Evidence for preventing EVRB in cirrhotic patients: A systematic review

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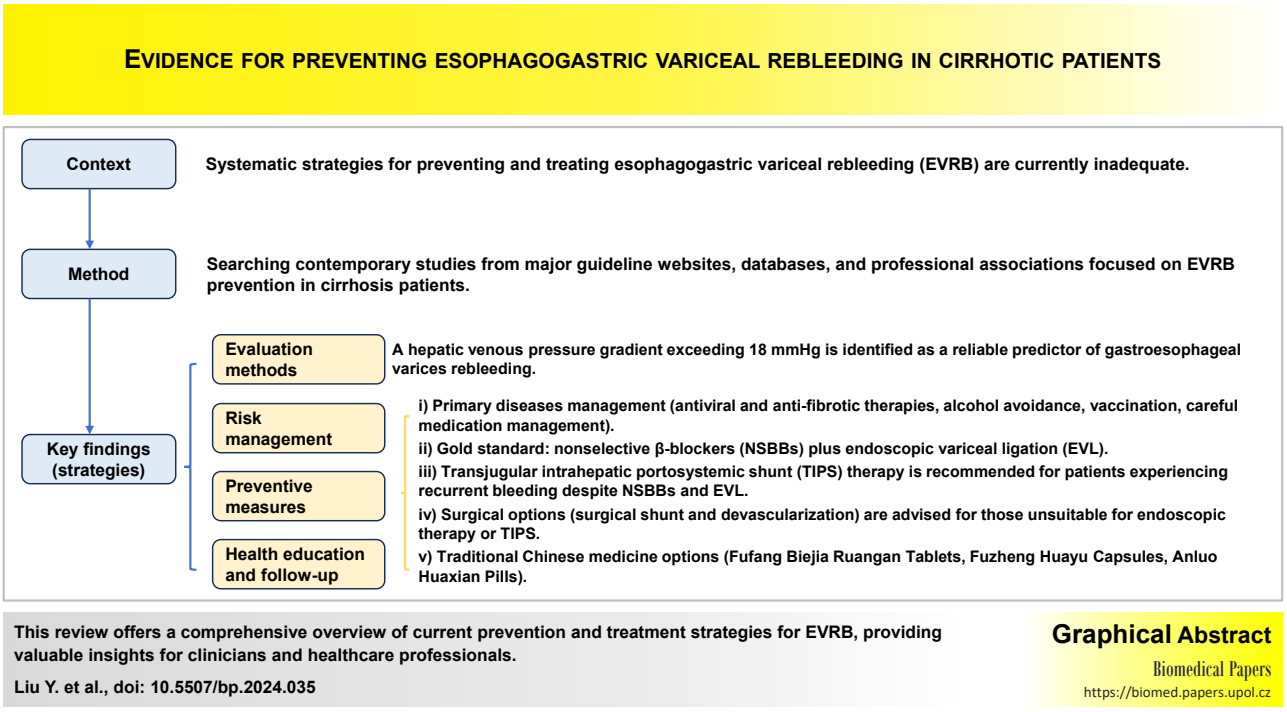
Systematic strategies for preventing and treating esophagogastric variceal rebleeding (EVRB) are currently inadequate. This systematic review aimed to update this critical gap by searching contemporary studies from major guideline websites, databases, and professional associations focused on EVRB prevention in cirrhosis patients. Key findings highlight evaluation methods, risk management, preventive measures, health education, and follow-up strategies. Notably, a hepatic venous pressure gradient exceeding 18 mmHg is identified as a reliable predictor of gastroesophageal varices (GOV) rebleeding. Effective management of primary diseases is crucial, with methods including antiviral and anti-fibrotic therapies, alcohol avoidance, vaccination, and careful medication management. The combination of nonselective β-blockers (NSBBs) and endoscopic variceal ligation (EVL) is established as the gold standard for secondary EVRB prevention. For patients experiencing recurrent bleeding despite NSBBs and EVL, transjugular intrahepatic portosystemic shunt (TIPS) therapy is recommended. Surgical options, such as surgical shunt and devascularization, are advised for those unsuitable for endoscopic therapy or TIPS, particularly in Child-Pugh A and B patients unresponsive to treatment. Additionally, traditional Chinese medicine options, such as Fufang Biejia Ruangan Tablets, Fuzheng Huayu Capsules, and Anluo Huaxian Pills, have shown promise in improving hepatic fibrosis and GOV in cirrhotic patients. This review offers a comprehensive overview of current prevention and treatment strategies for EVRB, providing valuable insights for clinicians and healthcare professionals.



Key words: liver cirrhosis, esophagogastric varices, prevention, rebleeding, evidence-based nursing

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INTRODUCTION

The morbidity and mortality of liver cirrhosis have increased annually[1]. Hepatic cirrhosis is the foremost cause of portal hypertension, which can lead to esophagogastric variceal rebleeding (EVRB) within 2 years and a recurrent early or late rebleeding episode[2]. EVRB is defined as the occurrence of a single episode of clinically significant rebleeding from portal hypertensive sources from 120 h or more after the initial bleeding and hemostasis[3]. Among those recovered from initial bleeding, untreated individuals were exposed to a high rate of rebleeding (60% within 1 year) and a mortality rate of 30% (ref.[4,5]). In clinical practice, secondary prophylaxis is commonly recommended for preventing further episodes of variceal bleeding and reducing associated mortality in cirrhotic patients, which generally involves drug therapy, endoscopic therapy, trans jugular intrahepatic portosystemic shunt (TIPS) and surgical portocaval shunts[6].

Indeed, the nursing care of EVRB is still highly relied on clinical experiences of nursing professionals. With the rapid development of medical technology, there is a rapid update in evidence-based clinical practices. To date, a series of guidelines and expert consensus have been promulgated in mainland China on the management of EVRB, but there is still a lack of systematic review on its prevention and management.

The aim of this systematic review was to summarize the evidence related to the prevention of EVRB in patients with cirrhosis.

MATERIALS AND METHODS

Search strategies

We searched all literatures, published before July 1, 2023, related to the prevention of EVRB in cirrhosis using a computer from top to bottom based on the 6S model[7]. Also, we searched the guideline websites, including Guidelines International Network (GIN), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines Network (SIGN), China Guideline Clearinghouse (CGC) and National Institute for Health and Clinical Excellence (NICE). The searched evidence-based databases included UpToDate, Cochrane Library, BMJ Best Practice and JBI model of evidence-based healthcare. The comprehensive databases included PubMed, Embase, Web of Science, Wanfang Digital Periodicals (WANFANG), China Biomedical Literatures database (CBM) and China National Knowledge Infrastructure (CNKI). Moreover, we also searched websites of the European Association for the Study of Liver (EASL), American Association for the Study of Liver Diseases (AASLD), the Italian Association for the Study of the Liver (AISF) and Asian Pacific Association for the Study of the Liver (APASL). Articles published in Chinese or English were eligible in the literature search. The key terms in the literature search were as follows: cirrhosis variceal hemorrhage, cirrhosis variceal bleeding, cirrhosis upper GI bleeding, cirrhosis upper gastrointestinal bleeding, cirrhosis recurrent bleeding, cirrhosis rebleeding, cirrhosis rehemorrhage, cirrhosis rehemorrhage, cirrhosis esophagogastric varices bleeding, cirrhosis esophageal and gastric varices bleeding, and prevent, guard against, control or treatment.

Inclusion and exclusion criteria

The inclusion criteria for the literatures were as follows: (i) studies involving patients with EVRB aged 18 yrs or more; (ii) studies focused on the prevention of EVRB in cirrhosis; and (iii) studies reporting guidelines, clinical decision-making, best clinical practice, expert consensus, evidence summary, and systematic review. We excluded literatures with incomplete information, duplicate publications, poor quality, literal translation, and simple interpretations on the guidelines.

Literature quality evaluation

The guidelines included were evaluated using the updated Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) (ref.[8,9]). Systematic review articles were evaluated using A Measurement Tool to Assess Systematic Reviews (AMSTAR) (ref.[10,11]). Expert consensus was evaluated using the corresponding evaluation standard of the Australian JBI Evidence-Based Health Care Centre (2016 version)(ref.[12,13]).

Two investigators reviewed the included literature independently, and then extracted the evidence from each study. In the case of any disputes between them, a detailed communication was held by the expert team. For the controversies of evidence from different sources, a decision was made on the principles that whether the evidence was sufficient, qualified, latest, and authoritative or not.

Evidence description and summary

The evidence recommendation levels, ranging from level 1 to level 5, were preliminarily determined based on the JBI Evidence Pre-Grading and Evidence Recommendation Level System (2014 Edition) after independent evaluation and grading by two investigators. Then an expert group was established to finally determine the recommendation level of evidence through two meetings. Recommendation levels included strong recommendation (level A) and weak recommendation (level B) (ref.[14]). The expert team consisted of five qualified members sophisticated in infectious diseases.

RESULTS

Description of the included literatures

The processes of literatures search and screening were summarized in Fig. 1. A total of 1,499 articles were found at first. We excluded the studies not meeting the inclusion and exclusion criteria in this study, those with poor quality, and those with non-eligible participants, research topics, literature types and publication time after deduplicating and reading title, abstract and full text. Finally, 8 literatures including 5 guidelines[3,15-18], 1 systematic review[19], and 2 expert consensuses[20,21] were included.

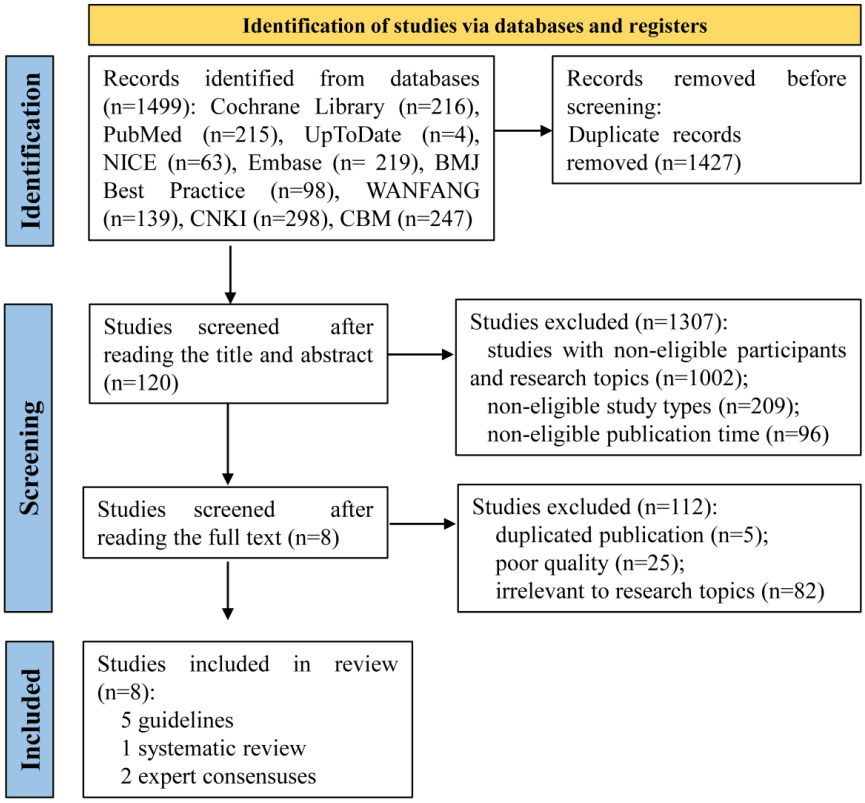

Fig. 1. The flow diagram of searching and screening literature.

Characteristics of the included literatures were shown in Table 1.

Quality evaluation results of the included literatures

Among the 5 guidelines included in this study, 2 were derived from UpToDate, and the others were from WANFANG (n=1), PubMed (n=1), and BMJ Best Practice (n=1), respectively. The standardized percentage of each evaluation index and two comprehensive evaluation results were shown in Table 2. One guideline from China with a lower score[18] than the other guidelines was also included as it was in line with China's national conditions and fully considered the characteristics of domestic patients. Two expert consensuses were extracted from PubMed and CNKI, respectively. The specific evaluation items and results were shown in Table 3. One systematic review was extracted from CBM, with evaluation items and results shown in Table 4.

Summary of evidence

After extracting the data on the prevention of EVRB from cirrhotic patients, data aggregation and summarization were given. Finally, twenty-four evidence of high quality was summarized (Table S1), involving four aspects of evaluation methods, risk management, preventive measurement, as well as health education and follow-up. Among these aspects, the preventive measurements were the most important, including treatment of primary diseases, pharmacological, endoscopy and interventional therapies, surgery, internal environment stabilization and nutritional support management, and traditional Chinese medicine (TCM)-based prevention.

DISCUSSION

Choosing appropriate evaluation methods, researching and intervening risk factors

Various evaluation methods have been used to identify the risk factors associated with early-stage rebleeding, which could prevent rebleeding and provide guidance for intervention[22]. Gastroscopy is effective for the diagnosis of esophagogastric variceal bleeding (EVB), with a sensitivity of more than 90% (ref.[23,24]). In addition, gastroscopy is an excellent guide for the selection of endoscopic treatment methods and treatment time nodes[25]. Thus, it has been recommended by several guidelines as the gold standard for EVB diagnosis, which can clear the grade of gastroesophageal varices (GOV) degree, diameter, location and the risk factors[18].

Some studies proposed that abdominal ultrasonography, with a low cost and a high vision[26], could reflect the severity of liver cirrhosis and portal hypertension[27-29]. CT can clearly assess the morphological changes of blood vessels and contribute to the risk prediction by visualizing the trunk, branches and collateral circulation of the portal vein[30]. Magnetic resonance imaging (MRI) is also excellent for predicting the risk of EVB (ref.[31]). Liver elastography is an auxiliary diagnostic method for the determination of portal hypertension in cirrhosis. Studies have shown that liver elastography could be used as an alternative for portal pressure index in decompensated cirrhosis, in order to identify the patients with a high risk of late-onset rebleeding[32]. However, these four diagnostic methods showed some clinical limitations[33]. Therefore, we

Table 1. Characteristics of included literatures (n=8).

Literature type	Literature source	Literature name	Publication time (year)	Ref.
Guideline	UpToDate	U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients	2015	3
	BMJ Best Prastice	EASL Clinical Practice Guidelines on nutrition in chronic liver disease	2019	15
	PubMed	Portal Hypertension and Ascites: Patient-and Population-centered Clinical Practice Guidelines by the Italian Association for the Study of the Liver (AISF)	2021	16
	UpToDate	Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases	2017	17
	Wanfang Digital Periodicals	Guidelines for the prevention and treatment of esophagogastric varices bleeding in portal hypertension with liver cirrhosis	2016	18
Expert consensus	PubMed	Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension	2015	20
	China National Knowledge Infrastructure	Expert consensus on the diagnosis and treatment of esophagus and fundus variceal bleeding in cirrhosis with portal hypertension (2019 edition)	2019	21
Systematic review	China Biomedical Literatures database	Dietary strategies and the relationships with prognosis after endoscopic treatments of gastroesophageal varices in patients with cirrhosis: a systematic review	2020	19

recommend them as auxiliary methods for the diagnosis of clinical portal hypertension.

Hepatic venous pressure gradient (HVPG), defined as the difference between portal venous pressure and intra-abdominal vena cava pressure, shows a great prediction value in the treatment as it can effectively assess the staging of cirrhotic patients and the judgement of complications[17]. It is considered to be the most accurate method for identifying patients with a high risk of rebleeding[34]. Specifically, a HVPG of >5 mmHg indicated the possibility of portal hypertension, while that of >10 mmHg, 12 mmHg and 20 mmHg indicated the possibilities of varicose veins, esophagogastric variceal bleeding, and a poor prognosis, respectively[35]. Unfortunately, there is still a lack of standardized procedures for HVPG detection in China, and HVPG has been rarely used in the secondary prevention of EVB (ref.[35]). We recommended the application of HVPG in the secondary prevention of patients with decompensated liver cirrhosis, which may provide a basis for early-stage prediction, treatment plans, and late-stage prognosis evaluation.

In terms of risk factors, Wang et al. included 252 cirrhotic patients with large esophageal varices, which demonstrated that Child-Pugh classification C, severe varicose veins (diameter of >20 mm), and red color (RC) of varicose veins, and the blood blister symptoms were associated with a high risk of bleeding[5]. Additionally, Zanetto et al. concluded that the predictors of early-stage rebleeding included Child-Pugh classification C, portal vein thrombosis, and the severity of portal hypertension defined by HVPG (ref.[36]). It is critical to develop more effective interventions targeting these risk factors.

Executing risk management

The diagnosis and treatment of EVB in cirrhosis involves the cooperation between the experts sophisticated in infectious diseases, gastroenterology, transplantation, radiology, ultrasonography and interventional therapy. This could overcome the limitations of conventional diagnosis and treatment model of EVB that is highly relied on the team from a certain department rather than multiple departments. Besides, such method fully takes the etiology, staging, liver conditions and complications of patients with cirrhosis and EVB into consideration, thereby formulating a reasonable, scientific, standardized and individualized diagnosis and treatment plan for patients[34]. Expert consensuses recommended that individualized diagnosis and treatment should be carried out based on multiple disciplines and multiple perspectives by a qualified team[21,34]. Although this evidence is from expert consensuses and its level is low (level 5), it is positioned as a level A recommendation by the experts of our study after comprehensive discussion. The reasons for recommendation are that the evidence caters to the patients' experiences and wishes.

In recent retrospective studies and case-control studies, scholars have found that endoscopic examination within 12 h of stable hemodynamics could identify the cause of bleeding in time and effectively reduce the rate of rebleeding within 120 h or more after the first bleeding

Table 2. Evaluation results of the quality of guidelines (n=5).

Guideline name	Standardized percentage of each evaluation index (%)						Comprehensive evaluation		≥ 60%	≥ 30%	Recommend-ation level	Ref.
	Scope and purpose	Participant	Protocol rigorousness	Clarity of results	Applicability	Editorial independence	score	result				
U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients	100	94	98	100	85	100	6.0	Recommend	6	6	A	3
European Association for the Study of the Liver	80.50	72.22	82.29	88.89	83.33	75.00	6.0	Recommend	6	6	A	15
Portal Hypertension and Ascites: Patient-and Population-centered Clinical Practice Guidelines by the Italian Association for the Study of the Liver (AISF)	94.44	63.88	83.33	94.44	77.08	91.06	6.0	Recommend	6	6	A	16
Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases	86.11	63.89	61.46	94.44	60.42	91.67	5.0	Recommend	6	6	A	17
Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases	66.67	61.11	46.88	94.44	25.00	8.33	4.0	Recommend	3	4	B	18

Recommendation level A means strong recommendation and recommendation level B means weak recommendation.

Table 3. Evaluation results of the quality of expert consensuses (n=2).

Evaluation item	Ref. 20 (de Franchis R)	Ref. 21 (Yang LY, Bai XL)
1. Whether the sources of the opinions were clearly identified	Yes	Yes
2. Whether the opinions were sourced from influential experts in related field	Yes	Yes
3. Whether the opinions were centered on the interests of population relevant to the study	Yes	Yes
4. Whether the conclusions were based on the results of the analysis, and whether the opinions were expressed logically	Yes	Yes
5. Whether the literature referred to other existing literatures	Yes	Yes
6. Whether there were inconsistencies between the opinions and previous literatures	Yes	Yes
Whether the literature should be included	Yes	Yes

Table 4. Evaluation results of the quality of systematic review (n=1).

Evaluation item	Ref. 19 (Qing Q. et al.)
01. Whether the research contents and inclusion criteria included PICO	Yes
02. Whether the research protocol was determined prior to systematic review implementation, whether there was a description of the inconsistency with the research protocol	Yes (but not entirely)
03. Whether the authors of the systematic review indicated the type of included studies	No
04. Whether the authors of the systematic review used a comprehensive search strategy	Yes (but not entirely)
05. Whether a double-repetition method was used to select articles	Yes
06. Whether a double-repetition method was used to extract evidences	Yes
07. Whether the authors of the systematic review provided a list of excluded literatures and explained the reasons for exclusion	Yes
08. Whether the authors of the systematic review described the included studies in detail	Yes
09. Whether the authors of the systematic review used appropriate tools to assess the risk of bias of each included study	Yes
10. Whether the authors of the systematic review reported the source of funding of each included study	No
11. Whether the authors of the systematic review used appropriate statistical methods to combine the findings when performing meta-analysis	Yes
12. Whether the authors of the systematic review assessed the risk of bias of each included study when performing meta-analysis	Yes
13. Whether the authors of the systematic review considered the risk of bias of the included studies when interpreting or discussing the results of each study	Yes
14. Whether the authors of the systematic review reasonably explained or discussed any heterogeneity in the research findings	Yes
15. If quantitative pooling was performed, whether the authors of the systematic review adequately investigated bias (small-sample study bias) and discussed its possible impact on the results	Yes
16. Whether the authors of the systematic review reported all sources of potential conflicts of interest, including any funding received to produce the systematic review	No
Whether the literature should be included	Yes

PICO: patient, intervention, comparison and outcome.

and mortality[36,37]. Mousa et al. proved that endoscopic management of acute EVRB within 12 h after admission was superior to that within 12–24 h (ref.[38]). In addition, multiple guidelines collectively recommend this evidence[3,16,17].

To date, less attention has been paid to the prevention of variceal rebleeding in patients with liver cancer. Therefore, preventive measurements have been seldom utilized in these patients[37]. Not much studies have focused on this perspective. For example, Chen Y et al. demonstrated that, if clinical conditions permit, secondary prevention could also effectively reduce the rate of rebleeding and mortality in patients with liver cancer[39]. Similarly, the guideline suggests that the prevention and treatment of EVB in cirrhotic patients complicated with liver cancer should follow the same principles as that in the counterparts without liver cancer[17].

Specialized care for patients with decompensated cirrhosis should be given in order to reduce hospitalization rate and improve survival[16]. These new one-to-one inter-

vention models included referral for patients, the building of a nursing team that was composed of specialized nursing staff, the establishment of a centrally managed database that incorporated all data of patients, and personalized medication and treatment recommendations[4,40].

Measures for preventing EVRB

Treating primary underlying diseases

According to previous study, etiological treatment could effectively reduce portal pressure and the risk of rebleeding[16]. Expert consensus suggests that the fundamental causes of EVB in cirrhosis were the changes in liver structure and function. These fundamental causes should be treated throughout the entire therapy[34]. Patients with viral hepatitis usually show a longer disease course and a higher risk of liver fibrosis. Antiviral therapy shows a positive role in ameliorating liver fibrosis and reducing portal hypertension[16,34]. Therefore, patients are recommended to receive antiviral therapy and anti-fibrotic therapy as soon as possible. In patients with alcohol-related liver disease, immediate and continuous cessation of alcohol consumption is crucial to improve liver function, thereby reducing the risk of rebleeding, decompensation, and death[36]. In addition to hepatitis A and B vaccines, patients are also recommended to receive other related vaccines such as influenza vaccine, which can protect the liver function and effectively prevent superimposed liver injury[41]. The cirrhotic patients with EVB should avoid taking drugs, supplements, and other substances such as hepatotoxic Chinese herbal preparations that can easily cause hepatic injury[42]. The cirrhotic patients with esophagogastric varices are susceptible to damage by several drugs that affect liver metabolism or renal excretion function, resulting in increased bleeding risk. Therefore, the dose of these drugs needs to be adjusted or avoided[43].

Implementing pharmacological, endoscopy or interventional therapies

Nonselective β-blockers (NSBBs) plus endoscopic variceal ligation (EVL) has been considered the gold standard for secondary prevention of EVRB in cirrhosis[4]. However, guidelines suggest that the situation and personal wishes should be fully considered when choosing secondary prevention. EVL therapy alone is recommended if the patients show any contraindication or intolerance to the combined intervention. NSBBs therapy should be used as monotherapy when cirrhotic patients are unable or unwilling to undergo EVL therapy[3,18]. Besides, TIPS can significantly reduce portal pressure, which is more effective than any other non-shunt procedure in preventing rebleeding[44]. Therefore, it has recently emerged as a salvage method for the patients with contraindications to NSBBs plus EVL therapy or those with poor response[45]. In addition, TIPS is recommended as first-line therapy in cirrhotic patients with portal vein thrombosis for the reason that it can also promote portal vein recanalization[21]. It is worth noting that although TIPS can improve renal function, prevent ascites and improve survival rate, it can also significantly increase the incidence of hepatic encephalopathy. Therefore, it needs to be evaluated by a professional team before clinical application[44].

Several clinical studies have shown that, for the patients with refractory ascites and severe circulatory dysfunction, NSBBs could affect hemodynamics, aggravate vasodilation in patients with decompensated cirrhosis, and lead to renal hypoperfusion, renal failure, and even death[36]. Therefore, guidelines proposed patients with refractory ascites and severe circulatory dysfunction (systolic blood pressure: <90 mmHg; serum sodium: <130 mmol/L; or hepatorenal syndrome) should reduce the dose of NSBBs or even termination. NSBBs can be reused only if circulatory dysfunction has improved[17], but with caution[44].

It has been reported that up to 50% of cirrhotic patients showed early-stage rebleeding, and increased mortality after hospitalization for gastrointestinal bleeding due to bacterial infection[36]. Therefore, prophylactic use of antibiotics is crucial for the management of cirrhotic patients with esophagogastric varices, which should be implemented immediately at the time of admission before endoscopy. Ceftriaxone is recommended as the first-choice antibiotic, and the resistance of patients should be considered before determining the relevant regimen. Prophylactic antibiotics should be administrated for no more than 7 days. Local conditions, treatment costs, and patient wishes should be considered before antibiotic prophylaxis[46].

Performing surgery

Surgical shunts and devascularization procedures have been partially replaced by pharmacological, endoscopic and TIPS therapies that show satisfactory outcomes in the prevention of rebleeding in cirrhotic patients with EVB. However, in some cases such as patients not suitable for endoscopic therapy or TIPS and those with Child-Pugh A and B liver function failed to the therapies, surgical shunt and devascularization are recommended. This is related to the fact that they can constrain the symptoms satisfactorily, promote a good long-term prognosis and reduce incidence of hepatic encephalopathy[47]. However, before surgery, it is necessary to improve various inspections to select an appropriate surgical method[21].

Currently, the curative method for patients with decompensated cirrhosis and portal hypertension mainly relies on liver transplantation[16,21]. The guidelines recommend that liver transplantation should be preferred for the Child-Pugh C cirrhotic patients with the highest risk of rebleeding. For cirrhotic patients with EVRB, liver transplantation is recommended[16,18,21]. However, due to the long waiting time of liver transplantation, effective measures should be taken to prevent rebleeding to gain more time for the subsequent liver transplantation[18]. Besides, treatment that may raise difficulties in liver transplantation should be avoided when performing surgical shunt and devascularization[48].

Maintaining a stable internal environment and a good nutritional state

Excessive blood transfusion could easily lead to rebleeding in patients with liver cirrhosis[49]. Therefore, the guidelines recommend that the hemoglobin range should be 70–90 g/L in most of these patients with stable hemodynamics to maintain a stable internal environment. This could avoid the rebound of portal hypertension and increased risk of rebleeding[3,17]. Thus, it is necessary to monitor the hemoglobin concentration, in order to avoid volume overload in clinical practice[50].

For patients with stable hemodynamics, patients should wait at least 48–72 h after an episode of acute variceal bleeding before enteral nutrition via oral or nasogastric tube[15]. Study has shown that the implementation of enteral nutrition at an early stage would lead to a significant increase in visceral blood flow. This would further lead to increased portal vein pressure and a high risk of rebleeding[51].

Improper diet could lead to early variceal rebleeding in patients after endoscopic surgery[52]. Therefore, a good nutritional state is the basis for the patient management[49]. Based on a cohort of 228 patients, Jiang et al. concluded that timely and effective oral nutrient supplementation could significantly improve the nutritional status of patients, thereby reducing the incidence of rebleeding[53]. A systematic review concluded that food-uptake within 8 h after endoscopic surgery did not increase the risk of bleeding and mortality. On the contrary, it could shorten the length of hospital stay and improve the psychological status of patients. The authors recommended that patients should firstly consider proactive oral diet after surgery and summarized a detailed, scientific, and standardized dietary strategy[19]. Our study recommends this strategy as one of the evidences in nutritional management.

Administrating of traditional Chinese medicine (TCM)

TCM has been commonly used in treating anti-hepatic fibrosis in clinical practice. The guideline recommended that the TCM anti-hepatic fibrosis should be implemented in the prevention and treatment of EVB in cirrhosis[18]. A number of studies on TCM have proved that Fufang Biejia Ruangan Tablets, Fuzheng Huayu Capsules, and Anluo Huaxian Pills significantly ameliorated the hepatic fibrosis and GOV in cirrhotic patients. However, TCM emphasizes treatment based on syndrome differentiation. Therefore, the basic treatment method and syndrome differentiation should be effectively combined before medication[54].

Setting up a follow-up team, standardizing health education, and intervening in the whole process

Poor cognition and treatment compliance and a standard management model of the inpatient department, outpatient department, endoscopic treatment room and other departments, have always been a threat to the effective treatment and prognosis of patients especially those with decompensated cirrhosis. Therefore, it is necessary to strengthen health education and optimize follow-up management[55]. Patients with EVB are suggested to take regular medication after discharge. However, due to irregular health education and follow-up, most patients showed a poor treatment compliance and a high rebleeding rate[56]. Standardizing health education, setting up a professional follow-up team, and whole-process intervention are necessary to reduce the rate of rebleeding and readmission[34,56].

Indeed, there are some limitations in our study. First, the publication languages of the literatures included in this study were only limited in Chinese and English. Secondly, the types of literatures were only published guidelines, systematic reviews, and expert consensus. These limitations may lead to the possibility of data bias.

CONCLUSIONS

This study summarized the best evidences for preventing EVRB in cirrhotic patients. These evidences involved four aspects, including evaluation methods, risk management, preventive measures, as well as health education and follow-up, which may provide a reference for clinical practice. However, the publication languages of the literatures included in this study were only limited in Chinese and English. The types of literatures were only published guidelines, systematic reviews, and expert consensus. Therefore, there is a possibility of data bias. We suggest that when applying these evidences, the conditions of clinical application and cultural differences should be fully considered, evidence-based transformation methodology should be followed, and the wishes of patients or their family members and clinical medical staff should be respected, thereby promoting the rational transformation of evidences into clinical practices.

Search strategy and selection criteria

Our research strategy was aimed at summarizing the evidence related to the prevention of esophagogastric variceal rebleeding (EVRB) in patients with cirrhosis to provide references for clinical and medical staff. We conducted a comprehensive literature search for studies on preventing EVRB in cirrhosis published before July 1, 2023, using the 6S model. We explored guideline websites (GIN, NGC, SIGN, CGC, NICE) and evidence-based databases (UpToDate, Cochrane Library, BMJ Best Practice, JBI). We also searched extensive databases, including PubMed, Embase, Web of Science, and Chinese databases (WANFANG, CBM, CNKI). Additionally, we reviewed resources from EASL, AASLD, AISF, and APASL. The search terms used included “cirrhosis variceal hemorrhage”, “cirrhosis variceal bleeding”, “cirrhosis upper GI bleeding”, “cirrhosis upper gastrointestinal bleeding”, “cirrhosis recurrent bleeding”, “cirrhosis rebleeding”, “cirrhosis rehemorrhage”, “cirrhosis rehemorrhage”, “cirrhosis esophagogastric varices bleeding”, “cirrhosis esophageal and gastric varices bleeding”, and “prevent, guard against, control or treatment”. Only English and Chinese language papers were reviewed. We included guidelines, clinical decision-making, best clinical practice, expert consensus,

evidence summary, and systematic review. We excluded incomplete, duplicate, low-quality studies, and those with simplistic interpretations of guidelines.

Authors contribution: YL: data curation, formal analysis, resources, visualization, writing – original draft; XW: conceptualization, investigation, supervision, writing – review and editing; YG: data curation, formal analysis, methodology; DN: resources, visualization, validation.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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Table S1. Summary of the best evidences for preventing esophagogastric variceal rebleeding in cirrhotic patients.

Evidence item	Evidence content	Evidence level	Recommendation level	Ref.
1. Evaluation methods	**1)** Gastroscopy is the gold standard for diagnosing GOV and EVB. The grade of GOV, the degree (weak, moderate or severe), diameter, location and the risk factors of varicose veins should be clearly indicated when performing gastroscopy.	1	A	18
	2) Ultrasonography, CT, magnetic resonance imaging and liver elastography can be used for auxiliary diagnosis of clinical portal hypertension.	1	B	26,30–32
	3) HVPG testing is recommended in qualified hospitals. HVPG of more than 5 mmHg indicate portal hypertension, more than 10 mmHg indicate the possibility of varicose veins, more than 12 mmHg indicate a high incidence of EVB, and more than 20 mmHg indicate a poor prognosis.	1	A	35
	4) Child-Pugh classification C, portal vein thrombosis or tumor thrombus, severe varicose veins (diameter of more than 20 mm), RC of varicose veins, and the blood blister symptoms are high-risk factors for rebleeding of esophagogastric varices. HVPG of more than 18 mmHg may be one of the most reliable predictors of GOV rebleeding.	2	B	5,36
2. Risk management	**1)** Qualified hospitals are recommended to implement the multi-department model for the diagnosis and treatment of liver cirrhosis and portal hypertension.	5	A	21,34
	2) Within 12 h after admission to the hospital, the prevention of variceal rebleeding should be started immediately and EGD should be performed once the hemodynamics is stable. The treatment plan should be determined according to the endoscopy.	1	A	36,37
	3) The prevention and treatment of esophagogastric variceal bleeding in patients with cirrhosis complicated with liver cancer should follow the same principles as that in non-liver cancer patients.	3	A	17
	4) New models of specialized care for patients with decompensated cirrhosis should be developed to reduce hospitalization rate and improve survival.	1	A	16
3. Preventive measures	**1) Primary underlying diseases treatment**			
	a. Attention should be paid to the treatment of primary diseases. Methods include antiviral therapy, anti-fibrotic therapy, avoidance of alcohol consumption, vaccination, avoidance of hepatotoxic substances, and adjustment of medication, prevention of liver superimposed injury, among others, which can effectively reduce portal vein pressure and significantly reduce the risk of bleeding.	1	A	16,34,36,41-43
	2) Pharmacological, endoscopy and interventional therapies			
	a. NSBBs plus EVL is the gold standard for secondary prevention of esophagogastric variceal rebleeding in cirrhosis and can improve survival. EVL therapy alone is recommended if the patients show any contraindication or intolerance to the combined intervention. NSBBs therapy should be used as monotherapy when cirrhotic patients are unable or unwilling to undergo EVL therapy.	1	A	4
	b. TIPS therapy is recommended in patients with recurrent bleeding after receiving NSBBs plus EVL (or EVL or NSBBs monotherapy due to intolerance or contraindication to combined therapy).	1	A	45
	c. In patients with liver cirrhosis and portal vein thrombosis, the efficacy of TIPS in preventing rebleeding after the first bleeding is significantly better than NSBBs plus EVL.	1	B	44,45
	d. Patients with refractory ascites and severe circulatory dysfunction (systolic blood pressure of less than 90 mmHg, serum sodium of less than 130 mmol/L, or hepatorenal syndrome) should reduce the dose of NSBBs or temporarily hold drugs. NSBBs can be reused only if circulatory dysfunction has improved.	1	B	17
	e. Prophylactic antibiotic therapy can reduce the rebleeding rate and bleeding-related mortality of esophagogastric varices, which should be implemented from admission.	1	A	46

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Table S1. Summary of the best evidences for preventing esophagogastric variceal rebleeding in cirrhotic patients. *(Continued)*

Evidence item	Evidence content	Evidence level	Recommendation level	Ref.
3. Preventive measures	**3) Surgery**			
	a. We recommend surgical operations, including surgical shunt, devascularization and their combination, are mainly used for patients with esophagogastric variceal bleeding who are not suitable for endoscopic therapy or TIPS, and patients with Child-Pugh A and B liver function who are ineffective in treatment.	1	A	47
	b. The Child-Pugh C patients are given priority to enter the waiting list for liver transplantation. According to hospital conditions and doctors' experience, selecting appropriate secondary prevention methods as the "bridge" for liver transplantation.	1	B	16,18,21
	4) Internal environment stabilization and nutritional management			
	a. For rebleeding in EGVB patients with liver cirrhosis caused by blood transfusion or excessive infusion, it is recommended that those with stable hemodynamics maintain hemoglobin at 70–90 g/L.	1	B	49,3,17
	b. Patients with stable hemodynamics are recommended to wait at least 48–72 h after the onset of acute variceal bleeding before resuming enteral nutrition via oral or nasogastric tube. Premature enteral nutrition increases splanchnic blood flow, which may increase portal pressure and rebleeding risk.	2	A	15
	c. Warm boiled water should be given in the early stage after endoscopic surgery. If there is no any side effect, warm and cool liquid food can be given, semi-liquid food can be given within 3–14 days after operation, and soft food can be given after 14 days after operation. It should be noted that overheated, too sour, too sweet, pungent, rough, indigestible foods are not edible, and low-protein, high-calorie, and high-carbohydrate foods are recommended. Patients require smaller more frequent meals with chew slowly.	1	A	49
	d. The first meal can be implemented within 4–8 h after endoscopic treatment. Early feeding within 8 h does not increase the risk of bleeding, death, or other complications.	1	A	53
	e. Proactive oral diet after endoscopic treatment is recommended. Management of enteral nutrition cannot effectively improve the prognosis of patients and may increase the potential risk of bleeding after endoscopic therapy.	1	A	19
	5) TCM: Fufang Biejia Ruangan Tablets, Fuzheng Huayu Capsules, and Anluo Huaxian Pills can significantly ameliorate the hepatic fibrosis and GOV in cirrhotic patients.	1	B	18
4. Health education and follow-up	**1)** Improving compliance of patients, strengthening health education and optimizing follow-up.	3	A	56
	2) Patients who have undergone endoscopic treatment should be followed up with endoscopy and implement whole-process intervention.	3	A	34,56

GOV: gastroesophageal varices; EVB: esophagogastric variceal bleeding; HVPG: hepatic venous pressure gradient; RC: red color; EGD: esophagogastroduodenoscopy; NSBBs: nonselective β-blockers; EVL: endoscopic variceal ligation; TIPS: transjugular intrahepatic portosystemic shunt; EGVB: esophagogastric variceal bleeding; TCM: traditional Chinese medicine.

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