

A Meta-Analysis of Risk Factors for Liver Cirrhosis Combined with Upper Gastrointestinal Bleeding in China

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Abstract: In order to systematically evaluate the risk factors for liver cirrhosis complicated with upper gastrointestinal bleeding in China, we searched CNKI, Wanfang Digital Journals Full-text Database (Wanfang), Weipu Journal Resource Integration Service Platform (VIP) and PubMed database on risk factors for liver cirrhosis combined with upper gastrointestinal bleeding in China, Newcastle-Ottawa Scale (NOS) used the most comprehensive data collection based on relevant case-control trials to evaluate the quality of the extracted literature combined with inclusion and exclusion criteria. Studies with a score of ≥ 7 were included and meta-analysed using RevMan 5.4. Finally, twenty-one articles met the inclusion criteria, the cumulative number of cases and controls were 2222 and 2785 cases. We can come to the conclusion that Spleen, gastric varices, esophageal varices, PT (prothrombin time), ascites, left gastric vein diameter, liver function child grade C, esophageal varices, liver cirrhosis, portal vein diameter, and alcohol consumption is an independent risk factor for liver cirrhosis combined with upper gastrointestinal bleeding in China, and the control of the above factors can effectively improve the risk of patients with liver cirrhosis and upper gastrointestinal bleeding in China.

Keywords: Cirrhosis with upper gastrointestinal bleeding; Risk factors; Case control

1. Introduction

Cirrhosis is a common digestive disease with serious consequences in China, and chronic, progressive and diffuse is the main feature of the disease [1]. One of the most common complications of cirrhosis is upper gastrointestinal bleeding, which has a high incidence (approximately 15.7% to 33%), heavy bleeding, predisposition to acute peripheral circulatory failure, and high mortality [2]. The main causes of high mortality in cirrhosis are hemorrhagic shock and massive bleeding. Patients with variceal rupture of gastric fundus venous vessels are prone to massive bleeding, and even shock or hepatic coma, especially in patients with recurrent gastrointestinal bleeding [3]. Massive bleeding in the digestive tract will be combined with other systemic infections, hepatic encephalopathy, hepatorenal syndrome, multiple organ failure, etc., which greatly affects the rescue time of patients and is an important factor causing rescue ineffectiveness [4]. Although there are many studies on the risk factors of upper gastrointestinal bleeding in cirrhosis at home and abroad, the relevant comprehensive systematic analysis is still blank, this study conducts a meta-analysis of the research literature on upper gastrointestinal bleeding published from January 2000 to December 2022, aiming to screen the risk factors related to upper gastrointestinal bleeding in cirrhosis, and confirm the strength of the association between each factor, so as to provide theoretical support for reducing the prevalence of upper gastrointestinal bleeding in cirrhosis.

2. Information and methodology

2.1. Literature search strategies

A foreign language search was conducted in Pubmed using "Cirrhosis with upper gastrointestinal bleeding" and "dangerous factor" or "risk factors" or "influence factors" or "association factors" or "related factors" as search terms. Cirrhosis combined with upper gastrointestinal bleeding", "risk

factors”, “case control” and free words (influencing factors, etiology, related factors, clinical experiments, case-control studies, clinical trials) combined to search Chinese databases such as CNKI, Wanfang and VIP for Chinese search.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion Criteria

(1) The design type was a case-control study; (2) Patients with cirrhosis and upper gastrointestinal bleeding confirmed by various medical institutions, the control group is patients with cirrhosis. (3) Domestic and foreign research results published on public routes from January 1, 2000 to December 15, 2022; (4) Data in the study results that can be converted with 95% confidence interval (CI), OR(odds ratio) value, and standard error (SE).

2.2.2. Exclusion criteria

(1) studies with incomplete data and no control groups were excluded; (2) duplicate publications were excluded; (3) review literature was excluded; (4) Literature that is neither Chinese nor English was excluded.

2.3. Literature screening, data extraction and quality evaluation

Read the full text to remove irrelevant literature and duplicate published clinical studies to identify documents that meet the inclusion criteria. The quality of studies meeting the inclusion criteria was then assessed by two reviewers against the Newcastle-Ottawa scale [5].

2.4. Data Processing

Review Manager 5.4 was used for meta-analysis. Heterogeneity between studies was analysed using Cochrane Q and the size of heterogeneity was assessed using I^2 . If the $P > 0.1$ and $I^2 < 50\%$, it means that there is no statistical heterogeneity among studies, so a fixed-effect model (FE) is used; Conversely, a random effects model (RE) was used; OR was selected for dichotomous data as a pooled statistic, and each effect size was expressed as a 95% CI. Funnel charts and Egger's method were used to detect and assess publication bias. The sensitivity analysis was performed by changing the data model to test the stability of the research results.

3. Results

3.1. Literature search results

A preliminary search was carried out in the database, 286 articles were obtained, and after the duplicate literature was eliminated, 219 documents were initially screened, 181 documents obviously unrelated to the theme were eliminated after reading the title and abstract, 38 literature were included in the second screening, 17 articles were eliminated after reading the full text, the full text was carefully read, and the inclusion and exclusion criteria were followed, and finally a total of 21 documents that met the conditions were included.

3.2. Basic characteristics and quality evaluation of literature inclusion

Among the 21 included literatures, all were case-control studies, published from 2000 to 2022, with a cumulative total of 2222 cases in the case group and 2785 cases in the control group. (Table 1)

Table 1: General features of the meta-analysis literature were included

Numbering	First author	Year of publication	Study area	Case group	Control group	Research factors	NOS score
1	Yuan Jing [6]	2014	Hangzhou	74	125	(1)(2)(3)	8
2	Chang Yufei [7]	2021	Beijing	90	90	(1)(3)(4)(6)(7)(8)	9
3	Chen Zhimin [8]	2015	Pingyang	320	246	(3)(6)(8)(9)	8
4	Cidan Zhuoga [9]	2008	Lhasa	53	44	(3)	7
5	Cui Xingliang [10]	2014	Handan	120	132	(3)(6)(8)(9)	8
6	Deng Xu [11]	2021	Yulin	52	128	(3)(4)(6)(7)(8)	9
7	Fang Yuan [12]	2020	Wuhu	31	19	(1)(2)(3)(9)	8
8	Luo Yizhen [13]	2014	Qinzhou	68	204	(3)(4)(9)	8
9	Han Dan [14]	2016	Urumchi	218	194	(1)(3)(6)(7)(8)	9
10	Huang Xu [15]	2019	Changchun	214	181	(6)(9)(11)	8
11	Yang Hongyu [16]	2018	Meizhou	40	40	(4)(5)(6)(7)	8
12	Liu Ruixian [17]	2018	Qu Jing	120	108	(3)(6)(8)(9)	8
13	Zhang Heyuan [18]	2022	Beijing	57	93	(1)(3)(9)(11)	8
14	Lu Jugang [19]	2019	Huangchaun	179	541	(6)	7
15	Yang Meirong [20]	2016	Tangshan	175	182	(1)(3)(9)(11)	8
16	Peng Huan [21]	2019	Shenzhen	60	60	(3)(4)(6)	8
17	Shao Hua [22]	2018	Anshan	80	120	(1)(3)(8)(11)	8
18	Shi Yanqing [23]	2018	Jiujiang	30	52	(1)(5)	7
19	Wu Xueling [24]	2022	Yingde	25	25	(1)(2)(3)(6)(9)	9
20	Wu Yanfang [25]	2015	Xi'an	160	123	(3)(6)(8)(9)	8
21	Su Linhong [26]	2015	Wenzhou	56	78	(3)(4)(9)(11)	8

Note: (1) Liver function child grading; (2) spleen thickness; (3) esophageal varices; (4) gastric varicose veins; (5) esophageal and gastric varices; (6) prothrombin time is prolonged; (7) the course of liver cirrhosis; (8) ascites; (9) enlarged diameter of the left gastric vein; (10) The inner diameter of the portal vein is enlarged; (11) Bad eating habits (drinking).

3.3. Meta-analysis results of liver cirrhosis combined with upper gastrointestinal bleeding risk factors

Splenomegaly, gastric varices, esophageal and gastric varices, prothrombin time, ascites, increased diameter of the left gastric vein, etc. were not heterogeneous ($P > 0.1$, $I^2 < 50\%$), so a fixed-effect model was used, while the random-effects model was used in contrast to liver function grade C, esophageal varices, liver cirrhosis course, increased portal vein diameter, and poor eating habits (alcohol consumption).

3.3.1. Association between liver function child grade and liver cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant ($P < 0.00001$), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 1.

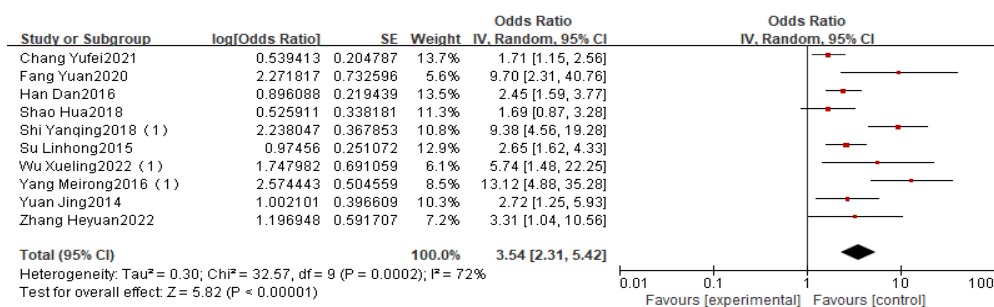


Figure 1: Forest plot of liver function child C-level analysis

3.3.2. Association between splenomegaly and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant ($P < 0.0001$), and the proportion of cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 2.

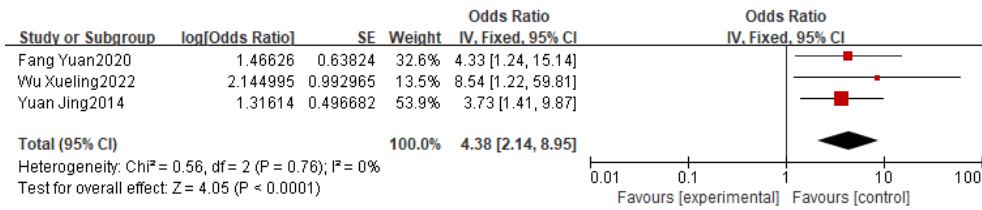


Figure 2: Forest plot for splenomegaly (thickness, length) analysis

3.3.3. Association between esophageal varices and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant (P<0.00001), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 3.

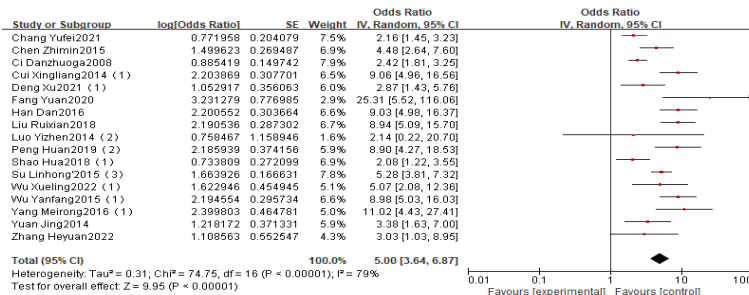


Figure 3: Forest plot of esophageal varices analysis

3.3.4. Association between gastric varices and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant (P<0.00001), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 4.

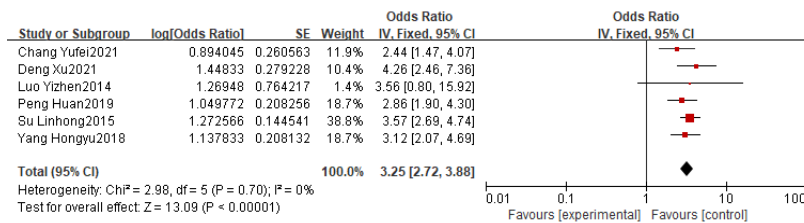


Figure 4: Forest plot of gastric varices analysis

3.3.5. Association between esophageal and gastric varices and cirrhosis combined with upper gastrointestinal bleeding

The difference was statistically significant (P=0.02), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 5.

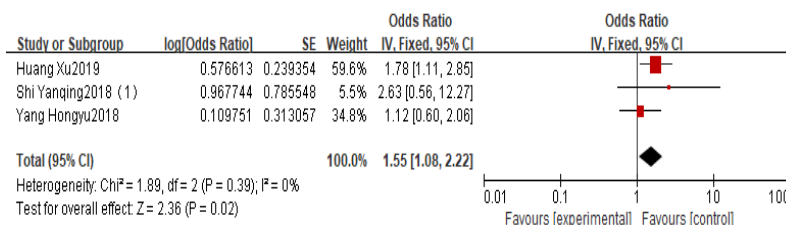


Figure 5: Forest plot of esophageal and gastric varices

3.3.6. Association between prolonged prothrombin time and liver cirrhosis combined with upper gastrointestinal bleeding

The difference was statistically significant (P<0.00001), and the proportion of liver cirrhosis

combined with upper gastrointestinal bleeding was higher in the case group, see Figure 6.

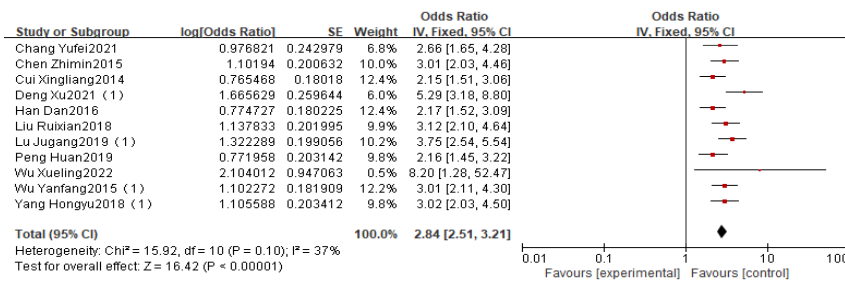


Figure 6: Forest plot for prothrombin time extension analysis

3.3.7. Association between the course of cirrhosis and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant (P=0.02), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 7.

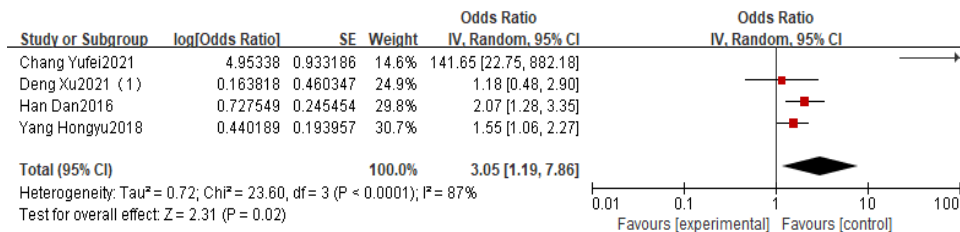


Figure 7: Forest plot of liver cirrhosis course analysis

3.3.8. Association between ascites and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant (P<0.00001), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 8.

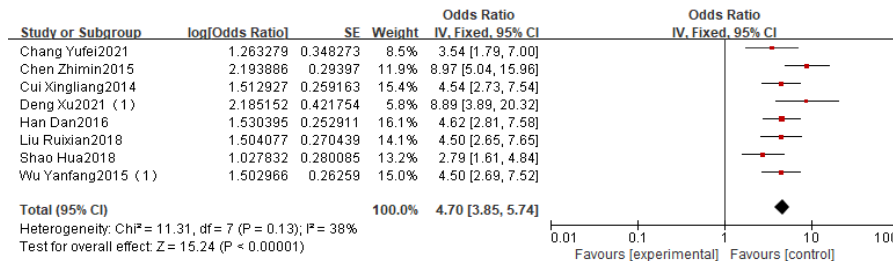


Figure 8: Forest plot for ascites analysis

3.3.9. Association between increased diameter of the left gastric vein and cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant (P<0.00001), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 9.

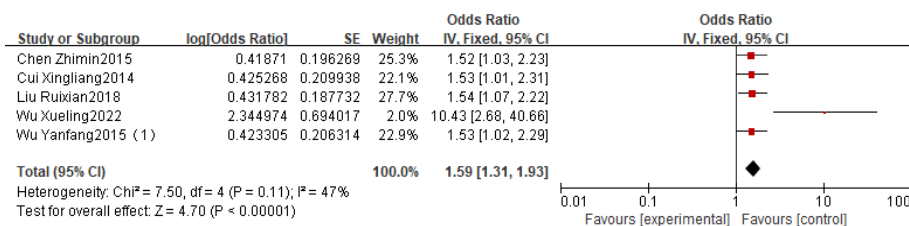


Figure 9: Forest plot of gastric left vein inner diameter increase analysis

3.3.10. Relationship between increased portal vein diameter and liver cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant ($P < 0.00001$), and the proportion of liver cirrhosis combined with upper gastrointestinal bleeding was higher in the case group, see Figure 10.

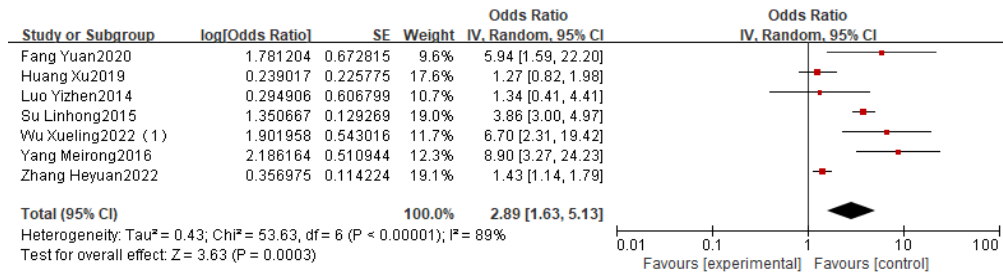


Figure 10: Forest plot of portal vein indiameter increase analysis

3.3.11. Association between poor eating habits (alcohol consumption) and liver cirrhosis combined with upper gastrointestinal bleeding

Tested for heterogeneity, the difference was statistically significant ($P < 0.00001$), and the proportion of cirrhosis combined with upper gastrointestinal bleeding was higher in the case Group, see Figure 11.

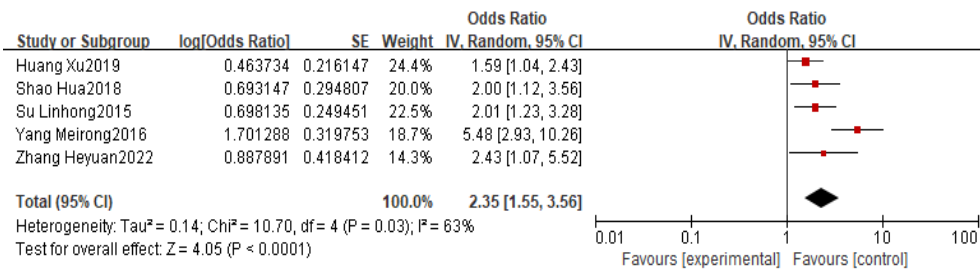


Figure 11: Forest plot for analysis of poor eating habits (drinking).

3.4. Analysis of risk factors

For risk factors for ovarian reserve decline, the pooled OR and 95% CI were measured using a fixed, random-effects model, respectively, and the results were highly similar, reflecting that the pooled results obtained in this study were generally reliable. This can be found in Table 2.

Table 2: Sensitivity analysis

Risk factors	Fixed-effect model		Random-effects model	
	Combine OR values	95%CI	Combine OR values	95%CI
Liver function child grade C	2.78	2.27-3.41	3.54	2.31-5.42
Splenomegaly	4.38	2.14-8.95	4.38	2.14-8.95
Varicose veins of the esophagus	4.22	3.69-4.82	5.00	3.64-6.87
Varicose veins of the stomach	3.25	2.72-3.88	3.25	2.72-3.88
Varicose veins of the esophagus and stomach	1.55	1.08-2.22	1.55	1.08-2.22
Prothrombin time is prolonged	2.84	2.51-3.21	2.88	2.45-3.38
Liver cirrhosis course	1.85	1.40-2.45	3.05	1.19-7.86
ascites	4.70	3.85-5.74	4.75	3.68-6.14
The inner diameter of the left gastric vein is enlarged	1.59	1.31-1.93	1.65	1.25-2.18
The inner diameter of the portal vein is enlarged	2.20	1.89-2.56	2.89	1.63-5.13
Poor eating habits (drinking)	2.20	1.72-2.81	2.35	1.55-3.56

3.5. Analysis of publication bias

11 factors included in Egger's test using Stata17.0 software were reported for publication bias, liver function grading, Symmetric tests such as ascites and increased diameter of the left gastric vein showed a $p < 0.05$, suggesting possible publication bias. The funnel plots of other risk factors generally maintained a symmetric relationship, reflecting good stability of the results of meta-analysis. The funnel plot of the well-studied risk factor index (esophageal varices) was plotted and symmetry test

was performed, indicating that $p=0.105>0.05$, indicating that the publication bias was basically well controlled, see Figure 12.

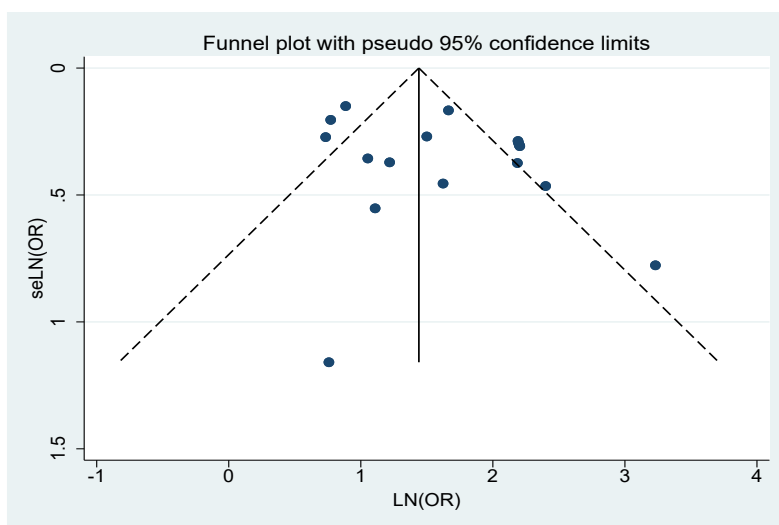


Figure 12: Funnel diagram of esophageal variceal analysis

4. Discussion

Studies have shown that the severity of liver disease correlates with the grade of esophageal varices, and approximately 85% of patients with child grade C cirrhosis have varicose veins [27]. Clinically, the commonly used indicators reflecting portal pressure are portal vein inner diameter and esophageal varices [28]. Although the increase in the portal pressure gradient itself leads to the formation of gastroesophageal varices, due to the high dynamics of the visceral circulation, the increased flow through them leads to their growth and eventually rupture [29]. The ability to supply blood to esophageal varices depends on the size of the gastric venous diameter, which can also increase the risk of bleeding when the gastric vein diameter increases. Another study has shown that when ascites forms, portal vein pressure increases, pressure drop in the upper gastrointestinal tract increases, and when it exceeds its capacity, it will cause upper gastrointestinal bleeding [30]. When entering the decompensation phase, liver function continues to deteriorate, resulting in impaired prothrombin synthesis, prolonged PT time, resulting in decreased platelet function, decreased coagulation function, at this time, when eating rough food, drinking, etc. will cause acute hemorrhage in the upper digestive tract [31].

Therefore, for patients with upper gastrointestinal bleeding, the key measure is to stop bleeding, rapid reduction of portal pressure is the key, somatostatin is a commonly used clinical drug, can quickly act on vascular smooth muscle to reduce portal pressure [32]. It can significantly improve the prognosis of patients, and prevent it early, pay attention to eating habits, reduce the frequency of drinking, and conduct regular physical examinations, reduce the risk of upper gastrointestinal bleeding in patients with cirrhosis, and improve the quality of life.

Limitations of this paper: (1) Some risk factors were included in a small number of articles; (2) The research areas included in the literature were 20 urban areas in China, and the research scale was small; (3) The included literature is a case control, and it is difficult to comprehensively analyze the risk factors for upper gastrointestinal bleeding in China's liver cirrhosis; (4) In the literature published in the open route, some of the literature does not have available data, or the research results are incomplete, and inevitably faces various biases, such as liver function grade, ascites and increased gastric left vein inner diameter risk factors.

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