed baseline liver fibrosis (mostly by biopsy) in patients with NAFLD or NASH. At baseline these 5 studies showed that most (67%) of patients had stage 0/1 fibrosis; 14% had F2; 12% F3 and 7% cirrhosis. Mortality was mainly cardiovascular related (about 40%) followed by cancer (20%) and liver disease (10%)[43]. There were no details comparing races within each study. In fact, one study had only Asians[45] and another 88% Whites[34]. A Canadian study did not mention race or ethnicity[46]. While baseline advanced fibrosis stage (F3/4) varied from 27% in Asians[45] to 12% in Whites[43], the percentages of MetS was also different (63% *vs* 33% respectively).

Within NAFLD, however, NASH on liver biopsy is less common in African-Americans (57%), but not significantly, *vs* Caucasians (73%)[47].

A recent meta-analysis[8] noted that 11 studies assessed stage of fibrosis (mostly by biopsy) in NAFLD and had data on race. The pooled proportion of patients with NAFLD and significant fibrosis (stages 3 and 4) was 19.5% [95% confidence interval (CI): 18.1-20.9]. The percentages were numerically highest in Whites (22.3%) and Hispanics (19.6%) and lowest among Blacks (13.1%). However, differences were not statistically significant for Whites *vs* Hispanics (RR 1.02, 95%CI: 0.94-1.11), and borderline significant for Whites *vs* Blacks (RR = 1.10, 95%CI: 1.00-1.22)[8]. A later paper showed that morbidly obese Black patients (mean BMI > 45) had lower % of NASH (4%) and lower % of fibrosis stages 3 and 4 (1.4%) *vs* Whites (17% and 9% respectively). The 2 groups had similar percentages of DM and hypertension[48]. A retrospective but well detailed study based on liver biopsy found advanced fibrosis (F3/F4) in 16% Caucasians *vs* 2.6% Blacks, despite the fact that the latter had greater BMI and higher DM rates. However, their lipid profile was healthier than Caucasians[49].

The most recent NHANES (1999-2016) evaluation[14] used the US Fatty Liver Index to define NAFLD and two noninvasive marker (FIB-4 and NAFLD Fibrosis Score) to assess advanced liver fibrosis (*i.e.*, stages 3 and 4). The results show that Latinos and Whites had higher likelihood of NAFLD (43% and 33%, respectively), *vs* Asians (20%) and African Americans (19%). Overall, mortality was associated with DM2 and FIB-4 but not race, and was higher in lean or overweight patients *vs* obese[14].

Interestingly, a work by Lomonaco *et al*[50] found that, when metabolic factors are controlled for, hepatic steatosis, inflammation and fibrosis scores (all by histology) were similar between Caucasians and Hispanics. A study assessing biopsy-confirmed NASH and comparing Latinos and Whites reported that the former were younger, had increased carbohydrate intake, and had a lower prevalence of hypertension[31]. However, while there were numerical different rates of F3/F4 (Whites and Blacks 30%, Asians 28% and Latinos 23%) these were not significant. Multivariable analysis identified only age, female gender, HTN and abnormal HOMA-IR as significantly associated with advanced fibrosis, but not race[31].

The preponderance of evidence shows that while Latinos have more NAFLD, they don't have significantly higher rates of advanced fibrosis. Studies based on liver biopsy, except one[31] have shown Black patients to have less fibrosis[8,49]. However, adequate controlling for the variables of the MetS has not been done.

NAFLD is associated with the development of hepatocellular carcinoma (HCC). One report demonstrated that patients with NAFLD have a 10-fold higher chance of developing HCC compared to controls[51]. The overall risk of HCC in NAFLD was low (estimated 0.02/100 patient-years), and it was higher in older (> 65 years) Hispanics and lower in Blacks: these subgroups were not matched by MetS risk[51].

Finding racial differences in mortality (especially liver mortality) in patients with fatty liver requires evaluation of a very large database. A NHANES analysis (1988-1994), looked at (mostly) NAFLD patients and found a correlation between high estimated liver fibrosis (by non invasive tests such as FIB-4) with mortality (both all cause and liver-related) up to 2006[52]. Unfortunately, liver mortality represented only 3% of the total mortality, so there were too few endpoints to make inferences about racial associations[52]. A review of total United States mortality captured in the latest National Vital Statistics (NVSS) database, showed that Hispanics with a diagnosis of NAFLD have lower mortality than Caucasians, although in both groups the trend is towards increased mortality the past 10 years: there was no attempt to adjust the data for underlying metabolic disease[53]. In 2016, the NIAAA issued a report on liver cirrhosis mortality. The age-adjusted mortality rates for cirrhosis "without mention of alcohol" were 50% lower in Blacks *vs* whites, but NAFLD codes were not specifically reported[54]. However, a paper looking at hospital charges, length of stay and mortality in non-Federal Community hospitals across the United States, showed that mortality was not statistically different across races in patients admitted with a NAFLD diagnosis[55].

More data on race-specific cirrhosis, HCC and mortality rate in patients with NAFLD are needed.

Response to therapy

There is considerably less data on racial responses to therapy for NAFLD. To date, this includes mainly weight loss strategies, including bariatric surgery.

Vilar-Gomez *et al*[56] published a small but well-designed study enrolling Cuban patients. They histologically documented decreased liver fibrosis (45% of patients) and resolution of NASH (90% of patients) when a 10% or greater weight loss was achieved [56]. The latter endpoint was noted in 10% of patients, all of them Cuban. However, diet and exercise may be beneficial to decrease liver steatosis in the absence of weight loss[24].

Behavioral therapy resulted in a maximum weight loss of 5 kg in Black patients, significantly less than 13 kg in Whites[57]. Metformin for one year significantly increased HDL-cholesterol (by 1-2 mg/dL) in White and Black patients: In Hispanics the HDL declined by approximately 1 mg/dL[58]. Lorcaserin lead to a placebo-adjusted weight loss of 3.2 kg, 2.7 kg and 1.4 kg in Whites, Blacks and Hispanics respectively[59]. Semaglutide as an injection for DM control showed minor changes in weight in different races[60].

A study in 3268 patients (1561 Hispanics, 660 Blacks, and 1047 Whites) examined the percentage of excess weight loss (EWL) after Roux-en-Y gastric bypass or adjustable gastric band placement[61]. EWL differed by ethnicity (-53% in Hispanics, -50% in Whites and -43% in Blacks), at 6 months post-operatively. These differences persisted at 1 and 2 years after surgery (-69%, -69% and -58%, respectively)[61]. A prior meta-analysis, looking at the percentage of EWL (between 12 and 24 mo post-

operatively) confirmed an average of 8% lower weight loss in Blacks compared to Whites[62].

In the future, large phase 3 studies using new NASH medications may uncover possible racial differences in baseline histology, and clinical liver outcomes. Those studies will have prospectively collected metabolic data, permitting investigators to assess risk by race, controlled for variables of the MetS[23].

CONCLUSION

In conclusion, there is convincing evidence that the prevalence of NAFLD depends on genetics and the prevalence of the MetS. Its individual components impact fatty liver differently in different populations. Socio-economic, dietary and lifestyle differences may also explain reported racial differences but have not been thoroughly studied in the NAFLD arena. In the United States, NAFLD and NASH seem more prevalent in Hispanics, however most studies have not been controlled for the individual variables of MetS, and this may have overestimated racial differences. African Americans have a lower prevalence of hypertriglyceridemia and this contributes to their lower prevalence of NAFLD despite higher rates of hypertension and DM. Fibrosis scores seem similar in Whites and Latinos: In most biopsy studies, Blacks have shown lower hepatic inflammation and fibrosis levels. There is no evidence that NAFLD mortality is higher in Latinos, and it may be lower in Blacks. We believe that there is presently insufficient evidence to confidently conclude that race, per se, plays a role in the development of the complications of NAFLD. Further studies, appropriately controlled for diet, exercise, and MetS parameters are needed.

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MINIREVIEWS

Torsion of spleen and portal hypertension: Pathophysiology and clinical implications

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Abstract

The displacement of spleen from its normal location to other places is known as wandering spleen (WS) and is a rare disease. The repeated torsion of WS is due to the presence of long pedicle and absence/laxity of anchoring ligaments. A WS is an extremely rare cause of left-sided portal hypertension (PHT) and severe gastric variceal bleeding. Left-sided PHT usually occurs as a result of splenic vein occlusion caused by splenic torsion, extrinsic compression of the splenic pedicle by enlarged spleen, and splenic vein thrombosis. There is a paucity of data on WS-related PHT, and these data are mostly in the form of case reports. In this review, we have analyzed the data of 20 reported cases of WS-related PHT. The mechanisms of pathogenesis, clinico-demographic profile, and clinical implications are described in this article. The majority of patients were diagnosed in the second to third decade of life (mean age: 26 years), with a strong female preponderance (M:F = 1:9). Eleven of the 20 WS patients with left-sided PHT presented with abdominal pain and mass. In 6 of the 11 patients, varices were detected incidentally on preoperative imaging studies or discovered intraoperatively. Therefore, pre-operative search for varices is required in patients with splenic torsion.

Key Words: Wandering spleen; Splenic torsion; Left-sided portal hypertension; Gastric variceal bleeding; Splenectomy

Core Tip: Wandering spleen (WS) is a rare disease. The repeated torsion of WS is due

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to the presence of long pedicle and absence/laxity of anchoring ligaments.WS is an extremely rare cause of left-sided portal hypertension and severe gastric variceal bleeding. This review comprehensively describes the pathophysiological mechanisms, clinico-demographic profile, and clinical implications of torsion of the spleen. In patients with splenic torsion, varices can be detected incidentally on preoperative imaging studies or intraoperatively. Therefore, pre-operative search for varices is required in patients with splenic torsion.

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INTRODUCTION

The displacement of spleen from its normal location to other places is known as wandering spleen (WS). It is a rare clinical entity in which the spleen is attached by a long vascular pedicle. It was first described by Van Horne in 1667[1]. WS-also known as splenoptosis or ectopic spleen or floating spleen or aberrant spleen-most commonly located in the pelvic cavity.

The spleen is anchored to its normal position by splenorenal and gastrosplenic ligaments. Due to absence or laxity of these ligaments, the spleen is displaced from the left hypochondrium to other places in the abdominal cavity. The laxity or absence of splenorenal and gastrosplenic ligaments can be caused by congenital or acquired pathology. Congenital causes of WS include an incomplete fusion of the dorsal mesogastrium and the parietal peritoneum, resulting in the absence of anchoring ligament formation[2,3]. While acquiring causes include pregnancy due to hormonal effects, lax abdominal wall in multiparous women or obese persons and splenomegaly. More than one risk factor can be involved in the pathogenesis of WS

The true incidence of WS is unknown. The incidence of WS was 0.2% in splenectomies performed in 1003 patients. The patient is usually asymptomatic and remains undiagnosed for long periods. A WS is usually diagnosed in childhood and the third and fourth decades of life, with a strong female preponderance. In a study, Viana *et al* [4] reviewed the data of 266 cases of WS and found that the average age at the time of diagnosis was 25.2 years, with a male-female ratio of 3.3:1.

More than half of the patients present with recurrent abdominal pain due to repeated torsion. Abdominal mass is the most common finding on examination[5-8]. In a systematic review, 197 (M:F = 1.5:1) pediatric patients with WS were analyzed, and abdominal pain was found to be the most frequent (43%) symptom[7]. Another systematic review was performed in 376 surgically treated patients of WS. Abdominal pain and abdominal mass were the most frequent clinical features. More importantly, nearly half of the patients presented with acute clinical onset[8]. The diagnosis of a complicated WS needs a high index of suspicion. Delay in diagnosis can lead to emergency surgeries. It can be avoided by reducing time-consuming repeated imaging studies[9].

WANDERING SPLEEN AND SPLENIC TORSION: AN OVERVIEW

WS can be complicated with splenic torsion, splenic infarction, hypersplenism and left-sided portal hypertension (PHT). Acute abdomen, splenic abscess, acute pancreatitis, pancreatic necrosis, gastric volvulus, pancreatic volvulus, intestinal obstruction, and gastric outlet obstruction are the other rare complications of WS[5,10-15].

Splenic torsion is the most common complication of WS. In a systematic review, splenic torsion was diagnosed in 56% of pediatric patients with WS[7]. The repeated torsion of WS is due to the presence of long pedicle and absence/Laxity of anchoring ligaments. Torsion usually occurs clockwise. Torsion of pedicle leads to increased back pressure in splenic vein (SV), resulting in parenchymal congestion, splenomegaly, and hypersplenism. Extreme torsion can lead to the arterial supply being compromised, causing infarction and necrosis. The enlargement of the spleen further aggravates

splenic torsion. Torsion can be precipitated by movements of the body, changes in intra-abdominal pressure, peristalsis, or distension of adjacent organs[16,17].

WS is diagnosed using abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging. US demonstrates the absence of spleen from its normal position and its location elsewhere in the abdominal cavity. US examination is limited by the presence of gas, suboptimal assessment of adjacent viscera and difficulty in identifying twisted pedicle and the infarcted spleen. CT scan is the preferred modality of investigation for the diagnosis of WS. CT scans delineate the exact location of the spleen and demonstrates the twisting of the splenic pedicle known as whirl sign-alternating radiolucent and radio dense bands formed due to splenic vessels and adjacent fat. The whorled appearance of splenic vessels and surrounding fat is diagnostic of splenic torsion. CT scans also demonstrate other associated findings, such as ascites and entrapment of the adjoining viscera secondary to torsion. Scintigraphy and angiography can also diagnose WS but are rarely used due to their high costs and invasive nature[18-21].

Splenopexy is the first-line treatment of WS and is indicated even in asymptomatic patients (except elderly and high-risk surgical candidates) because of the potential risk of serious complications. Detorsion and splenopexy are preferred in patients with torsion, whose spleen parenchyma is shown to be viable and without signs of hypersplenism. Splenectomy is considered in cases of splenic infarction, splenic vessel thrombosis (SVT), portal vein thrombosis (PVT), hypersplenism, PHT, and suspicion of cancer[5,22]. In recent years, there has been a growing trend toward more conservative and minimally invasive approaches, such as splenopexy or laparoscopic techniques[4,7,8,23,24]. Viana *et al*[4] reviewed the data of 266 cases of WS and found that splenectomy and splenopexy were performed in 70% and 29% of patients, respectively. The majority of patients had open surgery (79%), while about one-fifth of patients were treated using laparoscopic surgery. A very recent systematic review by Ganarin *et al*[7] showed that splenectomy and splenopexy were performed in 55% and 39% of surgically treated patients (n = 197), respectively. About half of the splenopexies were performed using minimally invasive surgery. Frequently used techniques were the placement of a mesh (46%) or the construction of a retroperitoneal pouch (31%). Overall, splenopexy was effective in 95% of cases.

SPLENIC TORSION AND PORTAL HYPERTENSION: PATHOPHYSIOLOGICAL MECHANISMS

Left-sided PHT, also known as segmental or sinistral PHT, is a rare cause of gastric variceal bleeding. It usually occurs as a result of SV occlusion caused by splenic torsion, extrinsic compression of splenic pedicle and SVT. Left-sided PHT should be suspected in those who have gastric and/or splenic varices in the absence of esophageal varices and deranged liver function test. WS is an extremely rare cause of left-sided PHT[16].

The torsion of WS occurs mainly due to absence/laxity of anchoring ligaments, long pedicle and splenomegaly. Splenic torsion can also be predisposed by other causes of splenomegaly, including chronic liver disease (CLD), malaria, myeloproliferative disease, lymphoproliferative disorders, infectious mononucleosis, and splenic haemorrhagic cyst[5]. The torsion of the splenic pedicle leads to increased back pressure in the SV, resulting in splenic parenchymal congestion and splenomegaly. The occlusion of the SV can be caused by the chronic torsion of the splenic pedicle, SVT, and direct mechanical compression by an enlarged spleen. SV occlusion leads to impaired venous return and retrograde filling of the short gastric and left gastroepiploic veins. Decompression of splenic venous outflow occurs through the short gastric veins, coronary vein, and left gastroepiploic veins, producing gastric varices[16]. A few cases of mesenteric varices have been described in WS patients without PVT. The mechanical occlusion of the portal vein at the level of superior mesenteric and SV confluence due to splenic torsion can explain the mechanism of formation of mesenteric varices[25-28]. The coexisting gastric volvulus can further obstruct the venous drainage of the proximal stomach, leading to the development of PHT[12]. The pathophysiologic mechanisms of PHT in WS patients are shown in Figure 1.

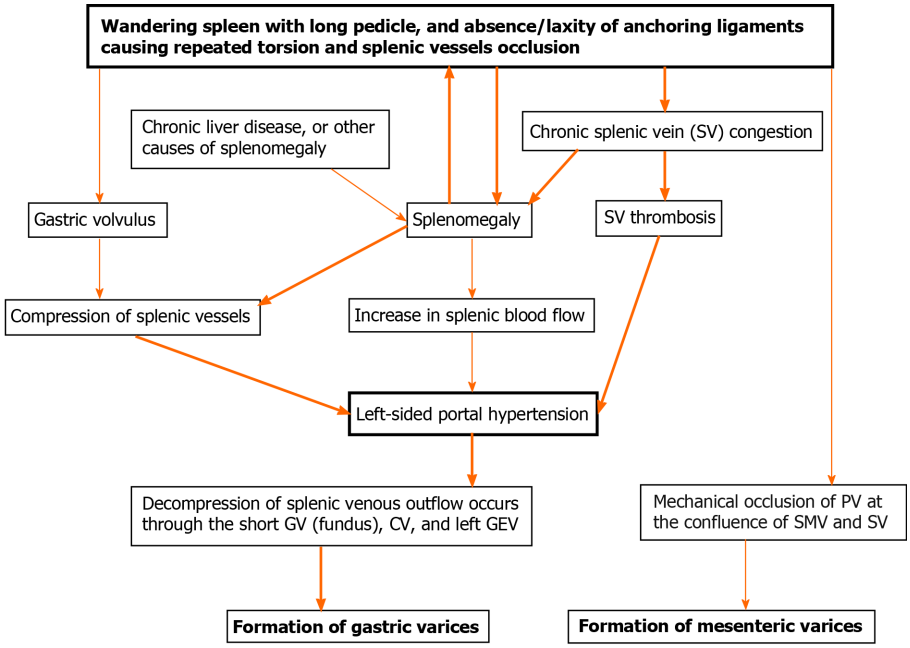

Figure 1 Schematic diagram of the mechanisms of varices formation in wandering spleen with splenic torsion. SV: Splenic vein; GV: Gastric varices; CV: Collateral vein; GEV: Gastroepiploeic vein; SMV: Superior mesenteric vein; PV: Portal vein. Please note that thick arrow denotes more frequent mechanism and thin arrow denotes less frequent mechanism.

SPLENIC TORSION AND PORTAL HYPERTENSION: CLINICAL IMPLICATIONS

Left-sided PHT is a rare manifestation of WS with torsion. Approximately 20 cases of WS with left-sided PHT have been described in English medical literature[5,11-13,25-39]. The clinico-demographic profile of the reported cases of patients with WS and PHT are summarized in Table 1. The majority of patients were diagnosed in the second or third decade of life (mean age: 26 years), with a strong female preponderance (M:F = 1:9). WS patients with PHT present earlier than WS patients without PHT. Upper gastrointestinal bleeding was the most common presenting complaint, followed by abdominal pain. The majority of the patients had gastric varices without esophageal varices, which is suggestive of left-sided PHT. Mesenteric varices and splenic varices were identified in about 25% of patients. In 14 patients, gastric varices were diagnosed in endoscopy or gastrointestinal series. In five patients, the presence of varices was only identified in imaging studies. One patient had intra-operative diagnosis of PHT. Splenectomy was performed on all patients, and the follow-up details of 14 patients revealed the disappearance of varices.

Esophageal varices are absent in WS patients with left-sided PHT. Coexisting CLD has been described in two-patients with WS[40,41]. Splenomegaly resulting from CLD can further aggravate the splenic torsion and PHT[40]. PVT has also been described in patients with WS[28,42,43]. Hence, the presence of esophageal varices in patients with WS warrants careful evaluation for coexisting CLD and PVT.

Splenectomy eliminates PHT, provides symptomatic relief, and prevents the relapse of varices (Table 1). However, splenectomy in patients with undiagnosed collaterals can be tricky due to increased blood loss. Splenectomy in these patients can necessitate additional transfusions of blood and blood products. Eleven patients of WS with undiagnosed PHT were presented with abdominal pain and mass. In six patients, varices were detected incidentally on preoperative imaging studies or discovered intraoperatively. Therefore, pre-operative search for varices with endoscopy and a good quality CT-scan are useful in patients with splenic torsion. These patients also require intra-operative inspection for small collaterals and careful dissection.

CONCLUSION

The repeated torsion of WS can lead to splenomegaly, SVT, hypersplenism, and, rarely left-sided PHT. The patients with WS and PHT usually present with gastric variceal

Table 1 Summary of reported cases of wandering spleen with portal hypertension, *n* (%)

Clinico-demographic features	Remarks	Frequency (%)
Reported cases (*n*)		20
Mean age (range)		26.15 (12-55) yr
Male:female ratio		1:9
Presenting complaints	Upper GI bleeding	9 (45)
	Abdominal pain	8 (40)
	Abdominal mass	2 (10)
	Acute pancreatitis	1 (5)
Type of varices	Gastric varices	18 (90)
	Mesentric varices	5 (25)
	Splenic varices	6 (30)
Diagnosis of varices	Endoscopy	12 (60)
	GI series	2 (10)
	Imaging only	5 (25)
	Intra-operative	1 (5%)
Venous thrombosis	Splenic vein	3 (15)
	Portal vein	1 (5)
Splenic infarction		4 (20)
Definitive treatment	Splenectomy	20 (100)
Post-operative variceal status	Documented (*n*)	14/20 (70)
	Resolved (*n*)	14/14 (100)

GI: Gastrointestinal.

bleeding. Nearly half of the WS patients with PHT can present without variceal bleeding. Splenectomy or splenopexy in patients with undiagnosed collaterals can be tricky due to increased blood loss. Therefore, pre-operative search for varices is required in patients with splenic torsion. They also require intra-operative inspection for small collaterals and careful dissection. Esophageal varices are absent in WS patients with left-sided PHT. Hence, the presence of esophageal varices in patients with WS warrants careful evaluation for coexisting CLD and PVT.

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MINIREVIEWS

Impact of coronavirus disease 2019 on prevention and elimination strategies for hepatitis B and hepatitis C

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has resulted in significant morbidity and mortality since its first case was discovered in December 2019. Since then, multiple countries have witnessed a healthcare system collapse due to the overwhelming demand for COVID-19 care. Drastic measures have been taken globally in order to curb the spread of the virus. However, those measures have led to the disruption of other aspects of healthcare, increasing the burden due to other medical conditions. We have also stepped back in achieving the ambitious goal set in place by World Health Organization to eliminate viral hepatitis as a public threat by 2030. Hepatitis B and C are chronic conditions with a significant worldwide burden, and COVID-19 has resulted in many hepatitis elimination programs slowing or stopping altogether. In this review, we elucidate the impact of the ongoing COVID-19 pandemic on the interventions targeted towards the elimination of hepatitis B virus and hepatitis C virus. Some of the salient features that we have covered in this review include hindrance to screening and diagnostic tests, neonatal vaccinations, the transmission dynamics affecting hepatitis B virus and hepatitis C virus, role of limited awareness, restrictions to treatment accessibility, and disparity in healthcare services. We have highlighted the major issues and provided recommendations in order to tackle those challenges.

Key Words: COVID-19; Chronic hepatitis; Review literature; Vaccine; World Health Organization; Pandemics

Core Tip: There has been a multi-fold impact of the pandemic on viral hepatitis elimination strategies. Due to supply chain disruptions, hepatitis B virus vaccination campaigns have been halted. Increased preference for home deliveries, poor antenatal

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care, and unavailability of at-birth hepatitis B virus vaccine has increased the risk of vertical transmission. With needle-sharing activities on the rise and closure of harm reduction centers, the spread of blood-borne infections including the hepatitis C virus has risen. Hospitals are either being avoided due to the fear of contracting severe acute respiratory syndrome coronavirus 2 or are being converted into coronavirus treatment wards, resulting in poor management of patients.

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INTRODUCTION

In December 2019 the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated and identified in Wuhan, China[1]. The coronavirus disease 2019 (COVID-19) pandemic that ensued, has led to 2.47 million deaths as of February 21, 2021[2].

This medical emergency shed light upon our fragile healthcare system worldwide and its vulnerabilities including the immense vacuum questioning our preparedness for the next pandemic[3]. Although we were able to achieve making vaccines in record time[4], the impact on human life and our economies are yet to be quantified.

On the other hand, hepatitis B virus (HBV) and hepatitis C virus (HCV) have had their impact quantified and have been studied for decades. In 2016, the World Health Organization (WHO) estimated the prevalence of chronic hepatitis B to be 257 million worldwide[5], while it was 71 million for chronic hepatitis C. Chronic hepatitis has a worldwide burden that is mostly clinically silent, as it goes undiagnosed in most low to middle-income countries (LMICs)[6,7].

We evaluated the sustainable development goals (SDGs) set in place by the WHO for the task of eliminating hepatitis B and C as a public health threat by 2030[8]. The SDGs include goals such as coverage of three-dose HBV neonatal vaccine, prevention of mother-to-child transmission, and harm reduction services such as sterile syringe set distribution for people injecting drugs. The efforts done to achieve these sustainable goals have been severely compromised due to the current pandemic.

Although it is debatable that having chronic viral hepatitis influences the outcomes of having the COVID-19[9-12], worse outcomes with acute respiratory distress syndrome in COVID-19 can be expected due to impaired immunity[1,13].

This review elucidates the impact of the COVID-19 pandemic on chronic viral hepatitis B and C; since hepatitis A and E contribute relatively less significantly to morbidity, mortality, and long-term impact[8]. We evaluated SDGs and current existing data in light of them. Some of the salient features, as shown in Figure 1, can be identified as a hindrance to screening tests and neonatal vaccinations, the transmission dynamics affecting HBV and HCV, the role of limited awareness, restrictions to treatment availability, and disparity in healthcare services.

DISRUPTED HEPATITIS B VACCINATION CAMPAIGNS

The COVID-19 pandemic brought in conditions and circumstances that were unusual for countries and the world as a whole with factors not previously anticipated. Although the rate of hepatitis B vaccinations has been steadily on the rise since the 1990s, we have learned that geopolitical factors, financial priorities, the image of the government, and the health sector have played a huge role in their success or failure [3]. A recent example within an epidemic can be found in the Ebola outbreak in 2013 in West Africa. Due to disrupted vaccination services, limited availability, and allocation of funds, a sharp rise in the incidence of measles was reported during the epidemic and in the months that followed[14].

The Institute for Health Metrics and Evaluation at the University of Washington showcased an overall drop in global vaccination coverage in 2020 to levels as low as those seen in the 1990s with words depicting its severity as "… we have been set back

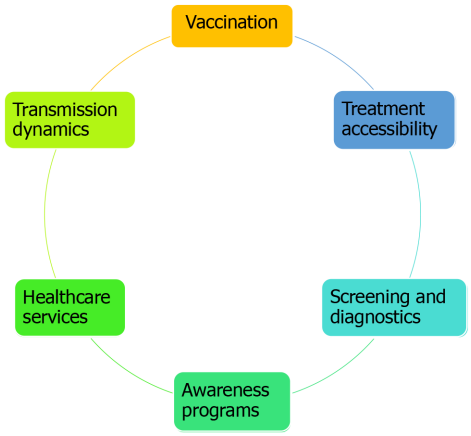

Figure 1 This wheel represents, in no particular order or flow, the focal points that give an insight to the impact of coronavirus disease 2019 on viral hepatitis.

25 years in 25 wk"[15]. High-income countries like the United States had a drop in pediatric vaccinations being ordered and administered after an emergency was declared on March 13, 2020[16]. Between February and April of 2020, the United Kingdom also saw a drop of almost 20% in the administration of measles, mumps, and rubella vaccines, as compared to 2019[17].

Reduced availability and provision of HBV vaccines during this COVID-19 pandemic will have detrimental effects on the incidence of HBV during infancy, childhood, and in later years, thus increasing the chances of chronicity in the generation to come. This severely impedes our progress to the 2030 elimination goals set in place by WHO[8].

Vaccination rates are not in line with the target goals set in SDGs in the LMICs[18], and poor screening in the case of viral hepatitis might pose a greater threat in the long run compared to the pandemic.

Despite being a high-value investment, vaccines are the most cost-effective way of avoiding disease[19]. The decline in measles, mumps, polio, and yellow fever can be credited to this. Nothing can truly represent the effectiveness of vaccines other than the global eradication of the smallpox virus. This disfiguring disease that had infected over 11 million people from 1920 to 1977, was eradicated in 1978 following a world-wide vaccination campaign.

Although the HBV vaccine is an effective modality, this modality does not exist for HCV. Progress has been made on HCV over the past few decades with the year 2020 being its limelight when Drs. Michael Houghton, Harvey Alter, and Charles Rice were awarded the Nobel Prize in Physiology/Medicine for their discovery of the HCV[20]. This raises hopes for a cure and even so a vaccine that will be beneficial for the years to come. Eliminating HCV as a global threat should be a priority as the disease is present actively in 71 million people and accounts for 500000 deaths annually[21,22].

Abbas *et al*[23] conducted a benefit-risk analysis study in Sub-Saharan Africa during the pandemic. The study compared the SARS-CoV-2 pandemic and its impact on routine childhood vaccination programs, encompassing several preventable diseases including hepatitis B as well as others such as diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, rotavirus, measles, meningitis A, rubella, and yellow fever. The model found that in a high-impact scenario, for every one excess COVID-19 death attributable to SARS-CoV-2 infections acquired during routine vaccination clinic visits, 84 deaths in children could be prevented by sustaining routine childhood immunization in Africa[23].

HBV vaccination campaigns have also been halted due to disruptions in the supply chain. LMICs regions like Pakistan and Sub-Saharan Africa were faced with a shortage of HBV vaccines during the pandemic[24,25]. The latter had breakdowns in the cold chain and limited financial support from the government[25]. Despite healthcare services being ramped up, changes in healthcare-seeking behavior led to a change in attitude resulting in reluctance for availing vaccinations[25]. The acceptance and readiness of vaccinations are closely linked to the fear of the linked disease and the trust placed in the government and its practices[26-28]. Due to heightened misinformation on media outlets and a general chaotic atmosphere worldwide, people had an anti-science sentiment and heightened distrust in most places[3]. Furthermore, the pandemic resulted in increased home-births, which hindered access to vaccines,

limiting dosages being given at birth[29].

INTERRUPTION IN THE TRANSMISSION DYNAMICS OF HEPATITIS B AND C

The actual numbers to quantify the effects on transmission dynamics in viral hepatitis spread are limited[3]. Even though as a result of movement restrictions and worldwide lockdowns, the physical spread is expected to decrease, such limiting behaviors give rise to risky attitudes on the part of undiagnosed and stable hepatitis. Alcohol consumption and unprotected sexual intercourse have increased. Drug abuse has been on the rise during the pandemic[30]. Disruption of needle exchange programs and harm-reducing services are already scarce in LMICs and with lockdowns in place and financial constraints, such limitations would result in cross-contamination of blood-borne viruses *via* needles especially HCV[31]. Stowe *et al*[32] reported the closing down of numerous harm reduction service centers in South Africa leading to rising in overdose cases in street-based heroin-using individuals. In general, the incidence of viral hepatitis will increase by the closing of harm reduction centers [33].

In Sub-Saharan Africa, liver diseases are highly prevalent although extremely underdiagnosed[25]. Being unaware of their viral hepatitis status creates ground for increased transmission dynamics in the population that already has limited funding for screening, vaccinations, and treatment as a whole. Government efforts will need a clear pragmatic strategy as the pandemic progresses to counter such transmission dynamics.

The chances of vertical transmission have also increased as the preference for home deliveries has surged during the pandemic[29]. There is an increased likelihood of missing out on routine HBV and HCV antenatal screening tests. The initial dose of HBV vaccine usually administered at birth could either be delayed or skipped. The intrapartum administration of hepatitis B immunoglobulin to decrease the vertical transmission has also been affected due to home deliveries. These above-mentioned limitations all increase the chances of vertical transmission, which will affect a generation that is to come, making them highly susceptible to chronic hepatitis due to early exposure.

LACK OF AWARENESS PROGRAMS FOR HEPATITIS DURING COVID-19 PANDEMIC

Lack of awareness is an issue faced by multiple LMICs. Increasing the awareness amongst the general population about modes of transmission of viral hepatitis, symptoms, screening and diagnosis, management, and follow-up plays an important role in elimination programs[34]. Measures taken during the pandemic have led to the closure of community-based education and screening programs and in-person events. A decrease in voluntary activities such as the NoHep program seems to have decreased the diagnosis rate[35].

A lack of information dispersal has been noticed during the pandemic in regards to people suffering from viral hepatitis. According to a study conducted by the World Hepatitis Alliance, 99 countries were sent a survey to access viral hepatitis services during the pandemic. Only 39 (30%) of 131 analyzable responses indicated adequate information on COVID-19 had been provided to people living with viral hepatitis in their country. One participant from Ukraine said that no specific information had been provided for people living with viral hepatitis, although information had been provided for people living with human immunodeficiency virus[36].

In low-income countries like Pakistan, new and known cases of HBV and HCV patients were compared between January to June of 2020 to the corresponding months in 2019. These 23 centers were mostly government-run with free of cost hepatitis treatment being provided. All the centers remained open, with no shortage of staff. Despite this, the centers still recognized a lesser number of new people coming in for treatment; for example, in January 2020 a mean number of 45 new patients registered in these centers when there were no cases, while in June 2020, the number has fallen by 84%[37]. This highlights the lack of awareness amongst individuals regarding the seriousness of viral hepatitis.

IMPAIRMENT IN SCREENING AND DIAGNOSTIC FACILITIES

One of the most important steps in eliminating viral hepatitis is to screen and diagnose in a timely fashion in order to start treatment and prevent transmission. Underdiagnosis is a key hurdle in eliminating viral hepatitis, as it can have a long-term impact on transmission dynamics.

In 2017, it was estimated that 91% of patients with chronic HBV and 80% of patients with chronic HCV had not been diagnosed. In a World Health Alliance survey conducted across 32 LMICs, only 36% of the respondents reported that testing services were accessible to people. The key issues identified in the survey were either the closures or avoidance of testing services[31]. A study revealed that within Sub-Saharan Africa, there was a reduction of 71%, 95%, and 83% in the number of patients in the hepatitis clinics of Burkina Faso, Tanzania, and the Gambia, respectively, from January to April 2020[38]. The primary reason for such a striking decline in the use of outpatient services was attributed to the fear of contracting the severe acute respiratory syndrome coronavirus 2. Similarly, a decline of 84% in HBV and 74% in HCV positive patients coming for a follow-up visit in district hepatitis clinics were recorded in Pakistan from January to June 2020[37].

In order to control the pandemic, multiple aggressive measures have been taken worldwide, leading to financial disruption of hospitals and healthcare services, often resulting in their closures[39]. There have also been shortages in the testing reagents of HBV and HCV due to global supply chain disruption. In Italy, a law was enacted in February 2020 to conduct graduated birth cohort screening for hepatitis, however, it had not been put into action as of May 2020. In Egypt, all the ongoing screening programs were also suspended in March 2020, as reported by Blach *et al*[40] to reserve polymerase chain reaction tests for COVID-19; all polymerase chain reaction testing for viral hepatitis was halted in Pakistan[37].

REDUCED ACCESS TO TREATMENT FACILITIES FOR CHRONIC HEPATITIS

In most countries, travel bans have been enforced, making access to critical care difficult. In multiple high-income countries, continuity of care is being maintained by utilizing telemedicine services. This has made it convenient for patients to have access to remote healthcare. However, in LMICs including Sub-Saharan Africa, telemedicine is impractical due to a lack of resources including cell-phones, internet services, and modes of payment[25]. The task of generating dedicated phone numbers for gastroenterology and hepatology services and spreading awareness regarding telemedicine amongst the population is not easily established in communities with a low literacy rate. Furthermore, it is difficult for the patients to understand or perform the investigations that the doctor asks them to do.

Even though all the LMICs are not facing or responding to the pandemic in the same way, there has been a global negative impact on access to treatment and care. For instance, even though a strict lockdown was not imposed in Egypt, HCV management centers had a 50% reduction in new patients and follow-ups[40]. A study conducted across three clinical sites in the United States, Japan, and Singapore reported a significantly decreasing trend in the number of patients who visited liver clinics across the three clinical sites during February, March, and April in 2018, 2019, and 2020[41]. Although most Spanish harm reduction centers continued to operate during the pandemic, there was a reduction in the number of clients using them, which resulted in decreased testing and increased discontinuation of ongoing hepatitis C treatment [42]. A web-based survey conducted in Italy revealed that initiation of HBV and HCV treatment was deferred in 23% of the centers, and even in patients considered at high risk for serious complications, treatment had been started in only 20%-28% of the cases [43].

In many countries including Egypt, medications are not manufactured and are imported from other countries. Interruption of the supply chain and necessary reallocation of healthcare resources has resulted in a remarkable shortage of medications for viral hepatitis, as reported by studies conducted in Egypt[44], Sub-Saharan Africa[38], and Pakistan[37]. In Italy, 26% of the hepatology wards had been converted to COVID wards, and 33% had bed reductions[43].

As a result of interrupted and substandard treatment of viral hepatitis, there is an increased risk of disease flares that could promote transmission and also increase resistance to viral drugs. Routine monitoring of laboratory investigations including

liver function tests and complete blood counts were also significantly reduced because of increased priority given to COVID tests, as reported by Mustafa *et al*[37]. This is likely going to result in higher rates of severe worse outcomes such as decompensated liver disease and hepatocellular carcinoma. Certain reports have suggested that medications such as tocilizumab and corticosteroids, which are commonly being used to treat COVID-19 infections, can result in the reactivation of dormant HBV infection [45,46]. This may be an important cause of increased morbidity and mortality in patients with a prior HBV infection as a rapid rise in alanine aminotransferase levels following viral reactivation can in some cases lead to a fulminant hepatic failure. Hence, antiviral prophylaxis against HBV reactivation should be considered[47]. Furthermore, it is also recommended that liver tests should be performed routinely in all COVID-19 patients, particularly the ones receiving remdesivir and tocilizumab, regardless of their baseline values[48].

WIDENING DISPARITIES IN HEPATITIS-RELATED HEALTHCARE

The pandemic is causing health care and socioeconomic inequalities between regions and countries. The communities most underserved by the healthcare systems have an increased risk of contracting the SARS-COV-2 virus and are more likely to have non-communicable comorbidities, which further increases the chances of COVID associated complications[3,49].

The WHO survey reported that in LMICs, treatment access has been hampered due to movement restrictions and suspension of clinical services. Fifty-two percent of the frontline health workers from the 32 LMICs reported that treatment was not accessible by patients[31]. However, only 8% of the respondents from the United States reported an issue with access to treatment. This highlights the discrepancy between high-income countries and LMICs, the latter suffering from more severe consequences as a result of the pandemic[36].

National economies are crumbling and most giants in the varied sectors are downsizing to get through the pandemic. This increases the risk for people living in countries where universally accessible health care systems are not present, especially in rural areas of LMICs like India and Nigeria where daily wage earners are limited to healthcare by access and out-of-pocket expenditure for medical facilities[36]. Similar cases have also been accounted for in the United States, a high-income country where almost 6.2 million people have lost their jobs, thus losing the medical insurance linked to their jobs, during the pandemic[50]. Health disparity has affected almost everyone in one way or the other but the basic difference lies in access to basic medical help.

Primary care settings and general practitioners, which have an essential role in hepatitis elimination, are now focusing on the COVID-19 pandemic and this change can further reduce both diagnosis and treatment rates of hepatitis patients. Countries with a low number of doctors to population ratio will be affected more[51,52].

OVERCOMING THE CHALLENGES

A pulse survey conducted across 100 countries of five different WHO regions not only provided an insight on the extent of healthcare disruption but also listed a few strategies that have been adopted by those regions to mitigate the impact of COVID-19 on essential health services during the pandemic[53]. Based on the approaches that the responding countries had implemented to overcome the healthcare disruptions, we have come up with a list of recommendations that can be utilized by researchers and policymakers to prevent transmission, increase screening and diagnosis, and provide prompt management of patients with HBV and HCV, to counter the impact of COVID-19 pandemic (refer to Figure 2). We can use this crisis as an opportunity to develop a healthcare system that is sustainable and does not collapse in case of continued morbidity and mortality due to the pandemic.

CONCLUSION

There is no doubt that drastic measures needed to be taken in order to curb the pandemic, but as a result of those measures, we might be stepping backward in achieving the goal of eliminating viral hepatitis by 2030. There is a dire need to come

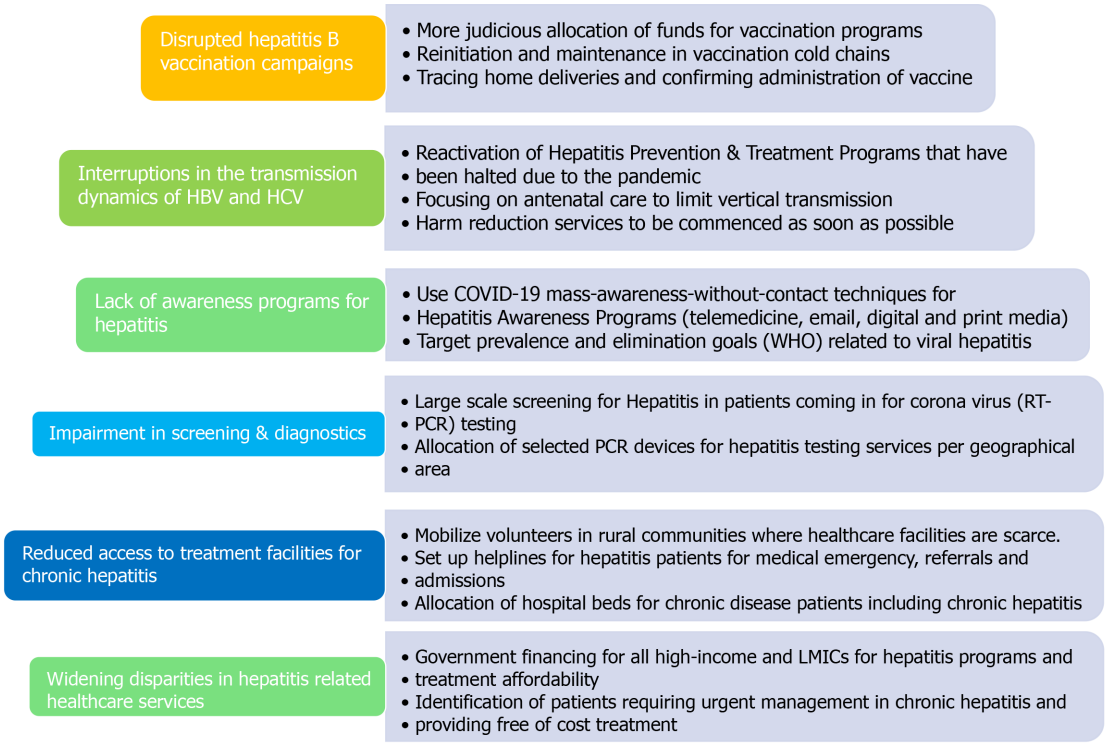

Figure 2 Overcoming the challenges. This figure addresses possible recommendations and solutions to the coronavirus disease 2019 pandemic crisis that has and is affecting our goal of achieving 2030 World Health Organization goal for elimination of chronic hepatitis B virus and hepatitis C virus. HBV: Hepatitis B virus; HCV: Hepatitis C virus; RT-PCT: Reverse transcriptase polymerase chain reaction.

up with guidelines that guarantee consistent care of patients with viral hepatitis, in case there is another wave of the pandemic. The impact of COVID-19 is going to extend beyond just the morbidity and mortality related to that disease. Hence, elimination efforts for viral hepatitis must be resumed as soon as possible.

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ORIGINAL ARTICLE

Retrospective Study

Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children and adolescents.

AIM

To determine the prevalence and risk factors of steatosis and advanced fibrosis using transient elastography (TE) in the United States' adolescent population.

METHODS

Using the National Health and Nutrition Examination Survey 2017-2018, adolescent participants aged 13 to 17 years who underwent TE and controlled attenuation parameter (CAP) were included in this study. Forty-one factors associated with liver steatosis and fibrosis were collected. Univariate and multivariate linear regression analysis were used to identify statistically significant predictors.

RESULTS

Seven hundred and forty participants met inclusion criteria. Steatosis (S1-S3), based on CAP, and advanced fibrosis (F3-F4), based on TE, were present in 27% and 2.84% of the study population, respectively. Independent predictors of steatosis grade included log of alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Independent predictors of fibrosis grade included steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure.

CONCLUSION

This study demonstrated a high prevalence of steatosis in the United States' adolescent population. Almost 3% of United States' adolescents had advanced fibrosis. These findings are concerning because a younger age of onset of NAFLD can lead to an earlier development of severe disease, including steatohepatitis, cirrhosis, and liver decompensation.

Key Words: Non-alcoholic fatty liver disease; Fatty liver; Metabolic syndrome; Cirrhosis, national health and nutrition examination survey; Pediatric; Adolescents

Core Tip: Adolescents in the United States were found to have a high prevalence of non-alcoholic fatty liver disease, which was estimated to be 27%. Nearly 3% were found to have advanced fibrosis diagnosed by transient elastography. The severity of steatosis was associated with alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Risk factors of fibrosis included steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure.

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INTRODUCTION

With the rise of obesity and metabolic syndrome among younger populations, non-alcoholic fatty liver disease (NAFLD) is a growing concern in adolescents. NAFLD has become the most common cause of chronic liver disease in children and adolescents, with a prevalence previously estimated to be 3%-10% in the global pediatric population[1,2]. The prevalence of NAFLD in children with obesity is exceedingly high at 40%-70%[3]. Unsurprisingly, the rates of NAFLD have grown with the rise of childhood obesity over recent decades. Other established risk factors include insulin resistance, metabolic syndrome, and dyslipidemia. The development of NAFLD in childhood is clinically important because of the progressive nature of the disease. Earlier development of NAFLD increases the risk of earlier-onset fibrosis and frank cirrhosis[4].

Liver biopsy is the gold-standard diagnostic test for NAFLD. It not only confirms the diagnosis of NAFLD, but can also grade the level of inflammation and stage the liver fibrosis. However, this invasive procedure is ill-suited to serve as a general screening tool. Non-invasive alternatives which include a physical exam, biochemical tests, and serum biomarkers for fibrosis are not reliable predictors of fibrosis[5,6]. Because fibrosis is the single most important predictor of long-term mortality in NAFLD, transient elastography (TE) has emerged as a non-invasive, reproducible modality in the assessment of patients with NAFLD. Using ultrasound, TE measures the liver stiffness as a proxy for fibrosis stage. Its accuracy has been demonstrated in adult patients with fibrosis secondary to chronic hepatitis B and C, alcoholic and non-alcoholic liver disease, and biliary disease[7-9]. TE's accuracy however is reduced by active hepatitis, increased waist circumference, recent eating, and liver congestion. In adults with NAFLD, TE has an area under the receiver operating characteristic for detecting advanced fibrosis (bridging fibrosis or cirrhosis) of 0.88[10]. In children and adolescents, TE has been validated for chronic liver disease, including NAFLD with similar accuracy, but the data are limited[11-14]. Further research is needed to confirm the liver stiffness thresholds for fibrosis used in the pediatric population.

In addition to liver stiffness, modern TE is also able to calculate the controlled attenuation parameter (CAP). CAP is a quantitative measurement for steatosis. In adults, significant steatosis is defined by having more than 33% of the hepatocytes on a liver biopsy contain steatotic architecture. This correlates to CAP scores greater than 250 db/m[7]. Cut-offs for CAP of 248 db/m, 268 db/m, and 280 db/m were proposed

Statistics (NCHS). The survey collected multiple data sets, including demographic, interviews, physical examinations, and laboratory testing of biologic samples. It is available to the public.

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to correspond with steatosis ≥ 11%, ≥ 33%, and ≥ 66%, respectively[15]. CAP cut-offs in children are suspected to be similar[16,17], but require additional validation.

In the present study, we reported the prevalence of NAFLD characterized by TE and CAP in United States adolescents. Our study employed novel data from the unselected, general cohort of the 2017-2018 National Health and Nutrition Examination Survey (NHANES). We also assessed risk factors associated with NAFLD in this young demographic.

MATERIALS AND METHODS

Study population and study design

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States, conducted by the National Center for Health Statistics (NCHS)[18]. The survey collected multiple data sets, including demographic, interviews, physical examinations, and laboratory testing of biologic samples. NHANES protocol was approved by the NCHS Research Ethics Review Board.

Currently, NHANES has been collecting data in a 2-year cycle. The liver ultrasound transient elastography examination was first introduced in NHANES 2017-2018, which has been released in March 2020 along with other data files. Out of 9254 participants in NHANES 2017-2018, there were 740 participants aged younger than 18 years that met inclusion criteria for this study. The exclusion criteria included: (1) Incomplete TE exam status; and (2) Hepatitis B, hepatitis C, or hepatitis E infection. It is worth noting that alcohol consumption data in participants younger than 18 years is not publicly accessible and has not been published by the time of writing this article.

We included 41 factors associated with liver steatosis and fibrosis in this study: demographic (*i.e.*, age , gender, race/ethnicity, and smoking), body measurement (*i.e.*, body mass index (BMI), waist-to-height ratio, and waist-to-hip ratio), physical activities (days of physical active, hours of TV/videos watching, and hours of computer usage), diet (*i.e.*, energy, protein, carbohydrate, sugars, dietary fiber, fat, saturated fatty acids, and cholesterol), blood pressure (*i.e.*, systolic and diastolic), laboratory tests [*i.e.*, triglycerides, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, alkaline phosphatase, total bilirubin, total protein, albumin, iron, total iron binding capacity, transferrin saturation, ferritin, total cholesterol, direct HDL-Cholesterol, high-sensitivity C-reactive protein, platelet count, HbA1c, fasting glucose, and insulin)]. Additionally, we manually calculated LDL-cholesterol and homeostatic model assessment of insulin resistance (HOMA-IR) from the existing variables.

The above variables were chosen based on the availability of data in NHANES 2017-2018, the usage in clinical practice, and the supporting evidence that demonstrated an association with NAFLD. Additionally, we compared the predictive performance of liver fibrosis indices with the steatosis grade and fibrosis stage. Three liver fibrosis indices used in this study included (1) AST to platelet ratio index (APRI)[19]; (2) Fibrosis-4 (FIB-4) index[20]; and (3) Pediatric NAFLD fibrosis index (PNFI)[21].

Definitions

Assessment by liver ultrasound TE examination resulted in measurement of CAP. CAP is a standardized non-invasive measure for assessment of fibrosis and quantification of steatosis in NAFLD[22]. Cut-off values for median CAP score for different grades of steatosis (S0-S3) were derived from a meta-analysis on CAP technology. S0 was defined as a score of less than 248 dB/m (< 10% steatosis). S1 was defined as a score of 248 to less than 268 dB/m [10% to < 33% steatosis (mild)]. S2 was a defined as a score of 268 to less than 280 dB/m [33% to < 66% steatosis (moderate)]. S3 was defined as a score of 280 dB/m or more [≥ 66% steatosis (severe)][15]. Median CAP scores of 248 dB/m or greater (≥S1) were considered as suspected steatosis.

Participants were also categorized according to stage of hepatic fibrosis. The METAVIR scoring system was used for fibrosis staging (F0-F4)[23]. Stages of hepatic fibrosis ranged from no fibrosis (F0) through intermediate stages of hepatic fibrosis (F1-F3) to end-stage cirrhosis (F4)[24]. The degree of fibrosis was equivalent to the liver stiffness measured in kPa as calculated by liver ultrasound transient elastrography[25]. Stage F0-F1 were defined as a median stiffness < 7 kPa. Stage F2 was defined as a median stiffness of 7 to < 8.6 kPa. Stage F3 was defined as a median stiffness of 8.6 to < 11.5 kPa. Stage F4 was defined as a median stiffness ≥ 11.5 kPa. Participants with a median stiffness of 8.6 kPa or greater (≥F3) were considered to have

advanced fibrosis[26].

BMI was discretized into four classes (1) Underweight, BMI < 5th percentile; (2) Normal, 5th percentile ≤ BMI < 85th percentile; (3) Risk of overweight, 85th percentile ≤ BMI < 95th percentile; and (4) Overweight BMI ≥ 85th percentile[27]. Participants who smoked during the past 30 d or had ever smoked ≥ 100 cigarettes in their entire lives were classified as smokers in this study.

Statistical analysis

Statistical analyses were performed using STATA Release 16 (StataCorp LP, TX, United States). Categorical and ordinal factors were presented in frequency (%). Continuous factors were presented in median (interquartile range). All continuous factors were first tested for skewness; if the distributions were extremely skewed to the right (herein defined as skewness > 3), the factors were log transformed before using them as predictors in regression models. Since the response variables evaluated in this study are the steatosis grade (0 to 3) and the fibrosis score (0 to 4), linear regression model is an appropriate model for determining if predictors are significantly associated with each response variable. The significant factors in univariate level were included as predictors in stepwise regression to determine the significant predictors in multivariate level. The significance level was 0.05.

RESULTS

A total of 740 participants were included in the data analysis as shown in Figure 1. General characteristics of the study population are shown in Table 1. The median age was 15 years old with male comprising greater than 50% of the study population (n = 386, 52.16%). The largest race was Non-Hispanic White (n = 229, 30.39%), followed by Non-Hispanic Black (n = 171, 23.11%) and Mexican American (n = 130, 17.57%) respectively. The majority of the study population had a steatosis grade of S0 (n = 538, 72.8%) and fibrosis stages of F0 and F1 (n = 693, 93.65%). Steatosis (S1-S3) was present in 27% of the study population. Advanced fibrosis (F3-F4) was present in 2.84% of the study population. 53.33% (n = 392) of the study population had a normal BMI, while 28.71% (n = 211) were overweight and 0.54% (n = 4) were underweight.

Data concerning social history and physical activity were also analyzed. A smoking history was endorsed by 6 participants (0.84%). The percent of study participants who spent ≥ 5 h per day of watching TV in the past 30 d was 20.63% (n = 150). Similarly, 35.85% (n = 261) of study participants reported spending ≥ 5 h per day on the computer for the past 30 d.

Table 2 is a univariate analysis of participant characteristics stratified according to steatosis grade. Out of the 47 variables, there were 28 significant predictors. Statistically significant variables that were positively associated with steatosis grade in the multivariate analysis were log of ALT (P = 0.001), HOMA-IR (P = 0.006), waist-to-height ratio (P = 0.001), and BMI (P = 0.011) (Table 3).

Similarly, Table 4 is a univariate analysis of participant characteristics stratified according to fibrosis stage. Out of the 48 variables, there were only 9 significant predictors. In the multivariate analysis (Table 5), steatosis grade (P < 0.001), non-Hispanic black race (P = 0.002), a smoking history (P = 0.028), and systolic blood pressure (P = 0.035) were predictors of fibrosis stage that were statistically significant and positively associated with fibrosis stage.

The performance of liver fibrosis indices (APRI, FIB4, and PNFI) were summarized in Table 6. PNFI was the only significant predictor of steatosis grade. However, all liver fibrosis indices had very low positive predictive values (0%-3.26%) for predicting cirrhosis (F4).

DISCUSSION

This study reported the prevalence of steatosis and fibrosis in United States adolescents who participated in NHANES 2017-2018 as diagnosed by TE and CAP. We also identified predictors of steatosis grade and fibrosis stage in this study population. Although there was a recent study on a similar topic that utilized the same database from Ciardullo *et al*[28], the study designs were distinct as follows: (1) The maximum age in this study is 17 since the age 18 and above was used as a cut-off for many adult questionnaires in NHANES (*e.g.*, alcohol use, physical activity, and smoking); (2) We

Table 1 General characteristics of study population

	All participants (*n* = 740)
Age	15 (13-16)
Sex, *n* (%)	
Male	386 (52.16)
Female	354 (47.84)
Race, *n* (%)	
Mexican American	130 (17.57)
Other Hispanic	55 (7.43)
Non-Hispanic White	229 (30.95)
Non-Hispanic Black	171 (23.11)
Non-Hispanic Asian	83 (11.22)
Other race-including multi-racial	72 (9.73)
Smoking, *n* (%)	6 (0.84)
Steatosis grade, *n* (%)	
S0	538 (72.8)
S1	63 (8.53)
S2	39 (5.28)
S3	99 (13.4)
Fibrosis result, *n* (%)	
F0-F1	693 (93.65)
F2	26 (3.51)
F3	12 (1.62)
F4	9 (1.22)
Waist-to-height ratio	0.48 (0.43-0.55)
Waist-to-hip ratio	0.57 (0.53-0.63)
Body mass index, *n* (%)	
Underweight	4 (0.54)
Normal	392 (53.33)
Risk of overweight	128 (17.41)
Overweight	211 (28.71)
Days physically active at least 60 min	4 (2-5)
Hours/day watch TV or videos past 30 d, *n* (%)	
Less than 1 h	107 (14.72)
1 h	121 (16.64)
2 h	166 (22.83)
3 h	105 (14.44)
4 h	78 (10.73)
5 h or more	150 (20.63)
Hours/day use computer past 30 d, *n* (%)	
Less than 1 h	68 (9.34)
1 h	85 (11.68)
2 h	131 (17.99)

3 h	83 (11.4)
4 h	100 (13.74)
5 h or more	261 (35.85)

discretized the steatosis grades and fibrosis levels into 4 Levels each; (3) Advanced fibrosis was defined as ≥F3 (≥ 8.6 kPa) rather than ≥F2 (≥ 7.4 kPa); (4) We included more risk factors that were widely known to be associated with NAFLD (*e.g.*, smoking, physical activity, diet, and insulin resistance); and (5) Linear regression was used instead of logistic regression. For this reason, our results on prevalence and significant predictors are different from the previous study even though we used the same database.

We found that significant steatosis was present in over a fifth of the adolescents studied as indicated by a median CAP ≥ 248 dB/m and that advanced fibrosis (F3-F4) was present in 2.84% of the adolescents studied. Log of ALT, waist-to-height ratio, HOMA-IR, and BMI were significant predictors of steatosis in multivariate level. These four factors can be categorized into three groups that are commonly known as risk factors of NAFLD: liver chemistry (ALT), insulin resistance (HOMA-IR), and body fat (BMI and waist-to-height ratio). North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines suggested using ALT as a screening test for NAFLD with the cutoff levels of 22 mg/dL for girls and 26 mg/dL for boys[29]. BMI, waist-to-height ratio, and insulin resistance have been heavily documented as risk factors for hepatic steatosis in obese children[30,31]. In fact, insulin resistance plays a central role in the pathogenesis of non-alcoholic fatty liver disease[32].

Identifying predictors of fibrosis in adolescents is important because fibrosis has been shown to be a strong predictor of liver related complications and overall mortality[33]. Having sensitive and specific predictors of fibrosis allows us to effectively prevent and manage associated liver-related complications such as hepatocellular carcinoma and cirrhosis. In our study, multivariate stepwise regression revealed that the independent predictors of fibrosis were steatosis grade, non-Hispanic black race, smoking, and systolic blood pressure.

Non-Hispanic black race as an independent predictor of fibrosis that may be a proxy for other socioeconomic and environmental factors not collected in the research effort. Although the pathogenesis of NAFLD is not fully understood, NAFLD is widely accepted to be a genetic-environment-metabolism-related disease[34]. Consumption of refined carbohydrates and sugar-sweetened beverages have been associated with NAFLD[35]. In a study that documented self-reported sugar-sweetened beverage intake among college students, black undergraduates were found to have a higher intake of sugared beverages than compared to their contemporaries[36]. Additionally, non-Hispanic blacks are reported to have suboptimal diet quality and to not meet national dietary recommendations with lower intakes of total vegetables, milk, and whole grains than whites[37]. Our findings may reflect the dietary and environmental differences among black adolescents and requires further investigation.

Smoking has been identified as an independent risk factor of NAFLD in adult patients[38,39]. The presumed pathogenesis is through the consumption of toxins in cigarettes that affect the antioxidant system, which includes cytochrome P450 and inflammatory cytokines[35]. Our smoking sub-group was adolescents and underpowered with a sample size of 6, so further investigation is needed to confirm smoking as a specific predictor for fibrosis.

Previous animal model study showed that the steatosis of any cause was associated with hepatic inflammatory changes and fibrosis by causing oxidative stress and mitochondrial dysfunction[40]. However, there were limited clinical evidence on the association between steatosis and fibrosis in general pediatric or adolescent population. Systolic hypertension is known as a primary clinical feature of metabolic syndrome, which were previously reported as independence risk factor of NAFLD[41].

Additionally, we compared the performance of three liver fibrosis indices for predicting steatosis (S1-S3) and cirrhosis (F4). PNFI was the only liver fibrosis index having a PPV and sensitivity greater than zero. Although it was only index that can be used to predict NAFLD, the performance on this dataset was moderately high with an accuracy of 85.6%. The superior performance of PNFI could derive from the fact that it is the only index developed by using the liver biopsy in the pediatric population[21] while other two indices (APRI and FIB4) were originally developed from the adult population[19,20], which could perform poorly in pediatric or adolescent population.

Table 2 Univariate Analysis of participant characteristics and steatosis grade

	Steatosis grade				Coefficient	*P* value
	S0 (*n* = 538)	S1 (*n* = 63)	S2 (*n* = 39)	S3 (*n* = 99)		
Age	14 (13-16)	14 (13-16)	15 (14-16)	15 (14-16)	0.0562	0.016[a]
Sex						
Male	273 (50.74%)	29 (46.03%)	20 (51.28%)	64 (64.65%)	0.1747	0.027[a]
Female	265 (49.26%)	34 (53.97%)	19 (48.72%)	35 (35.35%)		
Race						
Mexican American	82 (15.24%)	11 (17.46%)	7 (17.95%)	30 (30.3%)	0.3542	< 0.001[a]
Other Hispanic	42 (7.81%)	5 (7.94%)	1 (2.56%)	7 (7.07%)	-0.0903	0.549
Non-Hispanic White	178 (33.09%)	18 (28.57%)	13 (33.33%)	20 (20.2%)	-0.2008	0.019[a]
Non-Hispanic Black	128 (23.79%)	10 (15.87%)	11 (28.21%)	21 (21.21%)	-0.0440	0.640
Non-Hispanic Asian	60 (11.15%)	8 (12.7%)	4 (10.26%)	11 (11.11%)	-0.0026	0.983
Other Race-Including Multi-Racial	48 (8.92%)	11 (17.46%)	3 (7.69%)	10 (10.1%)	0.0666	0.618
Smoking	4 (0.77%)	1 (1.59%)	0 (0%)	1 (1.04%)	0.0732	0.868
Waist-to-height ratio	0.45 (0.42-0.51)	0.54 (0.47-0.59)	0.57 (0.48-0.62)	0.6 (0.55-0.66)	6.5565	< 0.001[a]
Waist-to-hip ratio	0.56 (0.52-0.6)	0.6 (0.57-0.65)	0.63 (0.57-0.68)	0.64 (0.61-0.69)	6.6835	< 0.001[a]
Body mass index					0.6128	< 0.001[a]
Underweight	4 (0.75%)	0 (0%)	0 (0%)	0 (0%)		
Normal	349 (65.48%)	22 (34.92%)	10 (25.64%)	10 (10.1%)		
Risk of overweight	97 (18.2%)	14 (22.22%)	8 (20.51%)	9 (9.09%)		
Overweight	83 (15.57%)	27 (42.86%)	21 (53.85%)	80 (80.81%)		
Days physically active at least 60 min	4 (2-6)	3.5 (1-5)	4 (2-5)	4 (2-5)	-0.0167	0.348
Hours/day watch TV or videos past 30 d	2 (1-4)	2 (1-4)	3 (1.75-5)	2 (1-4.25)	0.0421	0.070
Hours/day use computer past 30 d	3 (2-5)	4 (2-5)	5 (2-5)	4 (2-5)	0.0560	0.014[a]
Diet						
Energy (1000 kcal)	1.82 (1.43-2.45)	1.75 (1.26-2.28)	1.62 (1.33-2)	1.71 (1.34-2.38)	-0.0732	0.145
Protein (mg)	63.59 (48.32-86.06)	63.15 (40.29-77.27)	53.38 (37.92-80.78)	64.1 (49.36-87.48)	-0.0732	0.145
Carbohydrate (mg)	230.94 (180.54-301.73)	233.36 (154.21-296.51)	213.08 (169.63-253.71)	219.06 (173.09-290.58)	-0.0005	0.178
Total sugars (mg)	94.74 (67.04-133.77)	89.84 (54.32-140.86)	75.37 (51.43-97.67)	90.5 (63.35-127.21)	-0.0008	0.224
Dietary fiber (mg)	12.85 (9.25-17.36)	12.2 (8.77-18.3)	12.5 (9.24-16.79)	12.2 (8.8-16.4)	-0.0051	0.368
Total fat (mg)	75.09 (55.41-97.52)	66.13 (43.61-93.44)	62.68 (45.53-83.34)	71.58 (47.42-95.31)	-0.0016	0.143
Total saturated fatty acids (mg)	25.07 (17.39-35.43)	24.43 (11.47-32.25)	18.7 (11.7-30.89)	22.91 (14.97-31.11)	-0.0044	0.122
Cholesterol (mg)	197 (132.88-320.5)	165 (90.25-305.5)	162 (72.38-283.63)	199 (134-279.25)	-0.0003	0.254
Systolic blood pressure (mm Hg)	106 (100-114)	108 (103.5-114.5)	112 (104-120)	112 (104-120)	0.0254	< 0.001[a]
Diastolic blood pressure (mm Hg)	62 (54-68)	60 (51.5-68)	62 (55.5-70)	60 (54-66)	-0.0038	0.222
Triglycerides, refrig serum (mg/dL)[1]	74 (57-98)	79 (62-103)	78.5 (70-105.5)	98 (68-159)	0.0051	< 0.001[a]
Uric acid (mg/dL)	4.7 (4-5.6)	5.1 (4.15-6.05)	5.45 (4.65-6.15)	5.75 (4.7-6.7)	0.1984	< 0.001[a]
Aspartate aminotransferase (IU/L)[1]	18 (16-22)	18 (15.25-21.75)	16.5 (15-21)	20.5 (18-27)	0.0151	0.002[a]
Alanine aminotransferase (IU/L)[1]	12 (10-15)	15 (11.25-19)	14 (10-17.5)	20.5 (14-34)	0.0372	< 0.001[a]
Gamma glutamyl transferase (IU/L)[1]	12 (10-15)	12 (10-18.75)	15.5 (10-19)	18 (12-24)	0.0375	< 0.001[a]

Alkaline phosphatase (ALP) (IU/L)	130 (87-225.75)	121 (86.75-235)	135 (75.5-188)	126.5 (99-188)	-0.0003	0.537
Total bilirubin (mg/dL)[1]	0.4 (0.3-0.6)	0.3 (0.23-0.48)	0.4 (0.3-0.5)	0.4 (0.3-0.4)	-0.3419	0.009[a]
Total protein (g/dL)	7.3 (7-7.5)	7.3 (7-7.5)	7.35 (7.15-7.6)	7.35 (7.2-7.6)	0.3620	0.002[a]
Albumin, refrigerated serum (g/dL)	4.3 (4.1-4.5)	4.3 (4.1-4.5)	4.25 (4.05-4.45)	4.2 (4-4.4)	-0.5553	< 0.001[a]
Iron frozen, serum (μg/dL)	85 (61-113)	86 (58.25-105.75)	69 (49.5-85.75)	75 (56-103)	-0.0027	0.013[a]
Total iron binding capacity (μg/dL)	348 (317.5-382)	366 (342-392.25)	360 (326.25-406.5)	356 (322-385)	0.0015	0.092
Transferrin Saturation (%)	24 (17-33)	23 (15.25-30.75)	19 (13.5-26)	22.5 (15-30)	-0.0104	0.004[a]
Ferritin (ng/mL)	39.2 (24.85-59.85)	35.25 (18.75-57.5)	30.85 (14.65-60.15)	59.2 (35-93.12)	0.0038	< 0.001[a]
Total cholesterol (mg/dL)	150 (134-168)	158 (132.75-174)	152 (139.5-166.25)	157 (139.25-178.75)	0.0032	0.035[a]
Low-density lipoprotein cholesterol (mg/dL)	78.8 (64.8-94.6)	85.8 (69.15-107.45)	82.5 (70.1-97.8)	87 (70.6-103.6)	0.0041	0.019[a]
Direct high-density lipoprotein cholesterol (mg/dL)	53 (46-61)	50 (46-56)	48 (41.5-55)	44 (39-51)	-0.0238	< 0.001[a]
HS C-reactive protein (mg/L)[1]	0.49 (0.32-1.01)	0.72 (0.35-1.51)	0.95 (0.43-1.89)	1.76 (0.87-3.74)	0.0448	< 0.001[a]
Platelet count (1000 cells/uL)	258 (228-292)	269 (228.5-318.5)	273 (239-307)	282 (248-313)	0.0026	< 0.001[a]
Hemoglobin A1c (%)[1]	5.3 (5.1-5.5)	5.3 (5.1-5.45)	5.3 (5.1-5.6)	5.4 (5.2-5.5)	0.2280	0.054
Fasting glucose (mg/dL)	97 (93-101)	98 (93.25-101.75)	101 (94-103)	99.5 (96-103)	0.0219	0.017[a]
Insulin (pmol/L)	54.96 (39.84-79.38)	101.1 (71.58-130.8)	88.32 (62.28-118.14)	129.63 (75.66-185.46)	0.0086	< 0.001[a]
Homeostatic model assessment for insulin resistance	2.23 (1.58-3.32)	4.08 (2.96-5.47)	3.56 (2.64-4.96)	5.34 (3.08-7.78)	0.1976	< 0.001[a]

[1]Skewness > 3.
[a]$P < 0.05$. HS: High sensitivity.

Table 3 Predictors of steatosis grade in multivariate level

Predictors	Coefficient (standard error)	*P* value
Alanine aminotransferase (IU/L)[1]	0.3912 (0.1159)	0.001
Homestatic model assessment for insulin resistance	0.0684 (0.0247)	0.006
Waist-to-height ratio	3.2299 (0.0912)	0.001
Body mass index	0.2335 (0.0912)	0.011

[1]Log-transformed predictor. Number of observations = 307; Adjusted $R^2 = 0.37$;

There are several limitations of this study. Our study population is of United States adolescents and may not be reflective of non-American populations. Alcohol was not measured in the study population and also presumed to be zero because the population was United States adolescents. The legal age to drink in the United States is 21 but for some people drinking alcohol begins in adolescence[42]. Another limitation is subgroup sample size which was seen subgroups such as smoking, F3, and F4. Low statistical power reduces the chance of detecting a true effect[43]. Some variables not available in the NHANES include hormonal levels and Tanner stages of the participants. Hypogonadism and low testosterone level are associated with an increased risk for NAFLD and NASH[44]. Additionally, low sex hormone binding globulin (SHBG) can be viewed as a marker for NAFLD in women with oligomenorrhea and/or hirsutism[45]. Since these variables were not included in the NHANES database, they were not accounted for. Lastly, though seeing increasing utility in diagnostic value, TE has not been traditionally studied in adolescents.

Table 4 Univariate Analysis of participant characteristics and fibrosis stage

	Fibrosis stage				Coefficient	*P* value
	F0 - F1 (*n* = 693)	F2 (*n* = 26)	F3 (*n* = 12)	F4 (*n* = 9)		
Age	15 (13-16)	15 (13-17)	14 (13-15)	15 (14.75-17)	0.0106	0.276
Sex						
Male	356 (51.37%)	17 (65.38%)	6 (50%)	7 (77.78%)	0.0533	0.105
Female	337 (48.63%)	9 (34.62%)	6 (50%)	2 (22.22%)		
Race						
Mexican American	123 (17.75%)	4 (15.38%)	0 (0%)	3 (33.33%)	-0.0049	0.909
Other Hispanic	53 (7.65%)	1 (3.85%)	1 (8.33%)	0 (0%)	-0.0535	0.393
Non-Hispanic White	222 (32.03%)	3 (11.54%)	2 (16.67%)	2 (22.22%)	-0.0685	0.054
Non-Hispanic Black	148 (21.36%)	13 (50%)	8 (66.67%)	2 (22.22%)	0.1309	< 0.001[a]
Non-Hispanic Asian	78 (11.26%)	4 (15.38%)	0 (0%)	1 (11.11%)	-0.0222	0.669
Other Race-Including Multi-Racial	69 (9.96%)	1 (3.85%)	1 (8.33%)	1 (11.11%)	-0.0230	0.679
Smoking	5 (0.75%)	0 (0%)	0 (0%)	1 (11.11%)	0.3967	0.032[a]
Waist-to-height ratio	0.48 (0.43-0.55)	0.49 (0.44-0.61)	0.49 (0.4-0.61)	0.5 (0.42-0.68)	0.3746	0.042[a]
Waist-to-hip ratio	0.57 (0.53-0.62)	0.59 (0.54-0.69)	0.6 (0.52-0.64)	0.59 (0.5-0.7)	0.2804	0.215
Body mass index					0.0330	0.079
Underweight	4 (0.58%)	0 (0%)	0 (0%)	0 (0%)		
Normal	370 (53.78%)	11 (42.31%)	6 (50%)	5 (55.56%)		
Risk of overweight	126 (18.31%)	2 (7.69%)	0 (0%)	0 (0%)		
Overweight	188 (27.33%)	13 (50%)	6 (50%)	4 (44.44%)		
Days physically active at least 60 min	4 (2-5)	4 (2-5)	2.5 (0.5-6)	5 (2.5-6)	-0.0039	0.597
Hours/day watch TV or videos past 30 d	2 (1-4)	2 (1-4)	2.5 (2-4.5)	2 (0-3.5)	-0.0027	0.779
Hours/day use computer past 30 d	3 (2-5)	5 (3-5)	4 (2.5-5)	3 (0.75-5)	0.0062	0.519
Steatosis grade					0.0757	< 0.001[a]
S0	518 (74.86%)	13 (50%)	3 (25%)	4 (44.44%)		
S1	57 (8.24%)	2 (7.69%)	3 (25%)	1 (11.11%)		
S2	35 (5.06%)	2 (7.69%)	2 (16.67%)	0 (0%)		
S3	82 (11.85%)	9 (34.62%)	4 (33.33%)	4 (44.44%)		
Diet						
Energy (1000 kcal)	1.8 (1.4-2.42)	1.5 (1.37-2.11)	1.62 (1.4-1.75)	1.75 (1.32-2.4)	-0.0225	0.282
Protein (mg)	63.69 (46.81-85.41)	50.66 (42.74-94.29)	59.33 (45.9-76.55)	68.03 (49.61-73.78)	-0.0004	0.405
Carbohydrate (mg)	230.55 (174.26-299.84)	202.56 (152.11-255.23)	204.26 (177.87-238.7)	242.27 (186.12-305.52)	-0.0001	0.671
Total sugars (mg)	92.59 (64.25-133.63)	87.43 (58.07-120.32)	75.76 (62.31-94.74)	94.74 (85.8-123.02)	-0.0001	0.697
Dietary fiber (mg)	12.7 (9.25-17.1)	10.8 (7.62-17.64)	10.4 (9.02-14.29)	12.85 (10.8-16.96)	-0.0018	0.461
Total fat (mg)	74.07 (52.04-97.34)	55.7 (45.07-79.29)	65.98 (50.43-78.07)	69.09 (45.95-97.94)	-0.0007	0.091
Total saturated fatty acids (mg)	24.72 (16.8-34.81)	21.06 (14.84-29.88)	23.04 (18.87-27.64)	22.84 (18.35-28.35)	-0.0020	0.083
Cholesterol (mg)	197 (129.13-317.63)	150.5 (85-213.25)	162.5 (118.38-228.88)	146.5 (124.75-310.25)	-0.0002	0.065
Systolic blood pressure (mmHg)	106 (102-114)	108 (103.5-126.5)	108 (100.5-120)	116 (113-122)	0.0066	< 0.001[a]
Diastolic blood pressure (mmHg)	62 (54-68)	64 (53-71)	56 (50.5-65.5)	60 (56-68)	-0.0001	0.967

Triglycerides, refrig serum (mg/dL)[1]	78 (61-104)	67.5 (50-111)	88 (61.75-161)	88.5 (56.5-121.5)	0.0276	0.471
Uric acid (mg/dL)	4.9 (4.1-5.8)	5 (3.7-6)	4.7 (3.3-5.98)	5.75 (4.2-7.45)	0.0079	0.560
Aspartate aminotransferase (IU/L)[1]	18 (16-22)	18 (15-25)	15 (14-23)	29 (20-32)	0.0882	0.137
Alanine aminotransferase (IU/L)[1]	13 (10-17)	14 (9-20)	12 (9.5-15)	20.5 (15-37.5)	0.0738	0.046[a]
Gamma glutamyl transferase (IU/L)[1]	13 (10-17)	12 (9-16)	12 (10-19.5)	20.5 (14-32.5)	0.0047	0.018[a]
Alkaline phosphatase (IU/L)	129 (88-222.5)	121.5 (81-205)	187 (127.75-242.75)	113 (105-129.5)	-0.0001	0.470
Total bilirubin (mg/dL)[1]	0.4 (0.3-0.5)	0.3 (0.2-0.6)	0.4 (0.3-0.5)	0.45 (0.35-0.7)	0.0178	0.577
Total protein (g/dL)	7.3 (7-7.5)	7.15 (6.8-7.3)	7.3 (7-7.63)	7.2 (7.15-7.45)	-0.0156	0.745
Albumin, refrigerated serum (g/dL)	4.3 (4.1-4.5)	4.05 (3.8-4.4)	4.2 (4.03-4.3)	4.3 (4.1-4.65)	-0.0744	0.229
Iron frozen, Serum (μg/dL)	83 (59-112)	80.5 (47-88)	88 (68-106)	67.5 (58-120.5)	0.0001	0.777
Total iron binding capacity (μg/dL)	352 (322-387)	346 (314-378)	355 (315.25-375.25)	314 (310-327.5)	-0.0009	0.018[a]
Transferrin saturation (%)	23 (17-32)	22 (15-26)	28 (19.25-31.5)	20 (18-39)	0.0013	0.377
Ferritin (ng/mL)	39.3 (24.5-62.1)	45.55 (24.45-61.85)	56.25 (29-71)	102.35 (35.75-141)	0.0009	0.030[a]
Total cholesterol (mg/dL)	151 (134-171)	140.5 (136-156)	161 (143-175)	131 (119-147.5)	-0.0010	0.102
Low-density lipoprotein cholesterol (mg/dL)	81 (66.2-97.6)	77.5 (64.2-92.6)	88.2 (71.6-91.4)	57.2 (55.5-80.1)	-0.0013	0.082
Direct high-density lipoprotein cholesterol (mg/dL)	51 (44-59)	49.5 (44-58)	50 (46-62)	49.5 (39-56)	-0.0012	0.426
HS C-reactive protein (mg/L)[1]	0.57 (0.35-1.39)	0.83 (0.34-1.34)	0.72 (0.37-1.12)	0.97 (0.53-7.09)	0.0240	0.134
Platelet count (1000 cells/uL)	262 (230-297.5)	275.5 (242-302.5)	262.5 (226-277)	262.5 (234-275)	-0.0001	0.769
Hemoglobin A1c (%)[1]	5.3 (5.1-5.5)	5.3 (5.25-5.6)	5.45 (5.25-5.65)	5.35 (5.15-5.6)	0.4629	0.098
Fasting glucose (mg/dL)	98 (94-102)	99 (94-103)	101 (95.5-104.25)	92 (89.75-95.75)	-0.0031	0.490
Insulin (pmol/L)	64.83 (43.38-99)	70.26 (45.87-183.17)	87.06 (59.28-160.28)	51.42 (27.29-127.14)	0.0005	0.291
Homeostatic model assessment for insulin resistance	2.61 (1.71-3.96)	2.66 (1.96-7.9)	4.08 (2.34-6.66)	1.95 (1.1-4.95)	0.0101	0.383

[1]Skewness > 3.
[a]$P < 0.05$. HS: High sensitivity.

Table 5 Predictors of fibrosis stage in multivariate level

Predictors	Coefficient (standard error)	*P* value
Steatosis grade	0.0730 (0.0172)	< 0.001
Race: Non-Hispanic Black	0.1352 (0.0430)	0.002
Smoke	0.4065 (0.1845)	0.028
Systolic blood pressure (mmHg)	0.0040 (0.0019)	0.035

Number of observations = 643; Adjusted R^2 = 0.0598.

CONCLUSION

In conclusion, this study showed steatosis and advanced liver fibrosis in 27.2% and 2.7% of United States adolescents, respectively. ALT, BMI, HOMA-IR, and waist-to-height ratio were predictors of steatosis, while steatosis grade, smoking, non-Hispanic black race, systolic blood pressure were predictors of fibrosis. Environmental, dietary, and social history are important information to gather from adolescents as these factors can contribute to a risk of steatosis and fibrosis. Given the progressive nature of chronic liver disease, the evidence of steatosis or advanced fibrosis in younger age could lead to increased steatohepatitis and cirrhosis in young adults.

Table 6 Predictive performance of liver fibrosis indices

Liver fibrosis indices (Predictor)		Outcome	Predictive performance				
Index	Cutoff		Accuracy	PPV	NPV	Sensitivity	Specificity
APRI	0.7	F4	98.45%	0%	98.8%	0.0%	99.7%
FIB4	1.3	F4	98.61%	0%	98.8%	0.0%	99.8%
PNFI	9	F4	85.31%	3.26%	99.1%	37.5%	85.9%
PNFI	3	S1-S3	85.60%	83.33%	86.2%	59.7%	95.5%

APRI: Aspartate aminotransferase to platelet ratio index; FIB4: Fibrosis-4 index; NPV: Negative predictive value; PNFI: Pediatric non-alcoholic fatty liver disease fibrosis index; PPV: Positive predictive value.

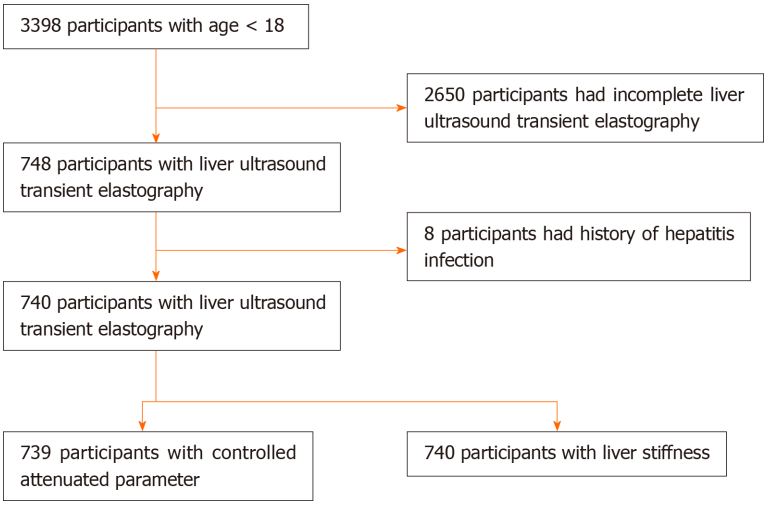

Figure 1 Study design flow chart.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children and adolescents.

Research motivation

With the rise of obesity and metabolic syndrome among younger populations, NAFLD is a growing concern in adolescents.

Research objectives

The authors aimed to determine the prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population.

Research methods

The authors studied adolescent participants aged 13 to 17 years who underwent TE and controlled attenuation parameter using the National Health and Nutrition Examination Survey 2017-2018.

Research results

There is a high prevalence of steatosis (27.2%) in the United States' adolescent population, with 2.84% having advanced fibrosis. Risk factors of steatosis grade included alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure were significant predictors of fibrosis.

Research conclusions

Adolescents with steatosis or advanced fibrosis could progress to increased steatohepatitis and cirrhosis in young adults.

Research perspectives

Environmental, dietary, and social history are important information to gather from adolescents as these factors can contribute to a risk of steatosis and fibrosis. Given the progressive nature of chronic liver disease, the evidence of steatosis or advanced fibrosis in younger age could lead to increased steatohepatitis and cirrhosis in young adults.

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SYSTEMATIC REVIEWS

Safety of liver resection in patients receiving antithrombotic therapy: A systematic review of the literature

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Abstract

BACKGROUND

Little is unknown about the effect of chronic antithrombotic therapy (ATT) on bleeding complication during or after hepatectomy. In addition, the safety and effectiveness of chemical prevention for venous thromboembolism (VTE) is still controversial.

AIM

To clarify the effect of ATT on thromboembolism and bleeding after liver resection.

METHODS

Articles published between 2011 and 2020 were searched from Google Scholar and PubMed, and after careful reviewing of all studies, studies concerning ATT and liver resection were included. Data such as study design, type of surgery, type of antithrombotic agents, and surgical outcome were extracted from the studies.

RESULTS

Sixteen published articles, including a total of 8300 patients who underwent hepatectomy, were eligible for inclusion in the current review. All studies regarding patients undergoing chronic ATT showed that hepatectomy can be performed safely, and three studies have also shown the safety and efficacy of preoperative continuation of aspirin. Regarding chemical prevention for VTE, some studies have shown a potentially high risk of bleeding complications in patients undergoing chemical thromboprophylaxis; however, its efficacy against VTE has not been shown statistically, especially among Asian patients.

CONCLUSION

Hepatectomy in patients with chronic ATT can be performed safely without increasing the incidence of bleeding complications, but the safety and effectiveness of chemical thromboprophylaxis against VTE during liver resection is still

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controversial, especially in the Asian population. Establishing a clear protocol or guideline requires further research using reliable studies with good design.

Key Words: Liver resection; Bleeding complication; Antithrombotic therapy; Thromboembolic complication; Thromboprophylaxis

Core Tip: A total of 16 published articles on antithrombotic therapy and hepatectomy have been reviewed systematically. The articles showed that the risk of thromboembolic and/or bleeding events in patients with continued preoperative aspirin was not different from those in patients with no antithrombotic or interrupted antiplatelet drugs, although pharmacological prophylaxis of venous thromboembolism is still controversial, especially when performing hepatectomy in Asian patient populations.

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INTRODUCTION

Heart disease, cerebrovascular disease, and cancer are the three leading causes of death in the world. With the aging of society in recent years, patients with cerebrovascular and/or cardiovascular diseases are increasingly required to undergo non-cardiac surgery. Most of these patients receive antithrombotic therapy (ATT) in order to prevent thromboembolic events. The perioperative period in patients undergoing ATT is at high risk for both thromboembolism and bleeding, which can be very cumbersome for surgeons[1-3].

ATT is classified into two types of drugs: Antiplatelet drugs and anticoagulants. Antiplatelet drugs are frequently used for prevention of cerebrovascular or cardiovascular diseases, and can prevent thromboembolism by reduction of platelet aggregation. Antiplatelet agents include thienopyridine (*e.g.*, clopidogrel, prasugrel, or ticlopidine), aspirin, and type III phosphodiesterase inhibitor (*e.g.*, cilostazol)[4]. Anticoagulants, on the other hand, prevent coagulation of blood by suppressing the coagulation cascade. They are usually used for deep vein thrombosis, atrial fibrillation, acute coronary syndrome, and cardiac endoprostheses. Anticoagulants are also used for perioperative thromboprophylaxis of venous thromboembolism (VTE). Oral anticoagulants include warfarin, factor Xa inhibitors (*e.g.*, apixaban, rivaroxaban, edoxaban), and direct thrombin inhibitors (*e.g.*, dabigatran)[4,5]. The latter two types are called direct-acting oral anticoagulants (DOACs) or non-vitamin K antagonist oral anticoagulants (NOACs), and now increasingly used. Table 1 summarizes the type and the duration of action of each antithrombotic agent.

Minimizing intraoperative and postoperative bleeding complication is an important challenges in liver resection, and several technical improvement has been demonstrated, such as Pringle maneuver or sustained low central venous pressure (CVP)[6-8]. However, sustained low CVP during hepatectomy may increase the risk of thrombosis in ATT-received patients. Rigorous perioperative management of antithrombotics and strict hemostasis are requisite to prevent both thromboembolic and bleeding events. To date, there has been no consensus on the safety of hepatectomy and proper perioperative management of antithrombotics in patients undergoing ATT, and the optimal thrombotic prophylaxis for VTE remains unknown.

The aim of the current review is to clarify the effect of ATT on thromboembolic and bleeding complications in liver resection.

Table 1 Types, specific agents, and acting duration of commonly used antithrombotic drugs

Class of agents	Type	Specific agents	Duration of action
Antiplatelets			
	Thienopyridines	Clopidogrel (Plavix), ticlopidine (Panardine), prasugrel (Effient), ticagrelor (Brilinta)	5-7 d[1]
	Type III PDE inhibitor	Cilostazol (Pretal)	2 d
	Acetylsalicylic acid	Aspirin	7-10 d
	Other NSAIDs	Ibuprofen (Brufen, Advil), loxoprofen (Loxonin), diclofenac (Voltaren) *etc.*	Varies
Anticoagulants			
	Heparin (unfractionated)	Heparin	1-2 h
	Heparin (LMWH)	Dalteparin (Fragmin iv), enoxaparin (Clexane, s.c.), nadroparin (s.c.)	6-12 h[2]
	Vitamin K antagonist	Warfarin (Coumadin)	5 d
	Factor Xa inhibitor (s.c.)	Fondaparinux (Arixtra)	1-1.5 d
	DOACs		
	Direct thrombin inhibitor	Dabigatran (Pradaxa)	1-2 d
	Factor Xa inhibitors	Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana)	1-2 d

[1]In ticlopidine, duration of action is 10-14 d.
[2]In dalteparin, duration of action is 2-4 h. PDE: Phosphodiesterase; NSAID: Non-steroidal anti-inflammatory drug; DOAC: Direct-acting oral anticoagulant.

MATERIALS AND METHODS

Papers published between 2011 and 2020, which were written in English, were collected from Google Scholar and PubMed. The following key words were adopted for searching: "liver resection or hepatectomy" AND "antithrombotic therapy, aspirin, clopidogrel, antiplatelet therapy, anticoagulation, warfarin, DOAC, or NOAC" AND "bleeding or hemorrhage". Only articles which were published in the peer review journal were included in the current review. Eligible study types include prospective cohort studies, retrospective cohort studies, randomized clinical trials, or case-control studies, but case reports, reviews, or guidelines were not included.

Duplicate articles were first removed, and then articles were excluded systematically by reviewing each study carefully. Eligible articles were finally determined after the quality of each study was evaluated according to the study design. Complete data, including study design, sample size, publication year, type of surgery, type of antithrombotics, and surgical outcome, were extracted from the studies. Bleeding events included two categories; postoperative bleeding complications (BC) and increased surgical blood loss (SBL).

RESULTS

Study characteristics

Collection and screening of research were performed from December 2020 to January 2021 (Figure 1). The current review included a total of 16 published articles, with 8300 patients undergoing hepatectomy. There were no randomized clinical trials, but only case-control studies or cohort studies. Ten of the 16 studies were observational cohort studies, and only one was prospective studies; 6 studies were on the management of patients with chronic ATT[9-14] (Table 2) and 10 studies were on the pharmacological prevention for VTE (Table 3)[15-24]. Among studies regarding the management of chronic ATT, two studies were investigated using the propensity score matching method[9,12]. Nine of the 10 articles on pharmacological prophylaxis for VTE were observational studies; one was multicenter prospective and 8 were retrospective cohort studies.

Of the 6 studies on the management of patients receiving chronic ATT, three focused on the safety of continued perioperative aspirin during hepatectomy[9,12,13]. In 10 studies on pharmacological prevention for VTE, patients were primarily controlled by low-molecular-weight heparin during the perioperative period.

Table 2 Reported data concerning bleeding complications of liver resection in patients with antithrombotic therapy

Ref.	Year, type	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Naito *et al* [9]	2020, PSM	Liver resection (n = 425)	Patients with continued ASA (n = 63); Patients not on continued APT (control, n = 362); Post-PSM: 63 *vs* 63 matched cases	BC 4.8% in continued ASA *vs* 4.8% in control (P = 1.00); SBL was identical (P = 0.54)	TE 1.6% in continued ASA *vs* 4.8% in control (P = 0.62); Mortality 1.6% *vs* 1.6% (P = 1.00)
Fujikawa *et al*[10]	2017, RCS	Liver resection (n = 258) including 77 laparoscopic liver resection	Patients with ATT (n = 100); Patients without ATT (control; n = 158)	BC 3.0% in ATT *vs* 3.8% in control (P > 0.05); No BC in laparoscopic surgery; SBL was identical	TE 1.0% *vs* 1.3% (P > 0.05); No TE in laparoscopic surgery; Mortality 1.0% *vs* 0% (P = 0.350)
Ishida *et al* [11]	2017, CCS	HBP surgery (n = 886) including 520 liver resection	Patients with ACT (n = 39); Patients with APT (n = 77); Patients without ATT (control, n = 770)	BC 0.0% in ACT *vs* 1.3% in APT *vs* 3.4% in control (P = 0.32); SBL was identical (P = 0.99)	TE 0% *vs* 1.3% *vs* 0.8% (P = 0.75); Mortality 0% *vs* 0% *vs* 1.2% (P = 0.50)
Gelli *et al* [12]	2018, PSM	Liver resection (n = 1803)	Patients with continued ASA (n = 118); Patients not on continued APT (control, n = 1685); Post-PSM: 108 *vs* 108 matched cases	Overall BC 10.2% in continued ASA *vs* 12.0% in control (P > 0.05); Major BC 6.5% *vs* 5.6% (P > 0.05)	Mortality 5.6% *vs* 4.6% (P > 0.05)
Monden *et al*[13]	2017, CCS	Liver resection (n = 378)	Patients with continued ASA (n = 31); Patients not on continued APT (control, n = 347)	Major BC 0% in continued ASA *vs* 0.3% in control (P > 0.05); SBL 450 mL *vs* 360 mL (P = 0.735)	TE 3.2% *vs* 0% (P > 0.05); Mortality 3.2% *vs* 0.9% (P = 0.291)
Fujikawa *et al*[14]	2019, CCS	HBP surgery (n = 105) including 37 liver resection	Patients with DOAC (n = 35); Patients with WF (control, n = 80)	BC 2.9% in DOAC *vs* 0% in WF (P = 0.304); SBL was identical (P = 0.782)	No TE event in both groups; No mortality in both groups

RCS: Retrospective cohort study; mRCS: Multicenter retrospective cohort study; CCS: Case-control study; PSM: Case-control study with propencity-score matching; ATT: Antithrombotic therapy; APT: Antiplatelet therapy; ACT: Anticoagulation therapy; ASA: Aspirin; LAP: Laparoscopic; SBL: Surgical blood loss; BC: Postoperative bleeding complication; TE: Thromboembolism.

Safety of liver resection in patients receiving chronic ATT

In all 6 studies regarding the management of ATT-received patients, the authors generally demonstrated the safety of hepatectomy even in patients with chronic ATT. Among patients undergoing chronic ATT, the rates of major and overall BCs were 0%-6.5% and 1.3%-10.2%, retrospectively; the incidence of postoperative thromboembolic complication was 0%-3.2%. In all included studies, the rates of bleeding and thromboembolic complications between ATT-received patients and those without ATT were not significantly different (Table 2).

The safety of continued perioperative aspirin during hepatectomy was focused on in 3 case-control studies, including 2 studies using the propensity score matching method[9,12,13]. All three studies have shown that continued preoperative aspirin is not associated with increased intraoperative and postoperative bleeding events in patients with chronic antiplatelet therapy during or after hepatectomy. These studies suggested that continued preoperative aspirin in patients with chronic antiplatelet therapy is safe and should be considered preferable even when performing hepatectomy.

Safety of chemical thromboprophylaxis for VTE

In 10 articles regarding pharmacological prevention for VTE, 9 were observational cohort studies, including 8 retrospective and 1 prospective studies. The included studies generally showed potentially elevated risks of BC in patients receiving pharmacological thromboprophylaxis; the rates of overall and major BCs in the group receiving pharmacological thromboprophylaxis were 5.2%-26.6% and 1.6%-10.9%, respectively. Concerning the efficacy of thromboprophylaxis, 3 studies showed that the occurrence of VTE in patients receiving pharmacological thromboprophylaxis was significantly lower compared to the control group[15,20,24], but the other 7 studies, including 2 studies from Japan[18,19] did not demonstrate its effectiveness due to the small sample size (Table 3).

Analysis of these studies have demonstrated a potentially high risk of postoperative bleeding in patients undergoing pharmacological prevention for VTE, but the efficacy of pharmacological thromboprophylaxis after hepatectomy has not been shown, especially in Asian patient population.

Table 3 Reported data concerning the safety of thromboprophylaxis for venous thromboembolism during liver resection

Ref.	Year, type	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Ainoa *et al* [15]	2020, RCS	Liver resection (n = 512)	Patients with preop TP (n = 253); Patients with postop TP (control, n = 259)	BC 15.0% in preop TP *vs* 13.9% in control (P > 0.05)	VTE 1.2% *vs* 9.7% (P < 0.0001); PE 1.2% *vs* 9.3% (P < 0.0001)
Ejaz *et al*[16]	2014, RCS	Liver resection (n = 599)	Patients with TP (n = 454); Patients without TP (control, n = 145)	Not mentioned	VTE 5.1% in TP *vs* 3.4% in control (P = 0.42)
Nathan *et al* [17]	2014, RCS	Liver resection (n = 2147)	Patients with early TP (n = 1295); Patients with late or no TP (control, n = 852)	Major BC 1.7% in early TP *vs* 1.6% in control (P > 0.05)	VTE 2.1% *vs* 3.3% (P > 0.05); Overall mortality 1.9%
Eguchi *et al* [18]	2020, mPCS	Major HBP surgery (n = 133) including 74 liver resection	Patients with TP [LMWH (enoxaparin), n = 133, single arm]	Major BC 2.3%; Minor BC 5.2%	No PE event in whole cohort
Hayashi *et al* [19]	2014, RCS	Major HBP surgery (n = 349) including 138 liver resection	Patients with TP (n = 207); Patients without TP (control, n = 142)	BC 26.6% in TP *vs* 8.5% in control (P < 0.05); Rate of major BC is identical	VTE 2.9% *vs* 7.7% (P > 0.05)
Wang *et al* [20]	2018, CCS	Liver resection (n = 233)	Patients with TP (LMWH, n = 117); Patients without TP (control, n = 116)	Not mentioned	VTE 0.85% in TP *vs* 13.8% (P < 0.05)
Kim *et al*[21]	2017, RCS	Liver resection (n = 124)	Patients with extended TP [LMWH (enoxaparin), n = 124, single arm]	BC 1.6% in extended TP	No VTE in whole cohort
Doughtie *et al*[22]	2014, RCS	Major HBP surgery (n = 223) including 110 liver resection	Patients with preop TP (LMWH, n = 93); Patients without preop TP (control, n = 130)	Major BC 10.9% in preop TP *vs* 3.1% in control (P = 0.026); SBL was identical	VTE 1.1% *vs* 6.1% (P = 0.05)
Melloul *et al* [23]	2012, RCS	Liver resection (n = 410)	Patients with TP (n = 410, single arm)	Not mentioned	PE 6% (24/410) in TP
Reddy *et al* [24]	2011, RCS	Major liver resection (n = 419)	Patients with TP (n = 275); Patients without TP (control, n = 144)	RBC transfusion rate 35.0% in TP *vs* 30.6% in control (P = 0.36)	CR-VTE 2.2% in TP *vs* 6.3% in control (P = 0.03); PE 2.2% *vs* 4.2% (P = 0.35)

mRCT: Multicenter randamized controlled trial; RCS: Retrospective cohort study; mRCS; multicenter retrospective cohort study; LMWH: Low-molecular-weight heparin; TP: Thromboprophylaxis; LAP: Laparoscopic; CR: Clinically relevant; BC: Postoperative bleeding complication; VTE: Venous thromboembolism; PE: Pulmonary embolism; AOR: Adjusted odds ratio.

DISCUSSION

As far as we know, the current study is the first systematic review to investigate the effect of ATT on thromboembolic and bleeding complications in hepatectomy. The current study reviewed 16 published articles with special reference to ATT, in which a total of 8300 patients receiving hepatectomy were included. Concerning the effects of chronic ATT administration on bleeding events, most of the studies showed that hepatectomy can be performed safely in patients receiving chronic ATT, even if they continue to have aspirin preoperatively. Regarding pharmacological prevention for VTE, some studies have reported that patients undergoing pharmacological prophylaxis may be at increased risk of bleeding, but their efficacy against VTE has not been proven especially in the population of Asian patients.

Minimizing intraoperative and postoperative bleeding complication is one of the most important tasks in hepatectomy, and several technical improvement has been demonstrated, such as Pringle's procedure, the liver hanging maneuver, or the two-surgeon technique[25-27]. Pringle's procedure is generally used during transection of the liver parenchyma in order to control hepatic inflow; sustained low CVP is usually employed in order to control backflow bleeding from the hepatic vein[8]. However, sustained low CVP may expose the ATT-received patients to the increased risks of stroke or myocardial infarction. Rigorous perioperative management of antithrombotic agents and strict procedures of hemostasis are requisite in order to prevent both thromboembolic and bleeding complications.

Regarding the management of chronically ATT-received patients, guidelines regarding ATT management during non-cardiac surgery were recently updated and demonstrated that the prevention of thromboembolism is more significant than prophylaxis of bleeding, since it might cause severe sequelae or death[5,28-31]. To date, there are little consensus or evidence on the safety of hepatectomy and proper

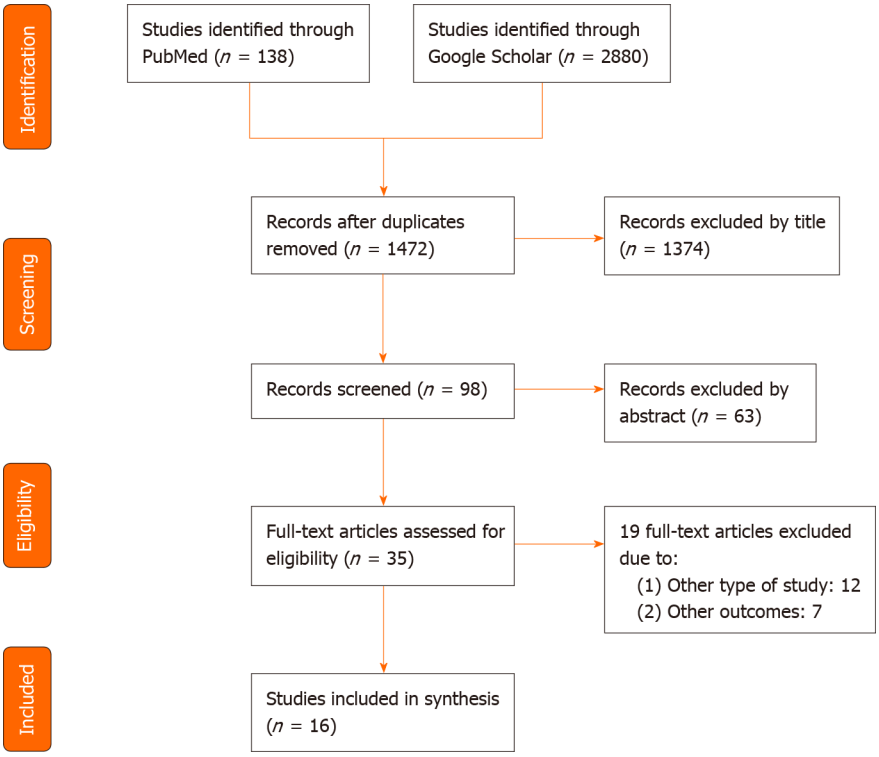

Figure 1 PRISMA flow diagram demonstrating articles selection process.

perioperative ATT management in ATT-received patients, and the optimal prevention for VTE also remains unknown.

Our hospital is a high-volume institution for referrals to patients with digestive cancer who are receiving ATT. Accordingly, we presently use a centralized management protocol in ATT-received patients undergoing digestive surgery including hepatectomy (Figure 2)[32], which was established and have been updated with reference to several guidelines and recently reported studies regarding perioperative ATT management for non-cardiac surgeries or endoscopic procedures[5,6,28-30]. The management consists of 3 ways according to ATT types; antiplatelets, warfarin, and DOACs. In patients with the risk of thromboembolism, preoperative aspirin monotherapy is sustained in antiplatelet-received patients, and warfarin is substituted by DOAC bridging (preferred) or heparin bridging. Regarding patients with DOACs, short-period discontinuation of DOACs (usually 1-2 d) is recommended and heparin bridging is usually not required, but heparin bridging might be considered if the thromboembolic risk is very high. Postoperatively, every antithrombotic drug is reinstituted as soon as possible.

Concerning the management of patients with antiplatelet drugs, some studies such as POISE-2 study have suggested that a slight increase in bleeding risk was observed in patients with continued antiplatelets during non-cardiac surgery[33,34], but most of other studies demonstrated that the bleeding events were not significantly increased [35,36]. Moreover, one large-scale retrospective cohort study was recently showed that the continued preoperative aspirin significantly reduced the rate of postoperative thromboembolism but was not associated with the occurrence of bleeding events[37]. In the current review, three studies showed that continued preoperative aspirin is not related to excessive SBL or increased occurrence of BC in patients with chronic antiplatelet therapy during or after hepatectomy[9,12,13]. Although the favorable management of antiplatelet-received patients during hepatectomy is still controversial, continued preoperative aspirin is one of the preferred options and should be considered.

In the clinical setting, when neurosurgeons or cardiologists judge the risk of thromboembolism as high, antiplatelet-recipient patients are sometimes managed by heparin bridging during perioperative discontinuation of antiplatelet drugs. This situation is probably because some cardiologists and surgeons are unaware of the preferred option of continued aspirin monotherapy for the perioperative management. The mechanism of heparin is different from that of antiplatelets, and heparin bridging is presently reported to be a significant risk factor for postoperative bleeding events

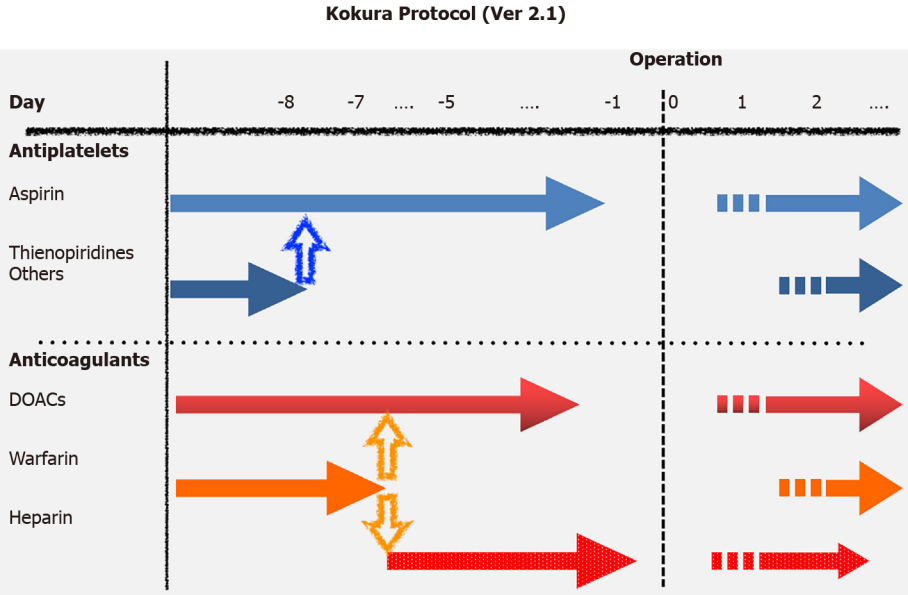

Figure 2 Recommended perioperative management protocol for patients undergoing antithrombotic therapy in case of hepatobiliary-pancreatic and gastrointestinal surgery. The management generally consists of 3 ways according to types of antithrombotic therapy; antiplatelet therapy, warfarin, and direct-acting oral anticoagulant (DOACs). In patients with thromboembolic risks, aspirin monotherapy is continued in patients receiving antiplatelet therapy, and warfarin is substituted by DOAC bridging (preferred) or heparin bridging. In case of DOAC, short-period discontinuation of DOACs (usually 1-2 d) without heparin bridging is generally recommended (with some modification needed if decreased renal function exists). Postoperatively, every antithrombotic agent is reinstituted as soon as possible (POD1-2). DOAC: Direct-acting oral anticoagulant.

[38,39]. Therefore, heparin bridging during antiplatelet discontinuation is not recommended and should not be used.

Concerning DOACs, only one report was included in the present review[14]. This study showed that perioperative short-period discontinuation of DOACs without heparin bridging was safe even for patients who undergo digestive surgery including hepatectomy, but patients who were managed by heparin bridging during DOAC discontinuation was at high risk of postoperative bleeding. Presently, DOACs are increasingly used for the prophylaxis of venous or arterial thromboembolic events. They are fast-acting drugs with their anticoagulant effect fading within 48 h after their withdrawal[28]. One large-scale multicenter prospective cohort study (the PAUSE study) was recently published, which examined outcomes in 3007 adult patients with atrial fibrillation who underwent DOAC therapy and received an elective non-cardiac procedure or surgery[40]. DOAC therapy was interrupted 1-2 d prior and reinstituted 1-2 d after the procedure or surgery. The occurrence of major bleeding 30 d after the procedure or surgery was 0.90%-1.85%, and arterial thromboembolic complication was occurred at the rate of 0.16%-0.60%. The study recommended that a centralized perioperative management of DOACs without heparin bridging can be performed safely for patients with atrial fibrillation. Although the PAUSE study included only a limited number of patients undergoing major gastroenterological surgery, the study included in the present review also suggested that the perioperative short-period cessation of DOACs without heparin bridging is the preferred management even for patients who receive major gastroenterological surgery including hepatectomy[14,37].

Regarding chemical prevention for VTE in hepatectomy, most of the studies included in the present review have demonstrated a potential risk of postoperative bleeding events in patients receiving pharmacological thromboprophylaxis, although its efficacy against VTE has not been shown, particularly in Asian patient population. VTE is fatal when it occurs during the perioperative period, and its prevention is of paramount importance. Although some guidelines in Western countries recommend pharmacological prevention for VTE during non-cardiac surgery[41-43], it is reported that there are racial differences in the rate of VTE between Western people and Asians [44]. In addition, in one systematic review regarding pharmacological prevention for VTE in Asian surgical patients[45], the risk of perioperative VTE in Asian patients is reported to be low even in the context of high risk for thromboembolism. The two large-scale cohort studies from Japan were recently showed that the incidence of clinically relevant VTE during or after major digestive surgery was 0-0.3%[37,46]. Currently, the safety and efficacy of pharmacological prevention with anticoagulation

drugs for VTE during hepatectomy is still controversial, particularly in Asian patient population. It is important to build evidence in order to classify risks individually according to each race is essential.

Summary and recommendations for future studies

Presently, the numbers of studies regarding the management of ATT during hepatectomy is limited. This patient population is expanding further, as the population ages and the prevalence of cardiovascular disease increases. Using reliable studies with good design, the definite guideline should be determined. Currently, one promising prospective multicenter cohort study was registered in the University Hospital Medical Information Network Clinical Trials Registry and is ongoing ["Study on the safety and feasibility of gastroenterological surgery in patients undergoing antithrombotic therapy (GSATT Study)", UMIN000038280]. In the future, the safety of ATT management during liver resection will be demonstrated by well-designed analyses like this study.

CONCLUSION

Hepatectomy in patients with chronic ATT can be performed safely without increase in the rates of bleeding complications, although the efficacy and safety of pharmacological prevention for VTE during hepatectomy remains controversial. Further investigation using reliable studies with good design must be required to establish definite protocol or guidelines.

ARTICLE HIGHLIGHTS

Research background

Little is unknown about the effect of chronic antithrombotic therapy (ATT) on bleeding complication during or after hepatectomy. In addition, the safety and effectiveness of chemical prevention for venous thromboembolism (VTE) remain controversial.

Research motivation

The goal of the present review was to clarify the effect of ATT on bleeding complications or increased surgical blood loss in hepatectomy.

Research objectives

The objective of the current systematic review was to investigate the effect of ATT on thromboembolism and bleeding in hepatectomy.

Research methods

Articles published between 2011 and 2020 were searched from Google Scholar and PubMed, and after careful reviewing of all studies, studies concerning ATT and hepatectomy were included. Data such as study design, type of surgery, type of antithrombotic agents, and surgical outcome were extracted from the studies.

Research results

Sixteen published articles, including a total of 8300 patients who underwent hepatectomy, were eligible for inclusion in the current review. All studies regarding patients undergoing chronic ATT showed that hepatectomy can be performed safely, and three studies have also shown the safety and efficacy of preoperative continuation of aspirin. Regarding chemical prevention for VTE, some studies have shown a potentially high risk of bleeding complications in patients undergoing chemical thromboprophylaxis; however, its efficacy against VTE has not been shown statistically, especially among Asian patients.

Research conclusions

Liver resection in chronically ATT-received patients can be performed safely without increase in the rate of bleeding complications, although the safety and efficacy of chemical thromboprophylaxis for VTE during liver resection is still controversial especially in Asian population.

Research perspectives

Further investigation using reliable studies with good design must be requisite to establish definite protocol or guidelines.

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META-ANALYSIS

Effects of intragastric balloon placement in metabolic dysfunction-associated fatty liver disease: A systematic review and meta-analysis

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Abstract

BACKGROUND

Metabolic dysfunction-associated fatty liver disease corresponds to a clinical entity that affects liver function triggered by the accumulation of fat in the liver and is linked with metabolic dysregulation.

AIM

To evaluate the effects of the intragastric balloon (IGB) in patients with metabolic dysfunction-associated fatty liver disease through the assessment of liver enzymes, imaging and several metabolic markers.

METHODS

A comprehensive search was done of multiple electronic databases (MEDLINE, EMBASE, LILACS, Cochrane and Google Scholar) and grey literature from their

article, revising the article and finally approving; de Oliveira CPMS and Bernardo WM conducted data analysis and interpretation and drafted the article .

Conflict-of-interest statement: Dr. Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work.

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inception until February 2021. Inclusion criteria involved patients with a body mass index > 25 kg/m^2 with evidence or previous diagnosis of hepatic steatosis. Outcomes analyzed before and after 6 mo of IGB removal were alanine aminotransferase (IU/L), gamma-glutamyltransferase (IU/L), glycated hemoglobin (%), triglycerides (mg/dL), systolic blood pressure (mmHg), homeostatic model assessment, abdominal circumference (cm), body mass index (kg/m^2) and liver volume (cm^3).

RESULTS

Ten retrospective cohort studies evaluating a total of 508 patients were included. After 6 mo of IGB placement, this significantly reduced alanine aminotransferase [mean difference (MD): 10.2, 95% confidence interval (CI): 8.12-12.3], gamma-glutamyltransferase (MD: 9.41, 95%CI: 6.94-11.88), glycated hemoglobin (MD: 0.17%, 95%CI: 0.03-0.31), triglycerides (MD: 38.58, 95%CI: 26.65-50.51), systolic pressure (MD: 7.27, 95%CI: 4.79-9.76), homeostatic model assessment (MD: 2.23%, 95%CI: 1.41-3.04), abdominal circumference (MD: 12.12, 95%CI: 9.82-14.41) and body mass index (MD: 5.07, 95%CI: 4.21-5.94).

CONCLUSION

IGB placement showed significant efficacy in improving alanine aminotransferase and gamma-glutamyltransferase levels in patients with metabolic dysfunction-associated fatty liver disease as well as improving metabolic markers related to disease progression.

Key Words: Intragastric balloon; Metabolic dysfunction-associated fatty liver disease; Homeostatic model assessment; Abdominal circumference; Body mass index

Core Tip: Metabolic dysfunction-associated fatty liver disease corresponds to the accumulation of fat in the liver and is linked with metabolic dysregulation. We evaluated the effects of the intragastric balloon in patients with metabolic dysfunction-associated fatty liver disease through the assessment of liver enzymes, imaging and several metabolic markers. Outcomes analyzed before and after 6 mo of intragastric balloon placement were alanine aminotransferase (IU/L), gamma-glutamyltransferase (IU/L), glycated hemoglobin (%) and other parameters related to metabolic disorders. This is the first systematic review and meta-analysis to assess the role of the intragastric balloon in the new definition of metabolic dysfunction-associated fatty liver disease.

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INTRODUCTION

The term nonalcoholic fatty liver disease, first proposed by Ludwig and collaborators in 1980[1] corresponds to a clinical entity that affects the histological structure and liver function triggered by the accumulation of fat in the liver unrelated to alcohol intake with a risk of developing nonalcoholic steatohepatitis and cirrhosis. It is estimated that this condition affects a quarter of the adult world population[2], and it will be the main cause of liver transplantation by 2030[3].

Recently, an international consensus panel of experts[4] proposed metabolic dysfunction-associated fatty liver disease (MAFLD) as a change in nomenclature and more appropriate term to reflect the pathophysiology and current knowledge of the

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disease rather than the outdated terms of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. The new definition is based on current knowledge of the role of metabolic dysfunction in the pathophysiology of fatty liver disease related mainly to obesity, type 2 diabetes mellitus and other metabolic disorders. Also, they provided diagnostic criteria to facilitate stratification and the subsequent management of patients along with new horizons for translational research and new treatments.

The natural history of fatty liver disease navigates through the initial stages of hepatic steatosis with progression to steatohepatitis and liver cirrhosis in certain chronic cases[5]. The treatment of these patients still represents a challenge[6]. Lifestyle changes and control of metabolic disorders are the mainstays of the therapeutic approach. Pharmacological therapies are promising but have not yet evidenced efficacy in regressing the inflammation and liver fibrosis associated with the evolution of the disease[7]. Bariatric surgery has gained notoriety, but the expansion of its indication as a form of treatment for MAFLD has been discussed in view of the added morbidity and irreversibility of different surgical modalities.

Research for alternative therapies is relevant in the treatment of MAFLD, with endoscopic bariatric and metabolic therapies, especially with the intragastric balloon (IGB), seen as a safe and less invasive treatment option[8-12]. The IGB is a widespread therapy for short-term control of obesity and its mechanism of action is based on the occupation of the gastric chamber, causing a delay in gastric emptying, an increase in the feeling of satiety and consequently a reduction in caloric intake. Currently, several models of IGB are available for clinical use, with variations in its design, volume, fluid *vs* air filled-balloons, implantation duration and efficacy[13].

This study aims to evaluate the impact of IGB placement on MAFLD through the assessment of liver enzymes, certain metabolic markers and imaging parameters.

MATERIALS AND METHODS

Protocol registration

This study was performed in conformity with the PRISMA[14] guidelines, and it was registered in the PROSPERO[15] database under the file number (CRD42020204485). The study was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo.

Eligibility criteria

Data search was made without limitations of language or publication date. The eligibility criteria adopted were: (1) population: patients with a body mass index (BMI) > 25 kg/m^2 with evidence or previous diagnosis of hepatic steatosis; (2) intervention: endoscopic IGB placement; (3) comparator: the outcomes in baseline and post IGB moments; and (4) outcomes: alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), glycated hemoglobin, triglycerides, systolic blood pressure, homeostatic model assessment (HOMA-IR), abdominal circumference and liver volume were analyzed.

Studies that did not involve the use of an IGB for at least 6 mo of duration were excluded.

Search and study selection

We performed a search in electronic databases (MEDLINE, EMBASE, Cochrane, LILACS) and grey literature, from their inception until February 2021. As a search strategy, we used descriptors available from the United States National Library of Medicine Medical Subject Headings and other related terms that increased the sensitivity of search as described in Table 1. Two independent reviewers conducted the assessment of eligibility criteria. Disagreements were resolved by consensus or consultation with a third reviewer.

Data collection process

The data related to the analyzed outcomes were tabulated in an Excel table and included the IGB model used as well as the average volume of filling of the balloons and the number of calories in the diet associated with the treatment. In the comparison studies between IGB and diet, only data from the balloon intervention group were extracted, and not all outcomes were evaluated in all studies. When data of the published articles were insufficient, the corresponding authors were consulted by e-mail for further elucidation.

Table 1 Search strategy

Search strategy	
Medline	[(intragastric OR bariatric endoscopy OR balloon OR balloons OR bubble OR bubbles OR gastric balloon OR balloons)] AND [(mafld OR non alcoholic fatty liver disease OR nafld OR fatty liver OR nonalcoholic steatohepatitis OR nash OR nonalcoholic steatohepatitis OR alanine transaminase OR aspartate aminotransferase OR gamma-glutamyltransferase OR alkaline phosphatase OR fatty liver OR steatohepatitis OR steatohepatitis OR steatosis of liver OR visceral steatosis OR visceral]
MEDLINE, Embase, Cochrane, LILACS	[(intragastric OR balloon)] AND [(fatty liver)]
Grey literature	[(intragastric OR balloon)] AND [(fatty liver)]

Table 2 Grading recommendations assessment, development and evaluation certainty evidence assessment table

	Certainty evidence assessment							Study event rates (%)		
	Participants (studies) follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With post-IGB	With pre-IGB	Risk difference with Pre-IGB
ALT	1114 (10 observational studies)	Not serious	Serious[1]	Not serious[2]	Not serious	Publication bias strongly suspected[3]	⊕⊕◯◯, Low	557	557	Mean 10.27 UI/L more (8.25 more to 12.29 more)
GGT	1014 (8 observational studies)	Not serious	Not serious	Not serious[2]	Not serious	None	⊕⊕⊕⊕, High	507	507	Mean 9.23 UI/L more (6.88 more to 11.58 more)
Hb1Ac	300 (6 observational studies)	Not serious	Not serious	Not serious[4]	Not serious	Publication bias strongly suspected[3]	⊕⊕⊕◯, Moderate	150	150	Mean 0.17 % higher (0.03 higher to 0.31 higher)
Triglycerides	564 (6 observational studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕, High	282	282	Mean 38.58 mg/dL higher (26.65 higher to 50.51 higher)
Systolic blood pressure	468 (3 observational studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕, High	234	234	Mean 7.27 mmHg higher (4.79 higher to 9.76 higher)
HOMA-IR	378 (5 observational studies)	Not serious	Serious[1]	Not serious	Not serious	None	⊕⊕⊕◯, Moderate	189	189	Mean 2.07 higher (1.64 higher to 2.49 higher)
BMI	912 (8 observational studies)	Not serious	Not serious	Not serious	Not serious	Strong association	⊕⊕⊕⊕, High	456	456	Mean 5.07 kg/m^2 higher (4.21 higher to 5.94 higher)
Waist	672 (7 observational studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕, High	336	336	Mean 12.12 cm higher (9.82 higher to 14.41 higher)
Liver volume	32 (2 observational studies)	Not serious	Not serious	Not serious	Serious[5]	None	⊕⊕⊕◯, Moderate	16	16	MD 303.24 higher (56.66 lower to 663.15 higher)

[1]Heterogeneity > 50%.
[2]Indirect measurement of hepatic steatosis.
[3]Presence of Outlier.
[4]Surrogate endpoint.
[5]Wide confidence interval. Overall certainty of evidence definition: ⊕◯◯◯: Very low-Any estimate of effect is very uncertain; ⊕⊕◯◯: Low-Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; ⊕⊕⊕◯: Moderate-Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; ⊕⊕⊕⊕: High-Further research is very unlikely to change our confidence in the estimate of effect; MD: Mean difference; IGB: Intragastric balloon; HbA1c: Glycated hemoglobin; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase; HOMA-IR: Homeostatic model; BMI: Body mass index.

Risk of bias and evidence quality

The risk of bias was assessed by the Risk of Bias in Non-randomized Studies-of Interventions tool[16]. The quality of evidence, expressed in high, moderate, low and very low, was assessed utilizing the objective criteria from Grading Recommendations Assessment, Development, and Evaluation (Table 2) using the GRADEpro-Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada)[17].

Statistical analysis

Our outcomes were continuous variables, and values of means and standard deviations were used for the statistical analysis. In studies that expressed the results in median and interquartile range, mathematical formulas were used for the data conversion[18].

The data of interest extracted from the selected studies were meta-analyzed using the RevMan software (Review Manager Software version 5.4-Cochrane Collaboration Copyright© 2020) using the inverse variance test. The mean values of each continuous outcome were calculated as well as the 95% confidence interval (CI). $P < 0.05$ were considered statistically significant, and the results were exposed through forest plots. Heterogeneity was calculated using the Higgins method (I^2)[19]. When heterogeneity < 50% was found, the fixed-effect model was used. In cases of heterogeneity > 50%, the funnel plot analysis was performed, and outlier cases were removed to maintain the analysis by a fixed effect. In cases where no outlier was evidenced, the analysis by the random effect model was performed. The correlation between outcomes was performed using the meta-regression using the Comprehensive Meta-Analysis tool version 2.2.057.

RESULTS

Study selection

The article selection process is shown in Figure 1. After applying the eligibility criteria, eleven articles were included in the qualitative analysis. Ten articles were included in the quantitative analysis, considering that one of the studies was a randomized controlled clinical trial. The individual results of each study are described in Table 3.

Risk of bias among the studies

Two studies presented moderate risk and eight studies presented low risk in the global analysis according to the Risk of Bias in Non-randomized Studies-of Interventions criteria. The study by Takihata *et al*[20] had a risk of serious bias in the classification of interventions because the patients themselves chose whether to participate in the IGB intervention group or the lifestyle modification (diet/physical exercise) group. The study by Nikolic *et al*[21] presented a moderate risk of lack of data due to the exclusion of participants due to a loss of follow-up in the study. The overall risk of bias in each study is detailed in Figure 2.

Meta-analysis

ALT (IU/L): Ten studies[20-29] with 508 patients were included in the meta-analysis of the outcome. The mean reduction in serum ALT values was 10.2 (95%CI: 8.12-12.3; $P < 0.01$) after 6 mo, favoring the use of the IGB. This analysis showed high heterogeneity ($I^2 = 56\%$), and the study by Bazerbachi *et al*[22] was identified as an outlier in the funnel plot analysis. After removing this study from the analysis, the heterogeneity remained at < 50% ($I^2 = 32\%$), maintaining the analysis by a fixed effect (Figure 3).

Table 3 Results of individual studies

Ref.	*n*	Balloon volume (cm^3)	ALT (UI/L)		GGT (UI/L)		HbA1c (%)		Triglycerides (mg/dL)		Waist (cm)		HOMA-IR		BMI (kg/m^2)		SBP (mmHg)	
			Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB	Pre-IGB	Post-IGB
Forlano *et al*[25], 2010	120	500	39.3 (25.6)	24.4 (10.0)	37.5 (20.5)	24.5 (17.1)	-	-	-	-	-	-	-	-	43.1 (8.0)	38.8 (8.0)	-	-
Bazerbachi *et al*[22], 2021	21	-	91.6 (59.9)	39.4 (25.4)	-	-	7.7 (1.6)	6.5 (1.2)	-	-	128.9 (15.4)	119.7 (16.9)	-	-	43.2 (6.8)	37.9 (6.6)	-	-
Nikolic *et al*[21], 2011	33	600	30 (23.25)	27 (16.75)	31 (50.75)	21 (36.75)	4.7 (0.50)	4.6 (0.45)	124 (86.25)	124 (124.75)	122 (21.00)	110 (14.25)	-	-	41.4 (5.25)	35.6 (5.25)	-	-
Donadio *et al*[23], 2009	40	500	30.7 (14.0)	23.4 (9.3)	29.8 (19.1)	28.0 (28.1)	5.4 (0.5)	5.3 (0.4)	134.1 (67.8)	118.8 (66.5)	125.9 (18.6)	115.8 (17)	4.1 (2.1)	2.7 (1.6)	44.8 (8.9)	38.9 (6.8)	129.3 (14.0)	122.6 (10.4)
Stimac *et al*[29], 2011	166	600	34.7 (31.5)	26.5 (23.1)	33.3 (23.3)	24.7 (16.9)	-	-	118.6 (87.6)	81.0 (66.4)	127.8 (16.7)	113.3 (18.9)	-	-	41.6 (7.5)	35.8 (7.9)	130.9 (14.5)	124.2 (14.1)
Takihata *et al*[20], 2014	8	Variable	57.1 (55.6)	43.1 (48.8)	53.0 (25.4)	40.1 (19.3)	6.70 (1.43)	6.38 (1.49)	223.2 (194.8)	153.2 (80.6)	129.2 (8.3)	123.8 (12.3)	12.3 (10.9)	8.0 (7.3)	45.2 (5.9)	41.0 (6.2)	-	-
Folini *et al*[24], 2014	40	-	25.9 (10.31)	18.1 (5.96)	27.8 (27.57)	17.9 (12.21)	6.5 (1.17)	6.0 (0.74)	-	-	130.2 (13.96)	118 (13.01)	5.2 (2.23)	2.3 (1.66)	43.8 (6.62)	38.2 (6.19)	-	-
Ricci *et al*[26], 2008	65	-	31.5 (19.33)	24.0 (10.67)	31.0 (16.05)	23.5 (12.6)	-	-	-	-	-	-	4.71 (2.11)	3.10 (2.79)	-	-	-	-
Sekino *et al*[27], 2011	8	1000	74.2 (49.67)	56.7 (42.40)	57.00 (23.11)	41.25 (14.74)	6.30 (1.15)	6.31 (1.29)	251 (168.9)	163 (62.0)	-	-	6.74 (1.27)	3.27 (1.18)	-	-	-	-
Tai *et al*[28], 2013	28	500	49 (45.25)	22 (23.25)	-	-	-	-	149.0 (49.00)	88.5 (39.75)	101.9 (8.9)	90.6 (9.3)	-	-	32.4 (3.7)	28.5 (3.7)	136.8 (14.30)	125.9 (11.15)

IGB: Intragastric balloon; HbA1c: Glycated hemoglobin; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase; HOMA-IR: Homeostatic model; BMI: Body mass index; SBP: Systolic blood pressure.

GGT (IU/L): Eight studies[20,21,23-27,29] with 479 patients were included in the outcome meta-analysis (Figure 4). The mean reduction in serum GGT levels was 9.41 (95%CI: 6.94-11.88; $P < 0.01$) after 6 mo of IGB use.

Glycated hemoglobin (%): Six studies[20-24,27] with 150 patients analyzed the effect of the IGB on glycated hemoglobin (Figure 5). The mean reduction in serum glycated hemoglobin values was 0.17% (95%CI: 0.03-0.31; $P = 0.02$) after 6 mo of IGB placement.

Triglycerides (mg/dL): Six studies[20,21,23,27-29] with 282 patients analyzed the effect

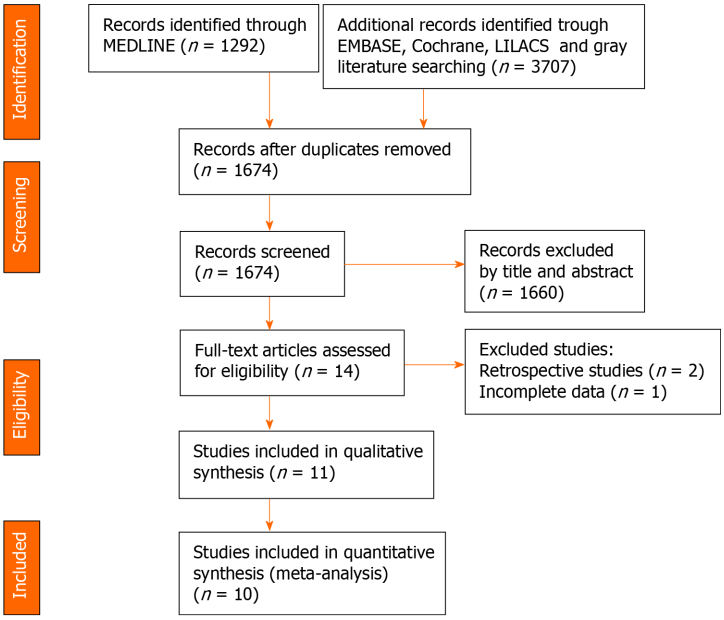

Figure 1 PRISMA flow diagram.

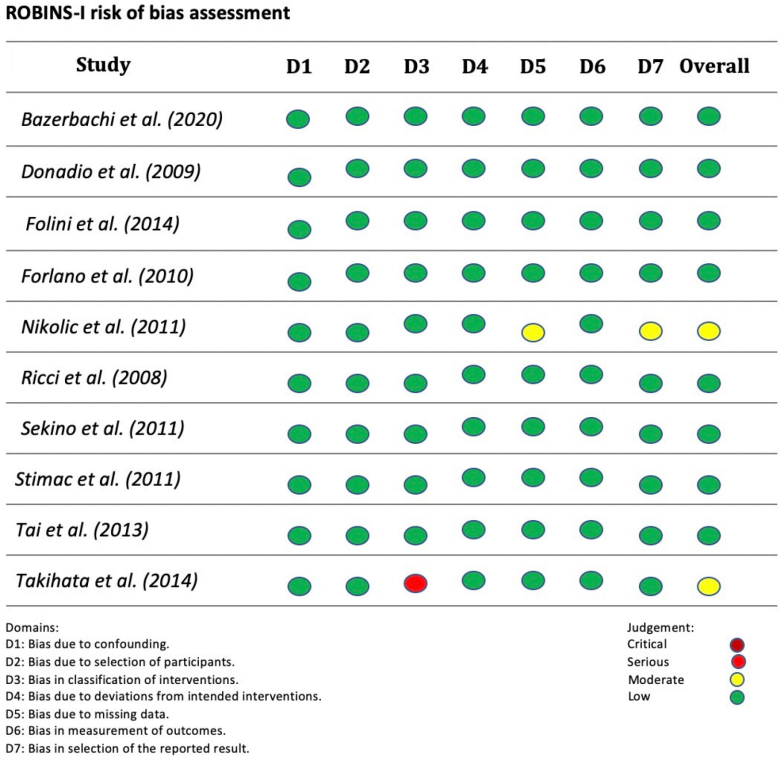

Figure 2 Risk of bias assessment (risk of bias in non-randomized studies-of interventions).

of the IGB on serum triglyceride levels (Figure 6). The mean reduction in triglycerides was 38.58 (95%CI: 26.65-50.51; $P < 0.01$) after 6 mo of use of the balloon.

Systolic blood pressure (mmHg): Three studies[23,28,29] with 234 patients analyzed the effect of the IGB on blood pressure levels (Figure 7). After 6 mo of IGB placement, the mean reduction in systolic blood pressure was 7.27 (95%CI: 4.79-9.76; $P < 0.01$).

HOMA-IR: Five studies[20,23-25,27], with 161 patients, were included in the outcome meta-analysis. The mean reduction in HOMA-IR values was 2.23 (95%CI: 1.41-3.04; $P < 0.01$) after 6 mo using the IGB (Figure 8).

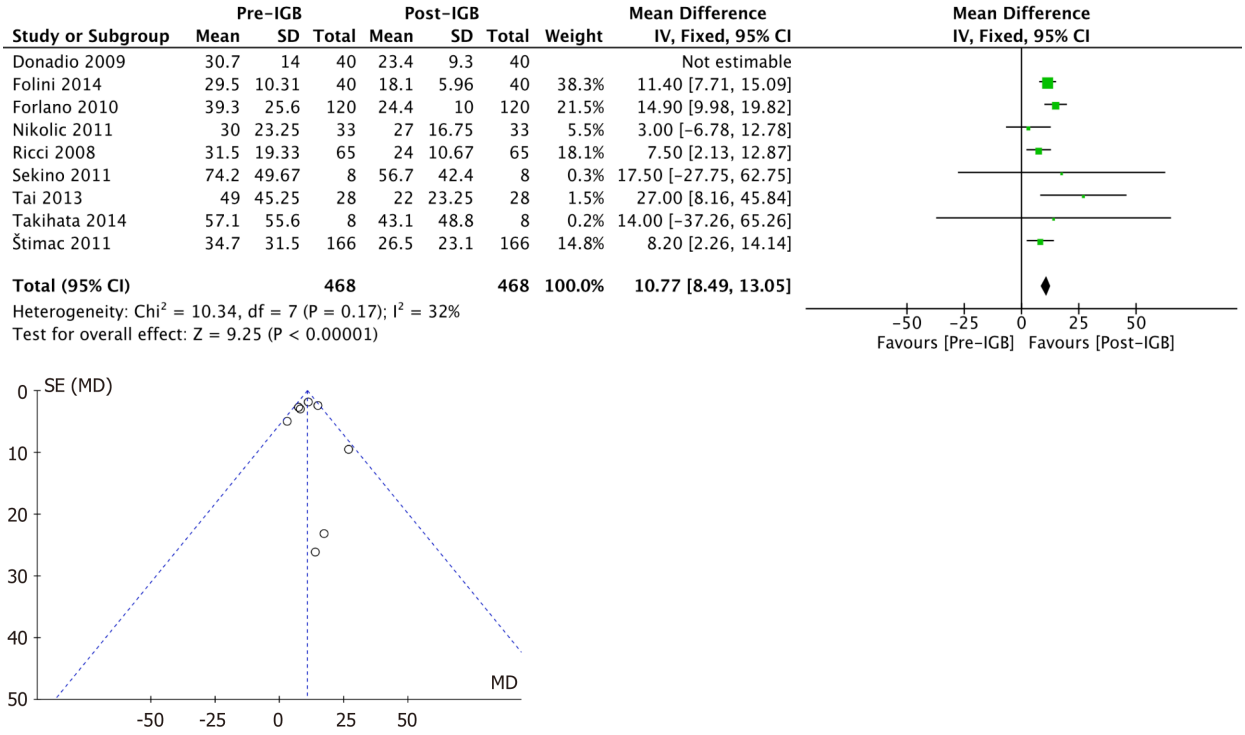

Figure 3 Forest plot of alanine aminotransferase and funnel plot without outlier. CI: Confidence interval; IGB: Intragastric balloon.

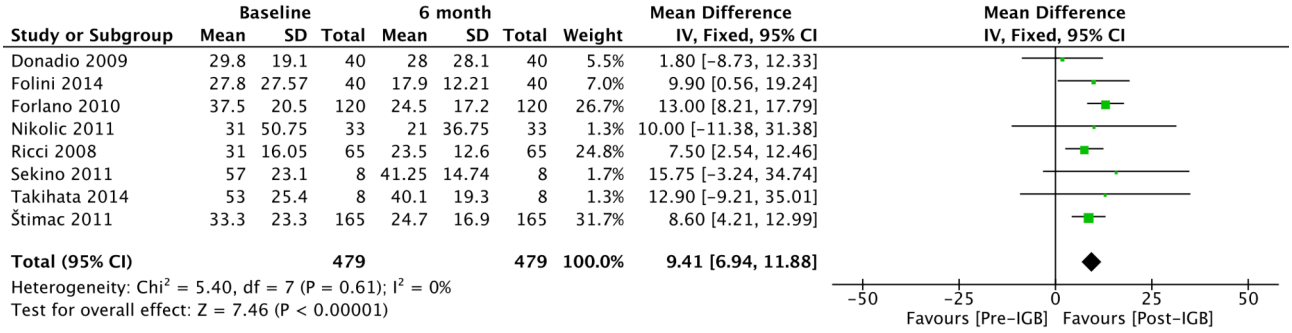

Figure 4 Forest plot of gamma-glutamyltransferase. CI: Confidence interval; IGB: Intragastric balloon.

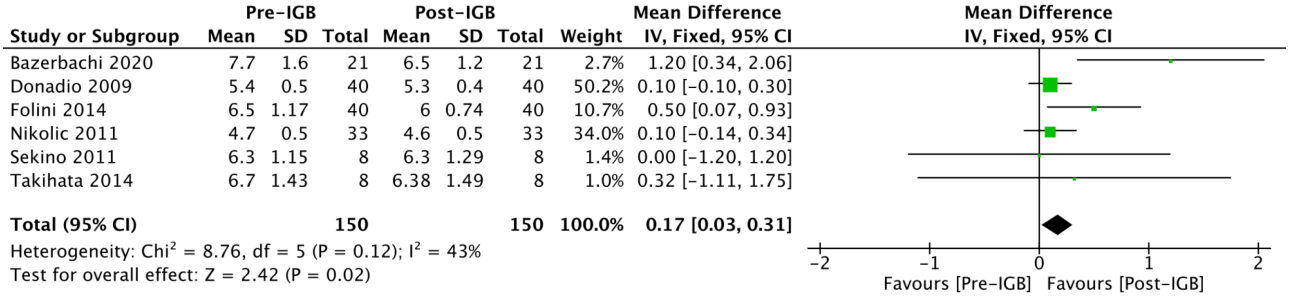

Figure 5 Forest plot of glycated hemoglobin. CI: Confidence interval; IGB: Intragastric balloon.

Abdominal circumference (cm): Seven studies[20-24,28,29], with 336 patients (Figure 9), were included in the outcome meta-analysis. The mean reduction in abdominal circumference was 12.12 (95%CI: 9.82-14.41; $P < 0.01$) after 6 mo of IGB use.

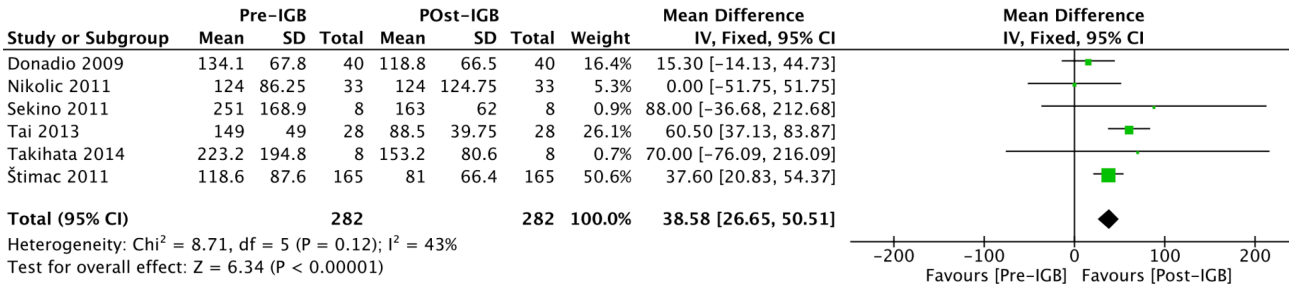

Figure 6 Forest plot of triglycerides. CI: Confidence interval; IGB: Intragastric balloon.

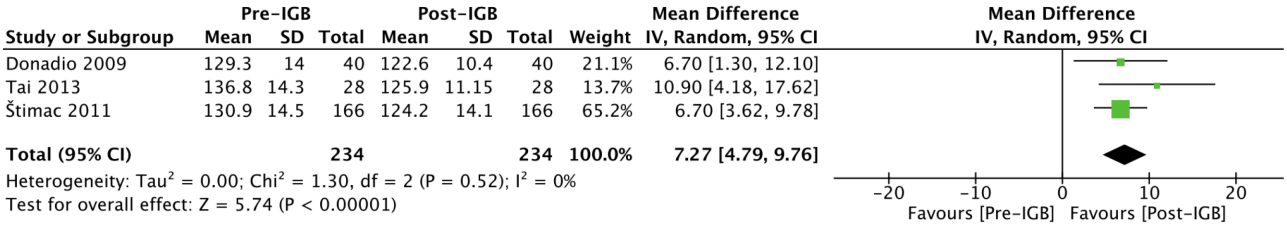

Figure 7 Forest plot of systolic blood pressure. CI: Confidence interval; IGB: Intragastric balloon.

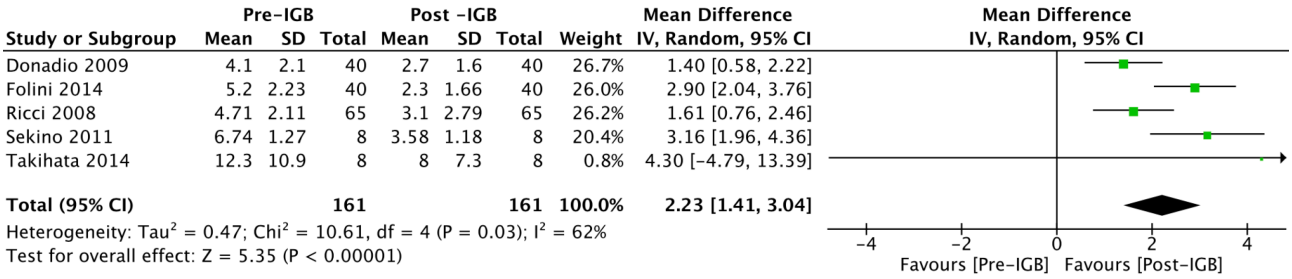

Figure 8 Forest plot of homeostatic model assessment. CI: Confidence interval; IGB: Intragastric balloon.

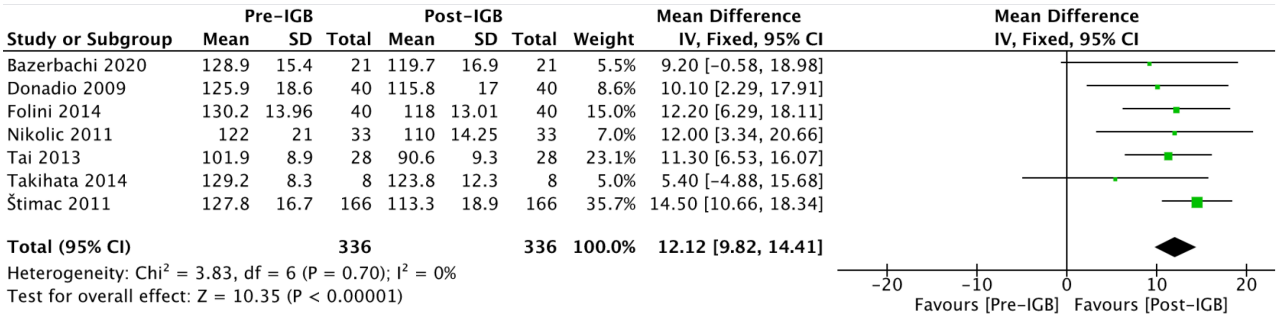

Figure 9 Forest plot of waist circumference. CI: Confidence interval; IGB: Intragastric balloon.

BMI (kg/m²): Eight studies[20-25,28,29], with 456 patients, were included in the outcome meta-analysis (Figure 10). The mean reduction in BMI was 5.07 (95%CI: 4.21-5.94; $P < 0.01$) after 6 mo of use of the IGB.

Liver volume (cm³): Two studies[20,27], with 16 patients, were included in the meta-analysis of the outcome (Figure 11). The mean reduction in liver volume was 303 cm³ (95%CI: -56.6-663.15; $P = 0.1$) after 6 mo of using the IGB but without statistical significance.

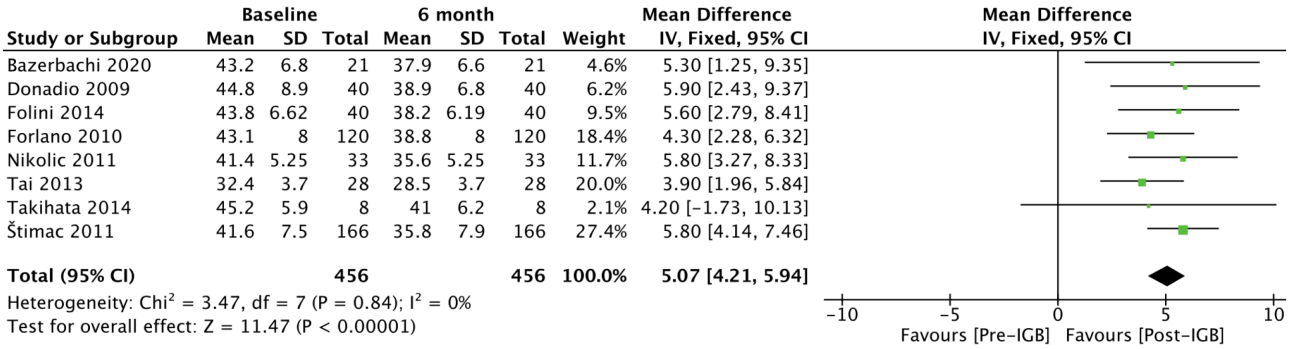

Figure 10 Forest plot of body mass index. CI: Confidence interval; IGB: Intragastric balloon.

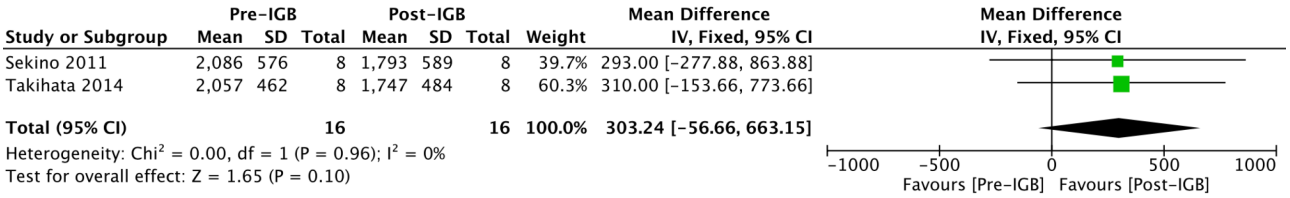

Figure 11 Forest plot of liver volume. CI: Confidence interval; IGB: Intragastric balloon.

Meta-regression

In the analysis by logistic meta-regression, there was no statistically significant correlation between the reduction in ALT and the reduction in BMI, with a $P = 0.37$. The graphical correlation between the outcomes is shown in Figure 12.

DISCUSSION

This is the first meta-analysis to assess the role of the IGB in the new definition of MAFLD. The IGB is an endoscopic bariatric and metabolic therapy for short-term management of obesity that has gained popularity due to its low rate of complications and reversibility[30]. Its mechanism of action is based on the occupation of space in the stomach causing a delay in gastric emptying, changes in gastric accommodation, neurohormonal effects, increased feelings of satiety and consequently a reduction in caloric intake[31]. A meta-analysis of randomized clinical trials published in 2020[13] evidenced that the IGB placement provided a loss of 17.98% of excess weight compared to the control group, showing to be an effective technique for weight loss. However, its metabolic effects were not evaluated.

The inclusion criteria for MAFLD showed that factors such as obesity, type 2 diabetes mellitus and metabolic disorders [increased waist circumference, increased blood pressure, lipidogram abnormalities, insulin resistance (IR) and increased C-reactive protein] were isolated variables related to progression to the most severe forms of liver disease under histopathological analysis[32,33]. Therefore, the control of progression factors is of fundamental importance in the management of these patients.

In the analysis of the metabolic parameters obtained by our study, we found results that show that IGB placement improves glycated hemoglobin, triglycerides, systolic blood pressure, abdominal circumference and HOMA-IR parameters. The improvement in such outcomes reflects a positive effect of IGB on metabolic dysfunction parameters, which are inclusion criteria in the new MAFLD classification and nomenclature.

The main relationship between obesity, fatty liver and metabolic syndrome appears to be in IR. IR is associated with a decrease in circulating adiponectin, a hormone secreted by adipocytes, that triggers fatty acid oxidation in the liver, favoring the increase and accumulation of visceral fat[34]. According to Bazerbachi *et al*[22], IGB has a weight-dependent pathway and a weight-independent pathway justifying the improvement in both the metabolic and inflammatory profiles of liver disease. The first is related to an improvement of IR in peripheral organs. The second, in turn, is

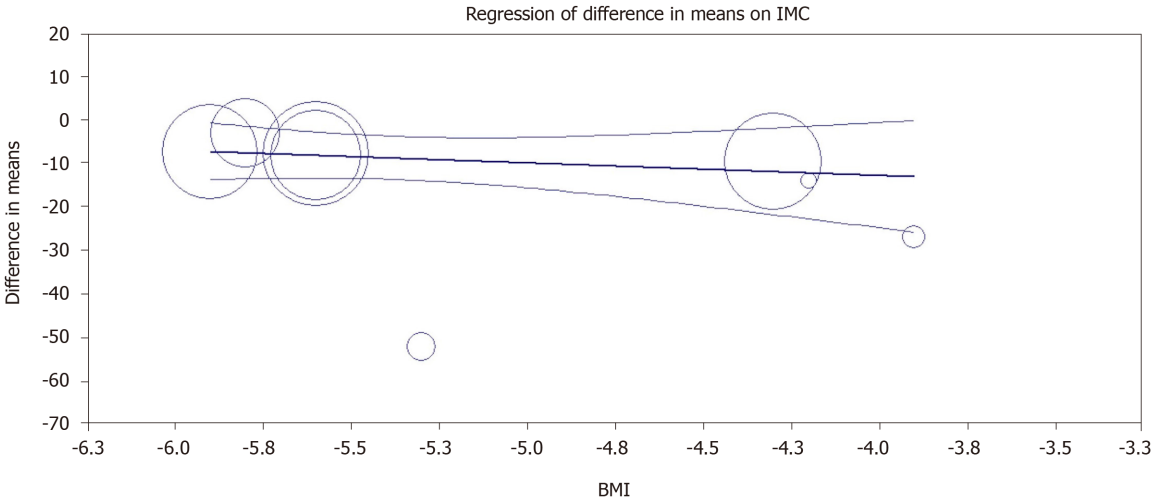

Figure 12 Meta-regression and the correlation between alanine aminotransferase and body mass index. BMI: Body mass index.

linked to a downregulation in ghrelin and hunger control, a reduction of postprandial glycemia and an improvement of the action of Sirtuin 1[35]. In this sense, the improvement of IR, represented by the evaluation of HOMA-IR[36], a mathematical model that assesses IR and functional capacity of pancreatic beta cells, seems to have a fundamental role in the positive impact of IGB on MAFLD.

In the meta-regression correlating the reduction in BMI with the reduction in liver enzymes, no statistically significant relationship was found between the two variables, showing that the improvement in ALT levels was an independent outcome of weight loss after the use of the IGB.

As demonstrated in the results of our meta-analysis, there were a statistically significant reduction in ALT and GGT levels, inferring a significant positive response in the progression of MAFLD. Although the histological evaluation by percutaneous liver biopsy is the gold standard in the evaluation of the degree of steatosis and steatohepatitis and the presence of fibrosis, this still presents limitations regarding its availability and risk of adverse events (AEs). The main AEs range from transient hypotension and pain to more serious complications such as bleeding, pneumothorax and death. A case series of 847 patients described by Filingeri *et al*[37] reported an incidence of post-procedural bleeding of approximately 2.4%.

Considering the risk of AEs, the use of alternative methods to assess clinical evolution and improvement, such as biomarkers and certain imaging methods, is necessary. The use of liver enzymes as an indirect marker of liver steatosis is controversial. Studies have shown that elevated liver enzymes can be used as a predictor of liver inflammation in obese individuals regardless of metabolic syndrome[38]. In patients undergoing bariatric surgery, the reduction in ALT and GGT is a predictor of improvement in lobular inflammation and liver fibrosis assessed in biopsies[39]. However, patients with advanced fibrosis may have normal transaminase levels[40].

Two of the studies found in our data search[10,22] demonstrated histopathological improvement in liver biopsies 6 mo after placement of IGB. Because they are studies with different designs, they could not be correlated in this meta-analysis. According to a randomized clinical trial[10] that included 18 patients, there was a statistically significant reduction in the nonalcoholic fatty liver disease Activity Score in the comparison between the use of IGB and sham procedure (decrease from score 5 to 2 with $P < 0.03$). A similar endpoint was found in the uncontrolled study conducted by Bazerbachi *et al*[22], which included 21 patients demonstrating histological improvement through nonalcoholic fatty liver disease Activity Score (decrease from score 4 to 1 with $P < 0.001$), an improvement in liver fibrosis measured by nuclear magnetic resonance and a reduction in ALT levels after 6 mo of IGB use.

In the assessment of the impact of IGB on image parameters of hepatic steatosis, the studies analyzed did not show linearity in the assessment methods. Folini *et al*[24] found a positive correlation between the improvement in the fraction of liver fat, measured by magnetic resonance imaging, and a reduction in GGT, BMI and waist circumference 6 mo after IGB placement. Similar results were evidenced by Bazerbachi *et al*[22], which found a reduction in hepatic fibrosis, measured on nuclear magnetic resonance elastography, after IGB use. In the meta-analysis of liver volume by

computed tomography, assessed by two studies involving 16 patients, a reduction of 330 cm^3 was observed after 6 mo of IGB placement but without statistical significance.

Regarding adverse effects, five studies[21,25,27-29] evaluated reported some AEs. The main ones being nausea, vomiting and abdominal pain, which were mostly controlled with symptomatic medications. Only three studies[21,25,29] reported early balloon withdrawal due to refractory symptoms. No study reported deaths or serious AEs. In a meta-analysis[41] including 6101 patients, nausea/vomiting and abdominal pain in 23% and 19.9% of patients, respectively, was described. Serious complications such as perforation and death were reported in 0.1% and 0.05%, respectively[41].

This study has some limitations. The short follow-up time (the studied outcomes were analyzed 6 mo after the insertion of the IGB) and the heterogeneity of the patients included in the studies shows how obesity is a plural disease that makes long-term results difficult to assess. Another limitation of our study corresponds to the indirect analysis of the improvement of hepatic steatosis employing liver enzymes, without a significant sample of histopathological analysis, considered as the gold standard as well as the existence of only one randomized controlled study on the subject. This showed the difficulty in including the biopsy in controlled studies due to its risks, costs and availability.

Because MAFLD is a disease with a high prevalence and complex pathophysiology that involves a multidisciplinary approach of the patients with dietary, pharmacological and often surgical interventions, the IGB should be considered as another tool in the therapy of this population. Its positive effects in the control of metabolic disorders, biomarkers of hepatic metabolism and histology of patients with MAFLD may play an important role in controlling this new worldwide epidemic.

CONCLUSION

The IGB showed significant efficacy in reducing liver enzymes in patients with MAFLD as well as improving metabolic parameters related to disease progression such as systolic blood pressure, triglycerides, HOMA-IR, waist circumference and glycated hemoglobin.

ARTICLE HIGHLIGHTS

Research background

Endoscopy has improved and has become the treatment of several diseases in recent decades. Bariatric endoscopy, through its various devices, helps in the treatment of obesity and its complications. Thus, the intragastric balloon (IGB) proves to be an effective and safe therapy for coping with this disease, and its indications have increased.

Research motivation

Metabolic dysfunction-associated fatty liver disease (MAFLD) corresponds to the accumulation of fat in the liver linked with metabolic dysregulation and has a high prevalence rate among the population. Unfortunately, no pharmacological therapy has yet shown efficacy in its treatment. In this sense, there is a need for new therapies to treat this new global epidemic.

Research objectives

We aimed to evaluate the effect of IGB in patients with MAFLD through the assessment of liver enzymes, imaging and metabolic markers in a systematic review of literature and meta-analysis.

Research methods

This systematic review was conducted according to the PRISMA guidelines and registered in PROSPERO international database. The search was performed in the electronic databases (MEDLINE, Embase, Cochrane, LILACS) and grey literature. The quality of evidence was assessed utilizing criteria from Grading Recommendations Assessment, Development, and Evaluation. The risk of bias was assessed by the Risk of Bias in Non-randomized Studies-of Interventions tool and the data were meta-analyzed using the RevMan software (Review Manager Software version 5.4-Cochrane

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Research results

Ten studies (non-randomized studies-of interventions) with 508 patients were meta-analyzed from an initial search of 1674 articles. The outcomes analyzed before and after 6 mo of IGB removal were alanine aminotransferase (IU/L), gamma-glutamyl-transferase (IU/L), glycated hemoglobin (%), triglycerides (mg/dL), systolic blood pressure (mmHg), homeostatic model assessment, abdominal circumference (cm), body mass index (kg/m^2) and liver volume (cm^3). After 6 mo of use, the IGB showed an improvement in alanine aminotransferase, gamma-glutamyltransferase, glycated hemoglobin, triglycerides, systolic blood pressure, homeostatic model assessment, abdominal circumference and body mass index. The liver volume analysis showed a non-statistically significant reduction.

Research conclusions

Our findings suggest that IGB had a significant improvement in liver enzymes (alanine aminotransferase and gamma-glutamyltransferase) in patients with MAFLD as well as improved metabolic biomarkers related to disease progression.

Research perspectives

Future studies should assess prolonged follow-up of patients after the intervention to analyze the long-term response to the improvements observed in the initial studies. A histological analysis using liver biopsies seems to be the best method of analyzing the effects of the IGB on the progression of MAFLD, and further studies should consider this method of evaluation.

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