Gastroenterology Research and Practice

Assessment and Treatment of Liver Cirrhosis

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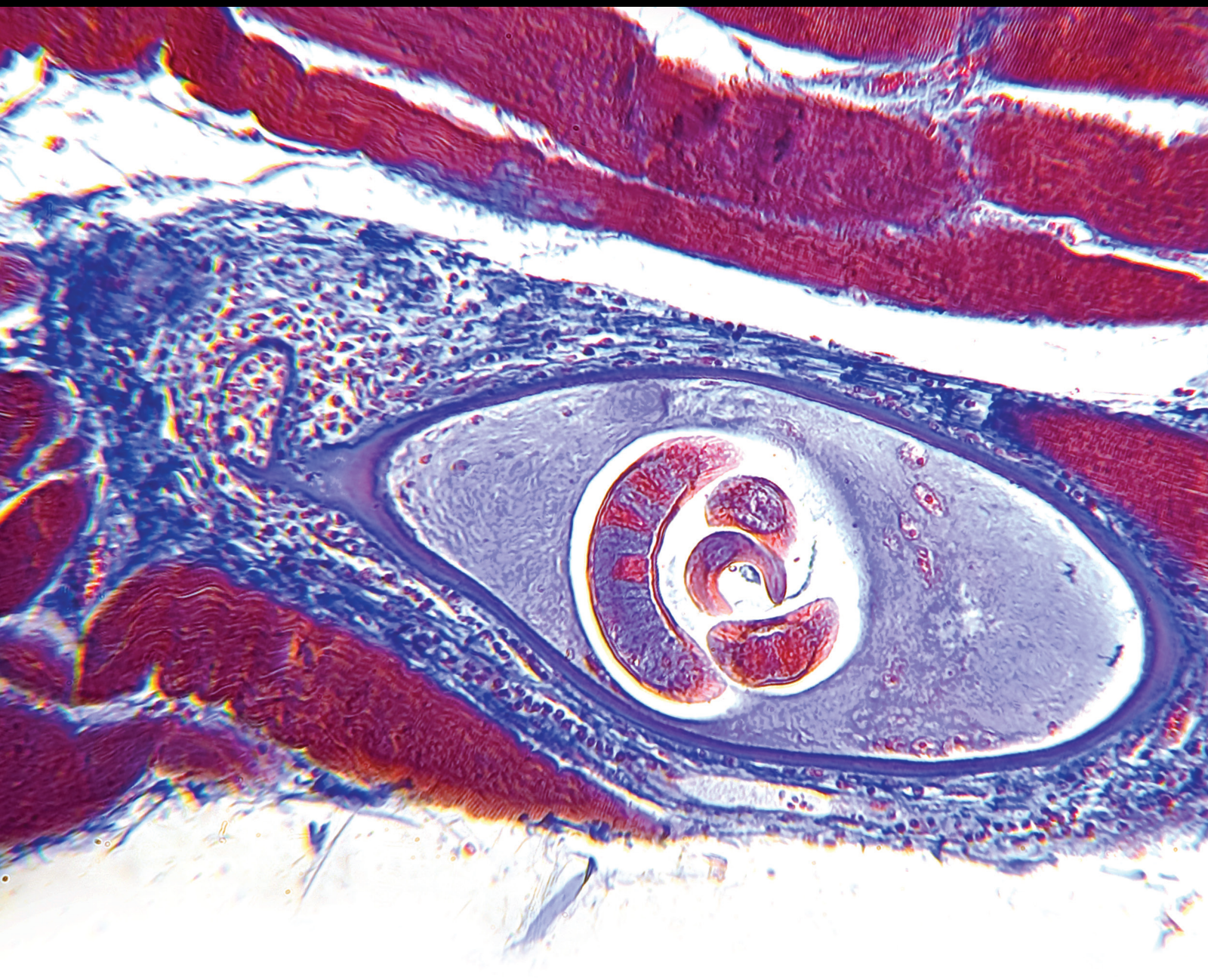

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Research Article

Acupuncture for the Treatment of Liver Cirrhosis: A Meta-analysis

Lu Qi,[1] **Shuang Li**,[2] **Jun Xu**,[1] **Jie Xu**,[1] **Wangzouyang Lou**,[1] **Liangbin Cheng**,[3] **and Chizhi Zhang**[3]

[1]*Hubei University of Chinese Medicine, Wuhan 430061, China*
[2]*The Second People's Hospital of Yichang, Yichang 443000, China*
[3]*Hubei Provincial Hospital of TCM, Wuhan 430061, China*

Correspondence should be addressed to Liangbin Cheng; 18971241243@163.com and Chizhi Zhang; zcz126@sohu.com

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Acupuncture is widely used in the clinical treatment of liver cirrhosis (LC) in China. However, the efficacy of acupuncture on LC has not been fully confirmed by systematic analysis. This current meta-analysis evaluated the impact effect of acupuncture on patients with LC. We conducted a systematic literature search of the China National Knowledge Infrastructure, the Chinese Biomedical Database (SinoMed), VIP medicine information system, Wanfang Data, PubMed, Cochrane Library, Web of Science, and Embase. Further, we used Review Manager 5.3 software for the analysis of the data and Stata 14.0 software for the Egger test to assess publication bias. Fifteen studies involving 1066 patients were included in the meta-analysis. The primary outcome was the efficacy rate of acupuncture therapy. The secondary outcomes were impact on acupuncture on liver function grading assessment and lab tests related to liver functions. The result suggested that acupuncture is an effective treatment option for patients with LC as a complementary therapy. However, the recommendation is weak due to some limitations of the included studies.

1. Introduction

Liver cirrhosis (LC), which is characterized by the formation of diffuse fibrous pseudolobules and the proliferation of blood vessels inside and outside the liver, is an advanced liver disease caused by various chronic liver diseases. LC is a cause of rising mortality and morbidity. Globally, 1.16 million people die from LC every year [1]. According to epidemiological surveys, hepatitis B virus (HBV) is the leading cause of LC in most parts of Asia and sub-Saharan Africa; alcohol abuse, hepatitis C virus (HCV), and nonalcoholic liver diseases are the main causes in developed countries [2]. At present, the primary treatment strategy includes cause-specific interventions and prevention of encephalopathy, portal hypertension, variceal bleeding, ascites, and other complications. The main treatment goals are to stop disease progression, improve the quality of life, and prolong survival time. Although numerous studies are being conducted, no drug on reversal of the disease is yet approved by the Food and Drug Administration for treating LC [3]. A lack of treatments for LC patients with decompensation or poor liver function makes LC a life-threatening disease and a major cause of death worldwide.

In recent years, studies and clinical observations have shown that traditional Chinese medicine is effective in the treatment of liver diseases, especially in the field of LC. As an important complementary and alternative medicine, acupuncture has a history of thousands of years in China. It has been proved to be effective and widely used in clinical treatment of hepatic diseases, such as nonalcoholic fatty liver disease (NAFLD) [4], chronic hepatitis B (CHB) [5], and LC [6]. Both ancient literature and modern scientific evidence showed that acupuncture, as a kind of complementary and alternative therapy, has a positive effect on LC. For many years, it is one of the therapy methods of LC in China. In addition, the effect of acupuncture on LC has been documented in numerous animal and clinical studies. Multiple mechanisms have been suggested to contribute to the therapeutic effect of acupuncture, including anti-inflammation effects and immunomodulatory and neurotransmitter regulation [7, 8]. Reviewing current studies of acupuncture on

LC treatment may provide opportunities to develop better therapeutic strategies for it. In view of the wide usage of acupuncture, we conducted a meta-analysis to summarize the effect of acupuncture on LC.

2. Materials and Methods

2.1. Search Strategy. The meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Randomized controlled trials (RCTs) on the efficacy of acupuncture against LC were searched by two authors independently until June 2020. The Chinese database mainly included the Chinese Biomedical Database (SinoMed or CMB), the China National Knowledge Infrastructure (CNKI), the VIP medicine information system (VIP), and Wanfang Data (WANFANG). English databases included PubMed, Embase, the Cochrane Library, and Web of Science. We also searched the Chinese Clinical Trial Registry (http://http://www.chictr.org.cn/), ClinicalTrials.gov (https://www.clinicaltrials.gov/), and the World Health Organization International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/) for unpublished trials. The following Medical Subject Headings (MeSH) terms and free text were used: "acupuncture", "liver cirrhosis", and "randomized controlled trial". Detailed search strategy is provided in the supplementary data (available here). We contacted the principal authors for any missing information.

2.2. Study Selection. Two reviewers independently screened the literature according to the inclusion criteria and exclusion criteria. We included randomized clinical trials that did not limit publication status and blinding. We allowed cointervention when it was applied equally to the experimental group and the control group. PICOS criteria for study selection are shown in Table 1.

The inclusion criteria were as follows: (a) RCTs with the acupuncture intervention group and the control group; (b) cointerventions which were also allowed when the cointerventions were administered equally to all intervention groups; (c) studies including clear diagnostic criteria and efficacy evaluation criteria; (d) patients with liver cirrhosis, regardless of age or gender; and (e) studies written in English or Chinese.

The exclusion criteria were as follows: (a) republished studies with the same data; (b) studies containing no original data; (c) animal experiments, reviews, case reports, or theoretical literature; (d) if there was no information on diagnostic or efficacy criteria; and (e) if complete data could not be obtained after much effort.

2.3. Data Extraction. In order to ensure the integrity and eligibility of the extracted data, two reviewers independently screened the literature back-to-back according to the inclusion and exclusion criteria. In case of disagreement, the literature was evaluated by a third reviewer, and consensus was reached through consultation. The following information included general information, diagnostic criteria, efficacy evaluation criteria, outcome indicators, and adverse reactions. The general information included author, year, and the number of participants and details of intervention. The primary outcome was the efficacy rate of acupuncture therapy. The secondary outcomes were impact of acupuncture on liver function grading assessment and outcomes related to liver function, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), Albumin (ALB), and total bilirubin (TBIL).

2.4. Quality Assessment. The risk of bias was evaluated using the Cochrane system, according to the following six items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. For each included study, the above six elements were evaluated sequentially with three levels of low, high, and unclear.

2.5. Statistical Analysis. A meta-analysis was performed using RevMan5.3 software provided by the Cochrane system. Relative risk (RR) was adopted for dichotomous variables and the mean difference (MD) and 95% confidence interval (CI) for the continuous variables. We tested heterogeneity using the I square (I^2) and P value (P). $P < 0.05$ or $I^2 > 50\%$ was considered to indicate substantial heterogeneity, and a random-effects model was used for calculation. Otherwise ($P \geq 0.05$ or $I^2 \leq 50\%$), a fixed effects model was used. The Stata 14.0 software was used for the Egger test to assess publication bias.

3. Results

3.1. Inclusion Study. The process of literature retrieval and study selection is shown in Figure 1. A preliminary search retrieved 1276 studies. After further screening of these studies, 16 studies were finally included [10–24].

3.2. Study Characteristics. The 15 selected studies included a total of 1066 patients and were all conducted in China (Table 2). Their trials compared the effects of acupuncture versus no acupuncture. Heterogeneous cointerventions were used in all trials and were equally used in the control group. In all trials, the control groups received a conventional comprehensive treatment (such as antivirus therapy and liver protection), while the experimental groups received acupuncture therapy combined with the same intervention methods as the control groups. All the studies compared manual needle acupuncture with nonintervention. Two of the studies involved infrared therapeutic apparatus, which were used equally in both groups (chen2017; deng2019). One study involved traditional Chinese medicine decoction, which was administered equally to all intervention groups (xia2019). Three of the fifteen studies received national or provincial or municipal academic funding, while the rest did not report information about funding.

3.3. Quality of Study. None of the 15 studies mentioned the use of blinding or allocation concealment. No studies reported participants dropping out or incomplete data. All of these studies were randomized. Four of them mentioned grouping by adopting a random number table and two by

Table 1: PICOS criteria for study selection.

Parameter	Criteria for studies
P (population)	Patients with liver cirrhosis
I (intervention)	Acupuncture
C (comparison)	No acupuncture
O (outcomes)	Efficacy rate of acupuncture therapy; impact of acupuncture on liver function grading assessment; outcomes related to liver function
S (study design)	Randomized clinical trials

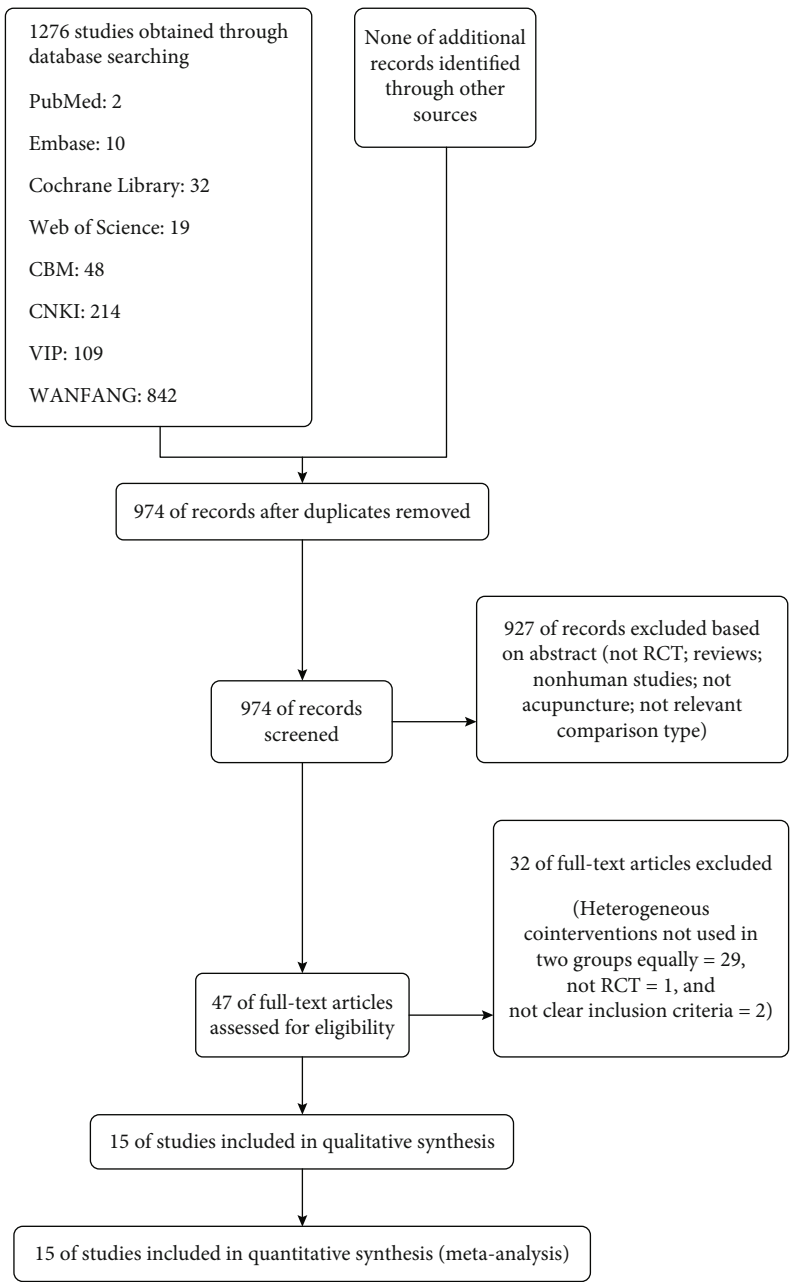

Figure 1: Flowchart of study selection.

Table 2: Characteristics of included studies.

Included study (year)	Study country	Number of subjects (*E*/*C*)	Intervening measure (*E*)	Duration (day)
Chen, 2017	China	47/40	Plus acupuncture on the basis of the control group	30
Deng, 2019a	China	25/25	Plus acupuncture on the basis of the control group	30
Deng, 2019b	China	30/30	Plus acupuncture on the basis of the control group	14
Du, 2015	China	45/45	Plus acupuncture on the basis of the control group	14
Fang, 2019	China	40/40	Plus acupuncture on the basis of the control group	30
Li, 2016	China	35/35	Plus acupuncture on the basis of the control group	10
Liu, 2018	China	40/40	Plus acupuncture on the basis of the control group	30
Qu, 2014	China	26/25	Plus acupuncture on the basis of the control group	14
Shen, 2013	China	30/30	Plus acupuncture on the basis of the control group	14
Xia, 2019	China	48/47	Plus acupuncture on the basis of the control group	28
Xiao, 2010	China	50/35	Plus acupuncture on the basis of the control group	14
Xie, 2018	China	38/38	Plus acupuncture on the basis of the control group	5
Yu, 2013a	China	40/40	Plus acupuncture on the basis of the control group	8
Yu, 2013b	China	21/21	Plus acupuncture on the basis of the control group	14
Zhang, 2014	China	30/30	Plus acupuncture on the basis of the control group	30

Note: *E*/*C* = experimental/control group.

drawing lots, and the remainder did not specify the method of sequence generation (Figure 2).

4. Meta-Analysis

4.1. Efficacy Rate. Thirteen trials including 926 patients reported changes in tefficacy rate as the end-point outcome. Heterogeneity was low ($P = 0.40$, $I^2 = 4\%$). A fixed effects model was used for the meta-analysis. The results showed that acupuncture could significantly improve the efficacy rate of patients with LC (RR = 1.31, 95% CI [1.22, 1.40], $P < 0.00001$; Figure 3).

4.2. Liver Function Grading Assessment. Some liver function grading scores are widely used to assess the response to therapy, such as the Child-Pugh score, MELD score, and MELD-Na score. However, none of the 15 studies reported impact of acupuncture on liver function grading assessment.

4.3. Alanine Transaminase (ALT). Five studies had reported the ALT level in 371 patients. Heterogeneity was found to be low ($P = 0.38$, $I^2 = 5\%$), and the fixed effects model was adopted. The results showed that acupuncture combined with conventional treatment significantly reduced the level of ALT as compared with conventional therapy (MD = −15.16; 95% CI [-17.86, -12.46], $P < 0.00001$; Figure 4).

4.4. Aspartate Aminotransferase (AST). AST levels were reported in four studies involving 276 patients. There was no heterogeneity between studies ($P = 0.67$; $I^2 = 0\%$), and the fixed effects model was used for the meta-analysis. The results showed that when compared with the control group, acupuncture treatment resulted in a significant improvement in AST level (MD = −14.39, 95% CI [-22.34, -6.44], $P = 0.0004$; Figure 5).

4.5. Albumin (ALB). Five trials including 371 patients reported data regarding this end-point. There was a high level of heterogeneity between studies ($P < 0.00001$; $I^2 = 93\%$), and the random effects model was used for meta-analysis. The results suggested that acupuncture might improve the ALB level in the patients (MD = 4.28, 95% CI [0.87, 7.70], $P = 0.01$; Figure 6).

4.6. Total Bilirubin (TBIL). TBIL values were reported in five studies involving 371 patients. Heterogeneity was absent ($P = 0.83$, $I^2 = 0\%$). The fixed effects model was adopted. The results of meta-analysis suggested that the TBIL level of the acupuncture group was significantly lower than that of the control group, and the difference was statistically significant (MD = −5.25; 95% CI [-6.68, -3.82], $P < 0.00001$; Figure 7).

4.7. Bias Analysis. Publication bias was analyzed by a funnel plot. Possible asymmetries were found from the funnel plots (Figure 8). To further assess publication bias quantitatively, the Stata version 14.0 software for the Egger test was used. The results indicated that publication bias was not significant ($P = 0.415$; Figure 9).

5. Discussion

Acupuncture is often thought to be multilayered, multitargeted, and multieffective; it can benefit patients with chronic liver disease. Modern research has shown that acupuncture treatment can cause improvements at different levels, including structural, cellular, and molecular biology. The clinical effect of acupuncture is mainly reflected in improving liver function, alleviating clinical symptoms, and regulating immune function of the patients [25, 26]. The therapeutic mechanisms of acupuncture include inhibiting hepatic stellate cell activation and proliferation, reducing oxidative

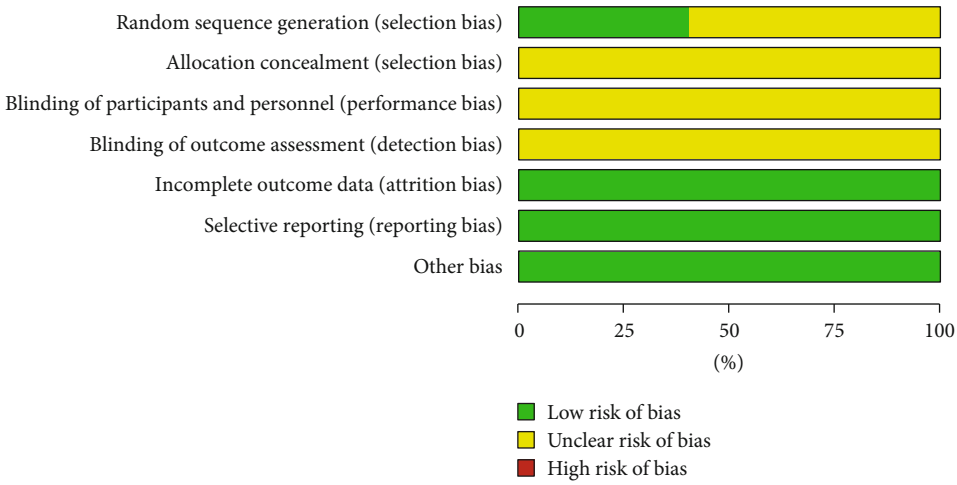

Figure 2: Risk of bias graph: review of authors' judgments regarding each risk of bias item presented as percentages across all included studies.

Study or subgroup	Acupuncture Events	Acupuncture Total	No acupuncture Events	No acupuncture Total	Weight	Risk ratio M-H, fixed, 95% CI
Chen, 2017	19	47	9	40	3.2%	1.80 [0.92, 3.52]
Deng, 2019a	22	25	13	25	4.2%	1.69 [1.13, 2.53]
Deng, 2019b	26	30	19	30	6.2%	1.37 [1.01, 1.86]
Du, 2015	36	45	30	45	9.8%	1.20 [0.93, 1.55]
Li, 2016	33	35	27	35	8.8%	1.22 [1.00, 1.49]
Liu, 2018	38	40	31	40	10.1%	1.23 [1.02, 1.47]
Qu, 2014	23	26	14	25	4.7%	1.58 [1.09, 2.30]
Shen, 2013	29	30	24	30	7.8%	1.21 [1.00, 1.46]
Xia, 2019	45	48	35	47	11.5%	1.26 [1.05, 1.51]
Xiao, 2010	49	50	30	35	11.5%	1.14 [0.99, 1.32]
Xie, 2018	35	38	24	38	7.8%	1.46 [1.12, 1.89]
Yu, 2013a	39	40	33	40	10.8%	1.18 [1.02, 1.37]
Yu, 2013b	18	21	11	21	3.6%	1.64 [1.05, 2.55]
Total (95% CI)		**475**		**451**	**100.0%**	**1.31 [1.22, 1.40]**
Total events	412		300			

Heterogeneity: chi^2 = 12.54, df = 12 (P = 0.40); I^2 = 4%

Test for overall effect: Z = 7.59 (P < 0.00001)

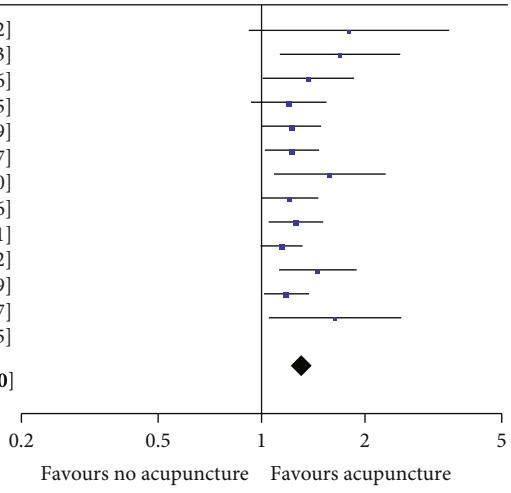

Figure 3: The efficacy rate of acupuncture versus no acupuncture. Both I^2 and P are used as the criteria for heterogeneity test. ✦: pooled relative risk; —■—: relative risk and 95% CI.

Study or subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	No acupuncture Mean	No acupuncture SD	No acupuncture Total	Weight	Mean difference IV, fixed, 95% CI
Fang, 2019	43.58	14.34	40	59.53	19.94	40	12.6%	−15.95 [−23.56, −8.34]
Shen, 2013	42.9	25.22	30	48.87	36.38	30	2.9%	−5.97 [−21.81, 9.87]
Xia, 2019	32.12	8.12	48	48.23	7.23	47	76.3%	−16.11 [−19.20, −13.02]
Xie, 2018	45.63	22.45	38	52.1	25.5	38	6.2%	−6.47 [−17.27, 4.33]
Zhang, 2014	45.64	42.46	30	60.07	31.6	30	2.0%	−14.43 [−33.37, 4.51]
Total (95% CI)			**186**			**185**	**100.0%**	**−15.16 [−17.86, −12.46]**

Heterogeneity: chi^2 = 4.19, df = 4 (P = 0.38); I^2 = 5%

Test for overall effect: Z = 11.01 (P < 0.00001)

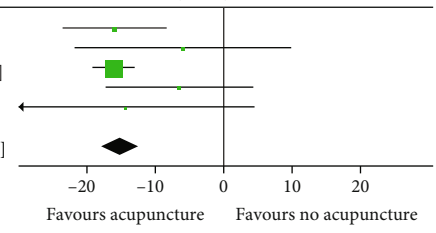

Figure 4: Impact of acupuncture on ALT. Both I^2 and P represent the criteria for the heterogeneity test. ✦: pooled mean difference; —■—: mean difference and 95% CI.

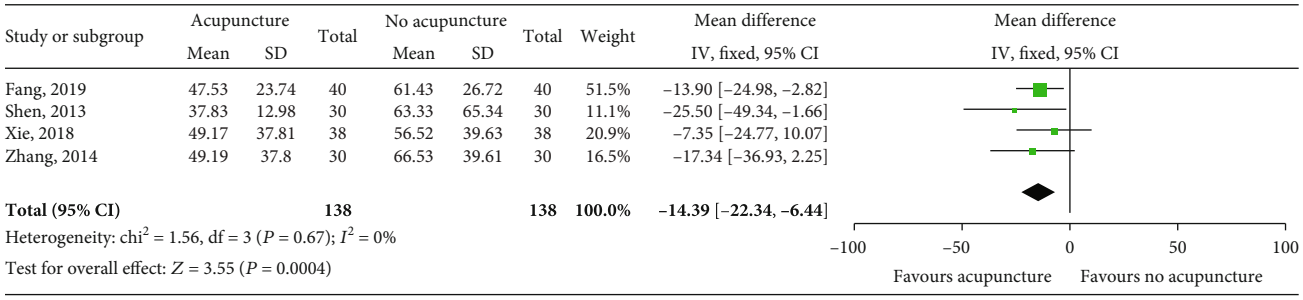

Figure 5: Impact of acupuncture on AST. Both I^2 and P represent the criteria for the heterogeneity test. ✦: pooled mean difference; —■—: mean difference and 95% CI.

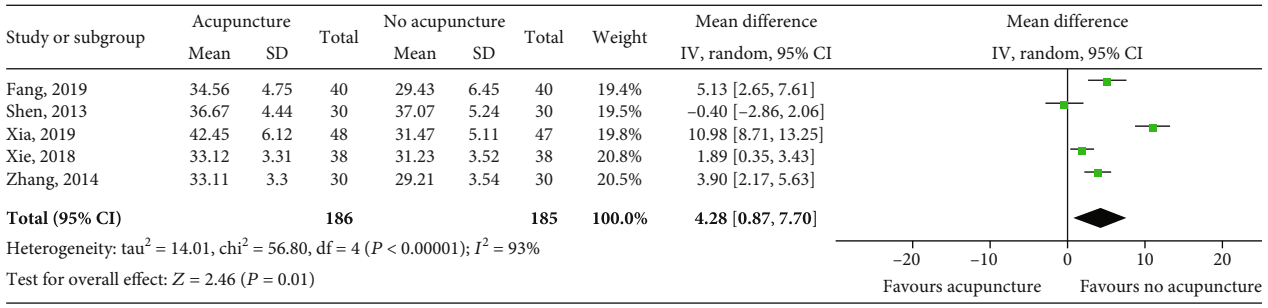

Figure 6: Impact of acupuncture on ALB. Both I^2 and P represent the criteria for the heterogeneity test. ✦: pooled mean difference; —■—: mean difference and 95% CI.

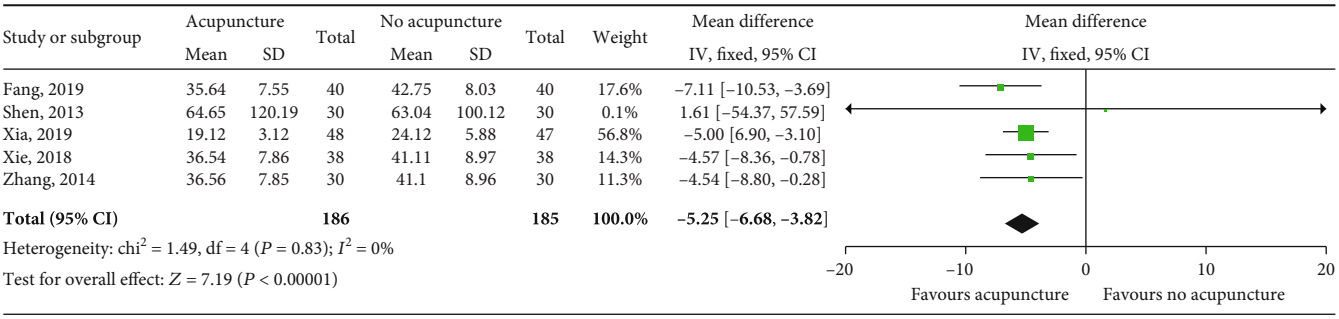

Figure 7: Impact of acupuncture on TBIL. Both I^2 and P represent the criteria for the heterogeneity test. ✦: pooled mean difference; —■—: mean difference and 95% CI.

stress, inhibiting inflammatory response, and promoting lipid metabolism of hepatocytes [27–29]. Animal studies have confirmed that acupuncture has a positive effect on improving gastrointestinal motility and tissues of LC. Multiple animal studies reported that acupuncture promotes ECM degradation of the liver tissue, possibly related to activation of the TGF-β/Smad signaling pathway or inhibition of the PDGF signaling pathway. Animal studies also showed that acupuncture has beneficial effects on inflammatory responses caused by dyslipidemia through regulating contain receptors of Kupffer cells, such as scavenger receptors, complement receptors, and pattern recognition receptors. Thinning of fibrous septa, mitigation of necrosis induced by inflammatory responses, and reduction of extracellular matrix were observed in the liver after acupuncture treatment [30, 31]. More importantly, these positive effects have also been demonstrated in controlled clinical trials [32, 33]. The regulating effect of acupuncture on different cellular and molecular pathways supports its clinical application for treatment of LC.

To date, there is a lack of comprehensive systematic review and meta-analysis on the effect of acupuncture for LC treatment. The purpose of our meta-analysis was to find current evidence on the clinical application of acupuncture for this disease. It is indicated that acupuncture at specific acupoints was beneficial to patients with LC, had no hepatotoxicity and few adverse reactions, and could be used as an adjuvant treatment for LC. According to the basic theory of traditional Chinese medicine, acupuncture needles are manipulated by flicking and rotating (defined as "manual needle acupuncture"), although it is known that acupuncture manipulation, frequency, duration of needle retention, and intensity of stimulation all affect the curative effect [34]. Manual needle acupuncture was applied in all the 15 tails.

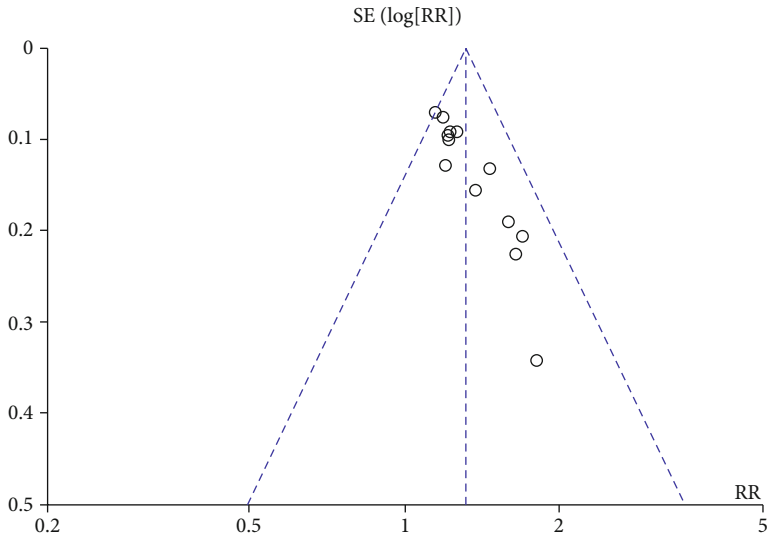

Figure 8: Funnel plot of acupuncture versus no acupuncture on efficacy rate.

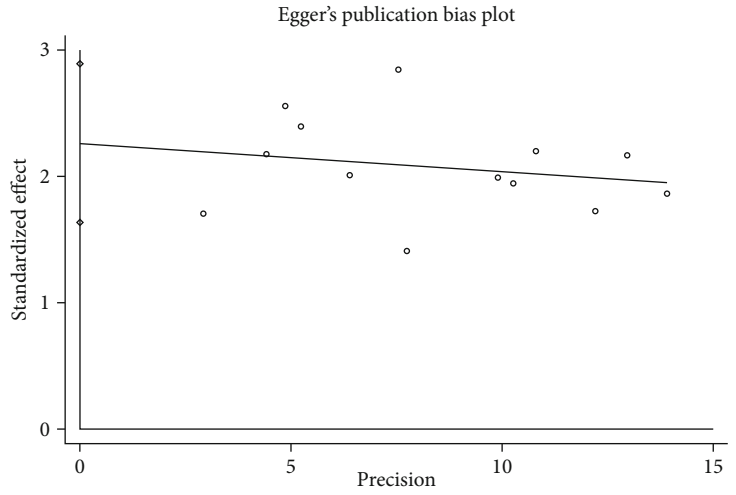

Figure 9: Egger's publication bias plot of the efficacy rate.

Due to the need for treatment based on syndrome differentiation in clinical trials, the choice of acupoints in these trials varied greatly. In the 15 included studies, some acupoints were used more often than others, such as Zusanli (ST36), Taichong (LR3), Tanyinjiao (SP6), Ganshu (BL18), Yanglingquan (GB34), and Zhongwan (RN12).

LC is a significant challenge for physicians. Since many patients have already developed decompensation when they visit hospitals, they often have jaundiced, fatigued, insomnia, abdominal distension, and an array of other symptoms. Five of the 15 included studies reported these symptoms. Four of them reported a decrease in symptom scores after acupuncture, and one trial reported reductions in the rate of symptoms. However, because these five studies used different scoring criteria, we could not merge the results. Since these studies did not report outcome about health-related quality of life, no evidence is available about whether acupuncture improves patients' quality of life.

All the included studies involved specific efficacy criteria, such as liver function immunoglobulin indices, liver fibrosis indicators, and ascites related indexes. All of them mentioned only that acupuncture is a safe and reliable therapy, but no adverse events were reported. Therefore, the evidence on the safety of acupuncture is weak.

Despite limitations of the included studies, this meta-analysis supports the effectiveness of acupuncture for LC. It suggests that acupuncture may benefit LC patients by improving liver function and alleviating the clinical symptoms. The problems of the included studies include small sample size, limited data, and deficiencies in research methods. All of the included clinical studies lacked long-term follow-up: only one study was followed for 1 year and reported recurrence rate of ascites, while others had short follow-up periods. The quality of each research methodology was not high. Because double-blind methods and allocation concealment were not applied, it was not possible to

eliminate potential placebo effect and selective bias during group assignment of participants. Since no literature with negative results was retrieved in this study, the existence of literature selection bias also could not be excluded. These factors affect the extent of the recommendation from the system of evaluation. In the future, multicenter and large sample studies with better study design should be adopted.

6. Conclusions

The meta-analysis suggested that acupuncture is a therapeutic option in patients with LC as a type of complementary medicine. Because the meta-analysis was based on studies with a relatively small sample, it is necessary to conduct strict, well-designed, large-scale, multicenter randomized controlled studies which further confirm the efficacy of acupuncture for LC treatment.

Data Availability

The extracted data used to support the findings of this study are included within the article. The search strategy data used to support the findings of this study are included within the supplementary information file. Other relevant data supporting this meta-analysis come from previously reported studies and cited data sets.

Conflicts of Interest

This study was not supported by any private business enterprise. In addition, all authors of this manuscript claim that they have no conflicts of interest and nothing to disclose.

Acknowledgments

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Supplementary Materials

The supplementary file contains the detailed search strategy. *(Supplementary Materials)*

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Research Article

The Presence of Ascites Affects the Predictive Value of HVPG on Early Rebleeding in Patients with Cirrhosis

Chuan Liu,[1] Ruoyang Shao,[2] Sining Wang,[3] Guangchuan Wang,[3] Lifen Wang,[3] Mingyan Zhang,[3] Yanna Liu,[4] Mingkai Liang,[4] Xiaoguo Li,[4] Ning Kang,[4] Jitao Wang,[4] Dan Xu,[4] Hua Mao ,[1] Chunqing Zhang ,[3] and Xiaolong Qi[4]

[1]*Department of Gastroenterology, Zhujiang Hospital, Southern Medical University, Guangzhou 510000, China*
[2]*Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510000, China*
[3]*Department of Gastroenterology, Shandong Provincial Hospital, Shandong University, Jinan 250000, China*
[4]*CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou 730000, China*

Correspondence should be addressed to Hua Mao; huam@fimmu.com and Chunqing Zhang; zhangchunqing_sdu@163.com

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Background and Aims. Gastroesophageal variceal bleeding is a serious complication of portal hypertension in cirrhotic patients and could be predicted by hepatic venous pressure gradient (HVPG). However, whether the presence of ascites affects the prognostic value of HVPG for patients with acute variceal bleeding is still unknown. This retrospective study is aimed at investigating the influence of ascites on predictive performance of HVPG for early rebleeding in cirrhotic patients with acute variceal bleeding. *Methods*. In this retrospective study, a total of 148 patients with cirrhosis hospitalized for acute variceal bleeding who underwent HVPG measurement and endoscopic variceal ligation (EVL) for the prevention of rebleeding were included. The receiver operating characteristic curve (ROC) and logistical regression method were employed to analyze the predictive performance of HVPG for early rebleeding. The locally weighted scatterplot smoothing approach was adopted to assess the monotonicity between bleeding risk and HVPG. *Results*. A significantly higher HVPG level was observed in patients with early rebleeding compared to patients without rebleeding in the nonascites cohort. When using HVPG to predict early rebleeding, there was a lower area under curve in the ascites cohort compared to the nonascites cohort. HVPG was recognized as a risk factor for early rebleeding by a logistic regression model only in the nonascites cohort. An overall monotonicity in the trend of change in HVPG and risk for early rebleeding was observed in the nonascites cohort solely. *Conclusion*. The predictive value of HVPG for early rebleeding in patients with cirrhosis that developed acute variceal bleeding is hindered by the presence of ascites.

1. Introduction

Gastroesophageal variceal bleeding (GVB) is among the most serious complications of portal hypertension in patients with cirrhosis and even leads to death [1]. Hepatic venous pressure gradient (HVPG) is a potent prognostic factor for patients with cirrhosis [2–4] and has been widely recommended to predict the presence of ascites, hepatic encephalopathy, variceal bleeding and rebleeding, and bleeding-related death [4, 5]. An HVPG higher than 20 mmHg indicates a significantly higher risk of early rebleeding in patients with acute variceal bleeding (AVB) [3, 6–8].

Other than GVB, ascites is also commonly developed in patients with cirrhosis especially those with more advanced disease condition. The enhancing activation of renin-angiotensin-aldosterone system (RAAS) as the disease progresses is considered the main pathophysiological process to induce the generation of ascites [9]. Thus, compared to patients without ascites, patients with ascites have a generally worse liver function and more intense hyperdynamic condition that causes instability in hemodynamics [10]. Besides, patients with multiple decompensation events like variceal bleeding combined with ascites, namely, patients experiencing "further decompensation," have worse prognosis than

those with one decompensation event [11, 12]. Furthermore, ascites itself as a physical influential factor could also play a disturbing role during HVPG measurement. While it is clear that ascites could influence hemodynamics [9, 10], there still lacks evidence to show whether the presence of ascites affects the prognostic value of HVPG in patients with AVB. In this study, we aim to investigate the influence of ascites on the predictive performance of HVPG for early rebleeding in cirrhotic patients with AVB.

2. Patients and Methods

2.1. Study Population. In this study, a total of 148 consecutive patients with cirrhosis were retrospectively recruited from Shandong Provincial Hospital between October 2010 and August 2018. The inclusion criteria were as follows: (1) patients hospitalized for AVB with clinically and/or pathologically diagnosed cirrhosis; (2) patients who received octreotide and emergency endoscopic therapy as an initial intervention to stop the acute bleeding and then endoscopic variceal ligation (EVL) (combined with nonselective beta-blocker (NSBB), or alone when there was an NSBB contraindication) for preventing rebleeding; (3) patients who accepted transjugular HVPG measurement after the emergency endoscopic therapy and within 7 days before and 18 days after the first therapy among the following EVL sequence; and (4) patients who were followed up till the 42nd day or developed rebleeding since accepting EVL. To avoid the influence of EVL on the accuracy of HVPG, patients who accepted HVPG measurement within 48 hours after EVL were excluded [13]. Early rebleeding was defined as rebleeding occurred within 42 days since EVL.

2.2. HVPG Measurement. HVPG measurements were performed using balloon catheters with a pressure transducer at the tip (Edwards Lifesciences, Irvine, Calif) complying with a reported protocol [14]. Before catheterization, a "zero measurement" was performed. The right hepatic vein was chosen for measurements whenever feasible. If stenosis or vein-to-vein shunt in the right hepatic vein was observed, the middle hepatic vein was chosen instead. The free hepatic venous pressure was measured close to the inferior vena cava (1-3 cm, approximately). Then, the balloon was inflated to occlude completely the chosen hepatic vein, and then, the wedged hepatic venous pressure was measured. Dynamic screening of each pressure was continued until the pressure reached a plateau, after which the values were recorded. All measurements were performed in triplicate at least, and the average value was taken as the result. HVPG was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure.

2.3. Statistical Analysis. Continuous variables were shown as the mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were shown as the number and frequency (%). The Mann–Whitney test was used to compare HVPG between nonearly rebleeding and early rebleeding in the ascites and nonascites subgroups. The receiver operating characteristic curve (ROC) was used to evaluate the predictive performance of HVPG for early rebleeding in the nonascites cohort and the ascites cohort, respectively. Univariate and multivariate logistic regression models were employed to calculate odds ratio (OR) and P value of HVPG and other potential risk stratification factors for rebleeding. For a multivariate logistic regression model, platelet (PLT), albumin (ALB), and HVPG were included. The locally weighted scatterplot smoothing (LOWESS) approach was adopted to assess the monotonicity between bleeding risk and HVPG in patients with and without ascites. All levels of significance were set at a two-sided 5% level. All analyses were performed using SPSS 22.0 IBM (IBM Corp., Armonk, NY) and R 3.5.3 (R Project for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients. A total of 148 patients meeting the inclusion and exclusion criteria were included, of which 106 patients received either propranolol or carvedilol combined with EVL. Patients included were followed up until at least the 42nd day or developed rebleeding since EVL. Early rebleeding occurred in 15 out of 148 patients (10.1%). Clinical characteristics of the studied cohorts are summarized in Table 1.

3.2. HVPG Remains Stable in Patients with Ascites Who Developed Early Rebleeding. During follow-up, 10 out of 79 patients with ascites (ascites cohort) and 5 out of 69 patients without ascites (nonascites cohort) experienced early rebleeding. We compared the HVPG level between patients with and without early rebleeding in both cohorts. In the nonascites cohort, a significantly higher HVPG level was observed in patients experienced early rebleeding compared to those did not (21.00 mmHg vs. 13.00 mmHg, $P = 0.009$) (Figure 1(a)). However, there was no significant difference in the HVPG level between patients with and without early rebleeding in the ascites cohort (Figure 1(b), median, 17.50 (12.34-21.00) mmHg vs. 14.50 (12.00-18.00) mmHg, $P = 0.207$).

3.3. Ascites Affects the Predictive Value of HVPG for Early Rebleeding. We used the area under the ROC curve (AUC) to assess whether the presence of ascites affects the predictive value of HVPG on early rebleeding. The ROC curves were plotted for the whole cohort, the ascites cohort, and the nonascites cohort (Figure 2). AUC values of HVPG for predicting early rebleeding showed a tendency to decrease in the three cohorts (AUC: 0.711 (0.570-0.851), 0.852 (0.694-1.000), and 0.624 (0.426-0.822) for whole, nonascites, and ascites cohorts, respectively) (Figure 2).

3.4. The Impact of HVPG on the Risk of Early Rebleeding Is Different in Patients with and without Ascites. To investigate the risk factors for early rebleeding in patients with and without ascites, univariate and multivariate logistic regression analysis were performed. In the nonascites cohort, HVPG was recognized as the only statistically significant risk factor with ORs of 1.350 ($P = 0.020$, univariate) and 1.350 ($P = 0.029$, multivariate) (Table 2). However, in the ascites cohort, HVPG failed to manifest a significant impact on the

Table 1: Clinical characteristics of the studied patients.

Variables	Patients ($n = 148$)	Ascites group ($n = 79$)	Nonascites group ($n = 69$)	P
Age (y), median (IQR)	51.5 (15.75)	53.0 (16.00)	50.0 (13.50)	0.071
Gender, n (%)				0.607
Male	46 (31.1)	53 (67.1)	20 (29.0)	
Female	102 (68.9)	26 (32.9)	49 (71.0)	
AST (IU/L), median (IQR)	33.5 (20.5)	34.0 (19.0)	33.0 (24.0)	0.745
ALT (IU/L), median (IQR)	25.0 (15.8)	25.0 (19.0)	25.0 (14.0)	0.917
PLT (10^9/L), median (IQR)	71.5 (72.5)	66.0 (71.0)	83.0 (78.0)	0.118
TBIL (μmol/L), median (IQR)	19.9 (10.7)	20.5 (12.1)	18.9 (9.85)	0.138
ALB (g/L), median (IQR)	33.4 (7.4)	31.2 (7.7)	34.7 (7.4)	<0.001
INR, median (IQR)	1.21 (0.25)	1.24 (0.25)	1.20 (0.16)	0.019
Accepting NSBB, n (%)	106 (71.6)	48 (60.76)	58 (84.06)	0.002
Ascites, n (%)	79 (53.4)	NA	NA	NA
Early rebleeding, n (%)	15 (10.1)	10 (12.66)	5 (7.25)	0.414
HVPG (mmHg), mean (SD)	15.0 (4.66)	15.46 (4.52)	14.44 (4.79)	0.158
Child-Pugh class, n (%)				<0.001
Child A	62 (41.9)	14 (17.72)	48 (69.57)	
Child B	73 (49.4)	53 (67.09)	20 (28.99)	
Child C	13 (8.8)	12 (15.19)	1 (1.45)	
Etiology, n (%)				0.165
Viral	87 (58.7)	53 (67.09)	34 (49.28)	
Alcoholic	16 (10.8)	8 (10.13)	8 (11.59)	
Autoimmunogenic	10 (6.7)	5 (6.33)	5 (7.25)	
Cholestatic	5 (3.4)	1 (1.27)	4 (5.80)	
Other	30 (20.3)	12 (15.19)	18 (26.09)	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; PLT: platelets; TBIL: total bilirubin; INR: international normalized; ALB: albumin; NSBB: nonselective beta-blocker; MELD: Model of End-stage Liver Disease; HVPG: hepatic venous pressure gradient; y: years; IQR: interquartile range.

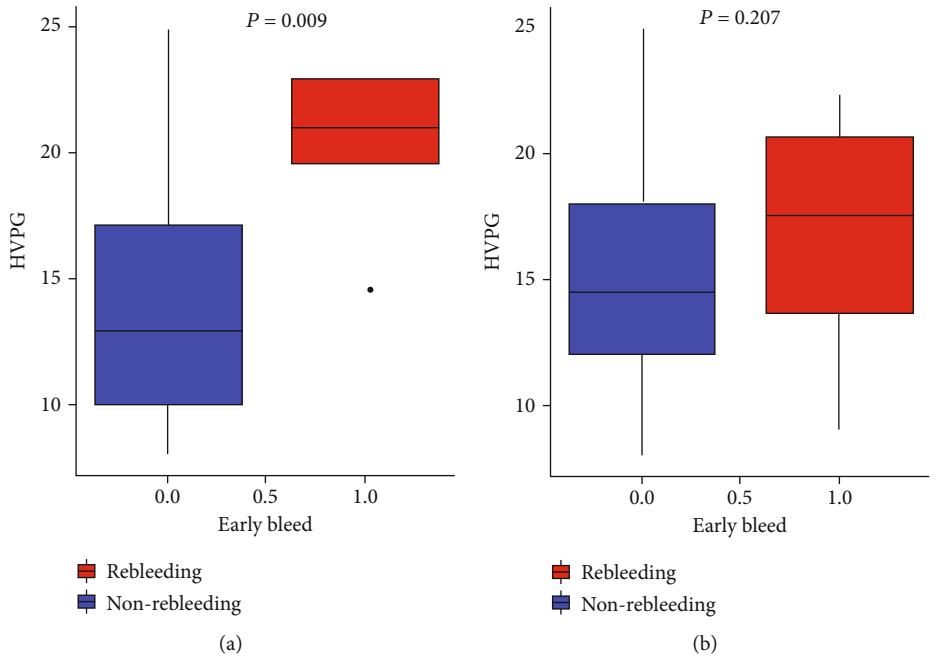

Figure 1: Comparisons of HVPG in patients with and without early rebleeding in (a) the nonascites cohort and (b) the ascites cohort. HVPG: hepatic venous pressure gradient.

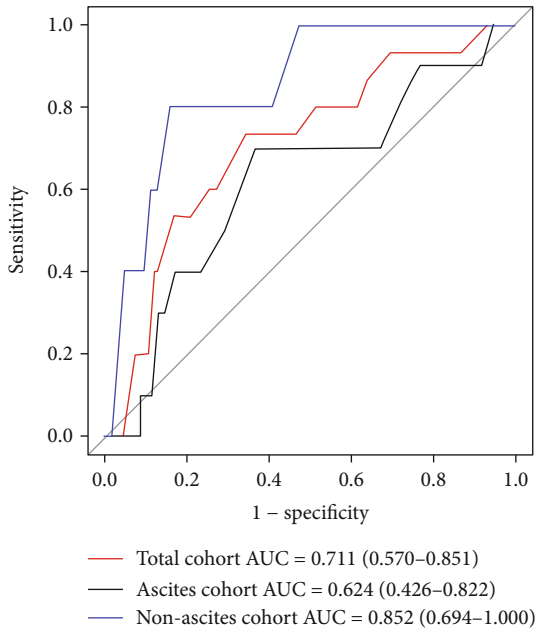

Figure 2: ROC curve of HVPG for predicting early rebleeding in the total cohort, the ascites cohort, and the nonascites cohort. AUC: area under the ROC curve.

risk of early rebleeding with ORs of 1.089 ($P = 0.253$, univariate) and 1.073 ($P = 0.380$, multivariate) (Table 3).

It is generally believed that the higher the HVPG of cirrhotic patients, the higher risk for rebleeding they suffer. So we believe that if the HVPG level is a risk factor of early rebleeding in a certain population, there should be an overall monotonicity in the trend of change in HVPG and the risk for early rebleeding. Therefore, we employed the LOWESS approach to generate a fitting curve that reflected the overall trend of change in HVPG and risk for early rebleeding in the ascites cohort and the nonascites cohort, respectively, in order to assess their monotonicity. As shown in Figure 3, an overall monotonicity was observed in the nonascites cohort but not in the ascites cohort.

4. Discussion

HVPG could filter the influence of the central venous system and abdominal pressure and is widely accepted as an accurate index for assessing portal hypertension [15–17]. It has been proved to be a potent and versatile prognostic factor in cirrhotic portal hypertension. HVPG ≥ 10 mmHg is regarded as the threshold for the occurrence of decompensation and is thus called clinically significant portal hypertension. Patients with clinically significant portal hypertension face significantly higher risks of developing varices, bleeding, other decompensation events, and hepatocellular carcinoma [2, 18, 19]. Patients with an HVPG ≥ 16 mmHg suffer from higher mortality [20–22] and bleeding risk [7, 23]. An HVPG above 20 mmHg is strongly predictive of failure to control bleeding, early rebleeding, and hemorrhage-related death [3, 24].

It is intuitive and generally successful to stratify bleeding risk using the stable portal pressure reflector, HVPG, based on the direct correlation between the elevation of portal pressure and risk of varices bleeding. However, there still exist confounding factors affecting either the accuracy of HVPG measurement or its capability to indicate the actual bleeding risk in patients with cirrhosis, especially those with more complex disease conditions, like patients with ascites.

In patients with cirrhosis, the presence of ascites is the consequence of the activation of RAAS initiated by portal hypertension. Approximately 60% of cirrhotic patients develop ascites in 10 years since diagnosis [25], and ascites is the first decompensation event in most patients [26, 27].

In studies that support the role for an HVPG higher than 20 mmHg to indicate a higher risk of treatment failure or early rebleeding, none of them performed subgroup analysis for patients with and without ascites [3, 6–8, 28]. However, as stated above, patients with ascites have generally more advanced disease condition and poorer liver function and are therefore more easily to develop endothelial dysfunction [29]. Under these circumstances, HVPG could not accurately reflect the portal pressure for it actually represents the pressure of the hepatic sinusoid. Besides, patients with ascites are in a more intense hyperdynamic state and with more unstable hemodynamics [10, 30]. These patients, even with relatively low HVPG, may suffer from higher risks of rapid increment of HVPG and exacerbation of disease that results in worse clinical outcomes, compared to patients with similar HVPG but without ascites. A significantly higher mortality was observed in patients with ascites compared to patients without any decompensation events, and the result was also similar when comparing patients with ascites and experienced bleeding to those who experienced bleeding but without other decompensation events [11, 12]. Also, although the elevation of portal pressure is considered the dominant factor of bleeding, the more complex condition in patients with ascites inevitably adds more influential factors and thus hinders the predictive performance of the single predictor, HVPG. Additionally, although HVPG could filter the influence of the central venous system and abdominal pressure theoretically, the measurement error introduced by respiratory cycle cannot be eliminated [31].

One possible solution to improve the early rebleeding-predictive performance is to combine HVPG with other clinical indicators to develop an extended predictive model. In a meta-analysis that included 118 studies, Child-Pugh, encephalopathy, hepatocellular carcinoma, bleeding, creatinine, prothrombin time, albumin, azotemia, ascites, and bilirubin were shown to be frequently used statistically significant prognostic parameters in patients with decompensated cirrhosis [32]. By introducing other clinical indicators, a model that covers different factors that influence clinical outcome from different aspects could be developed. A multiple factor model may be able to reflect the disease condition of patients in a more comprehensive manner, resulting in possible improvement in predictive performance. However, the more indicators included in a model, the less easy-to-use the model will be. Another possible attempt is to track the change of HVPG after acute bleeding. As reported by Ready et al., acute bleeding patients who did not develop early rebleeding showed an overall decreasing trend of HVPG after

Table 2: Univariate and multivariate logistic regression analysis in the nonascites cohort.

Variable	Univariate		Multivariate	
	OR	*P* value	OR	*P* value
Child-Pugh score	0.543 (0.061-4.807)	0.583		
HVPG	1.350 (1.049-1.737)	0.020	1.350 (1.032-1.765)	0.029
AST	0.988 (0.932-1.047)	0.681		
ALT	0.9996 (0.954-1.040)	0.863		
ALB	1.066 (0.889-1.278)	0.490		
TBIL	0.998 (0.979-1.018)	0.850		
PLT	0.997 (0.983-1.010)	0.614		
INR	6.989 (0.061-804.738)	0.422	1.014 (0.002-438.036)	0.996

HR: hazard ratio; HVPG: hepatic venous pressure gradient; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; PLT: platelets; INR: international normalized ratio.

Table 3: Univariate and multivariate logistic regression analysis in the ascites cohort.

Variable	Univariate		Multivariate	
	OR	*P* value	OR	*P* value
Child-Pugh score	3.278 (0.952-11.289)	0.060		
HVPG	1.089 (0.941-1.261)	0.253	1.073 (0.917-1.255)	0.380
AST	0.980 (0.942-1.019)	0.310		
ALT	0.969 (0.916-1.025)	0.267		
ALB	0.965 (0.864-1.078)	0.531		
TBIL	1.026 (0.993-1.061)	0.125		
PLT	0.980 (0.957-1.004)	0.096		
INR	17.052 (1.014-286.888)	0.049	14.364 (0.825-250.056)	0.068

HR: hazard ratio; HVPG: hepatic venous pressure gradient; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; PLT: platelets; INR: international normalized ratio.

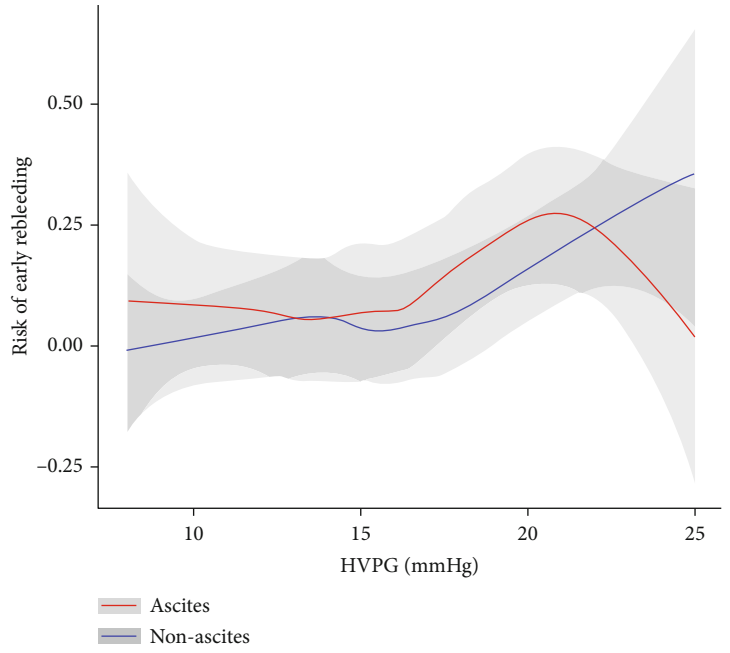

Figure 3: LOWESS curve for assessing the trend of risk for early rebleeding on HVPG in the ascites cohort and nonascites cohort.

the acute phase [28]. Overcoming the invasiveness and high cost of extra HVPG measurements, the emerging techniques for noninvasive prediction of portal pressure have achieved high accuracy using routine clinical data [1, 33–35]. These serum- or imaging-based methods may provide additional data that benefit our decision. Nevertheless, the sensitivity of these methods to the short-term change of portal pressure remains to be tested before being applied for dynamic monitoring.

Our study for the first time investigated the influence of ascites on the predictive value of HVPG for early rebleeding in cirrhotic patients with AVB. Yet, there are also several limitations. First, this study is a retrospective study including cases from a single center, which may be a possible source of bias. Second, subgroup analysis was not performed for patients with ascites of different intensities due to lack of original data. Third, not all the patients included received NSBB, and this heterogeneity may also be a source of bias. Fourth, patients were followed up for only 42 days, so no data on other events could be provided.

In summary, we found that patients with early rebleeding have a higher HVPG than those who did not in the nonascites cohort, but not in the ascites cohort. When using HVPG to predict early rebleeding, the AUC in the ascites cohort was significantly lower comparing to the nonascites cohort and the whole cohort. HVPG was recognized as a risk factor for early rebleeding in the nonascites cohort but not in the ascites cohort. An overall monotonicity in the trend of change in HVPG and risk for early rebleeding was observed in the nonascites cohort only using the LOWESS approach. Taking together, these findings suggested that the predictive value of HVPG for early rebleeding in patients with cirrhosis that developed AVB is hindered by the presence of ascites.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Hua Mao, Chunqing Zhang, and Xiaolong Qi are responsible for the study concept and design. Sining Wang, Guangchuan Wang, Lifen Wang, and Mingyan Zhang acquired the data. Chuan Liu, Ruoyang Shao, Yanna Liu, Mingkai Liang, Xiaoguo Li, Ning Kang, Jitao Wang, and Dan Xu performed the analysis and interpretation of data. Ruoyang Shao and Sining Wang drafted the manuscript. Chunqing Zhang, Hua Mao, and Xiaolong Qi are assigned to the critical revision of the manuscript. Chuan Liu, Ruoyang Shao, and Sining Wang contributed equally to this work.

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Review Article

Transjugular Intrahepatic Portosystemic Shunt Placement for Portal Hypertension: Meta-Analysis of Safety and Efficacy of 8 mm vs. 10 mm Stents

Jiangtao Liu,[1,2] Eric Paul Wehrenberg-Klee,[1] Emily D. Bethea,[3] Raul N. Uppot,[1] Kei Yamada,[1] and Suvranu Ganguli[1,4]

[1]*Department of Radiology, IR Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA*
[2]*Department of Gastroenterology, Chinese PLA General Hospital Hainan Hospital, Sanya, Hainan 572016, China*
[3]*Liver Center and Gastrointestinal Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA*
[4]*Department of Radiology, Division of Interventional Radiology, Boston Medical Center, Boston University School of Medicine, USA*

Correspondence should be addressed to Suvranu Ganguli; suvranu.ganguli@gmail.com

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Introduction. Hepatic encephalopathy (HE) following transjugular intrahepatic portosystemic shunt (TIPS) placement remains a leading adverse event. Controversy remains regarding the optimal stent diameter given that smaller stents may decrease the amount of shunted blood and decrease the risk of HE, but stent patency and/or clinical adequacy of portal decompression may also be affected. We aim to provide meta-analysis-based evidence regarding the safety and efficacy of 8 mm vs. 10 mm stents during TIPS placement. *Methods*. PubMed, Embase, Cochrane Library, and Web of Science were searched for studies comparing 8 mm and 10 mm stents during TIPS placement for portal hypertension decompression in cirrhotic patients. Randomized controlled trials and cohort studies were prioritized for inclusion. Overall evaluation of quality and bias for each study was performed. The outcomes assessed were the prevalence of HE, rebleeding or failure to control refractory ascites, and overall survival. Subgroup analysis based on TIPS indication was conducted. *Results*. Five studies with a total number of 489 cirrhotic patients were identified. The pooled hazard ratio (HR) of post-TIPS HE was significantly lower in patients in the 8 mm stent group than in the 10 mm stent group (HR: 0.68, 95% CI: 0.51~0.92, p value < 0.0001). The combined HR of post-TIPS rebleeding/the need for paracentesis was significantly higher in patients in the 8 mm stent group than in the 10 mm stent group (HR: 1.76, 95% CI: 1.22~2.55, p value < 0.0001). There was no statistically significant difference in the overall survival between the 8 mm and 10 mm stent groups. The combined risk of HE in the variceal bleeding subgroup was statistically lower (HR: 0.52, CI: 0.34-0.80) with an 8 mm stent compared with a 10 mm stent. The combined risk of both rebleeding/paracentesis and survival was not statistically significant between 8 mm and 10 mm stent use in subgroup analysis. *Conclusion*. 8 mm stents during TIPS placement are associated with a significant lower risk of HE compared to 10 mm stents (32% decreased risk), as well as a 76% increased risk of rebleeding/paracentesis. Meta-analysis results suggest that there is not one superior stent choice for all clinical scenarios and that the TIPS indication of variceal bleeding or refractory ascites might have different appropriate selection of the shunt diameter.

1. Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) placement for portal pressure decompression is a well-established treatment for complications of portal hypertension in cirrhotic patients [1–4]. New or worsened hepatic encephalopathy (HE) is one of the main adverse events after TIPS, with no pharmacological treatment able to completely prevent its incidence [5]. TIPS placement affects hepatic hemodynamics by reducing portal blood inflow to hepatocytes, decreasing hepatic portal perfusion and increasing ischemic injury with decreased hepatic function [6]. The amount of portal blood shunting also prevents hepatic detoxication of the blood and is closely related to post-TIPS HE [7]. The choice of a stent

diameter, and therefore the shunt size, balances the demands of portal decompression to prevent portal hypertension complications and shunt-related encephalopathy. Controversy remains regarding the optimal stent diameter owing to the theory that smaller stents may decrease the amount of shunting blood and decrease the risk of HE, but stent patency or clinical adequacy of portal decompression is also affected [8].

In the past decade, 10 mm diameter stents have been used most frequently during TIPS procedures, with reported HE rates of nearly 40% [2, 9]. Underdilation of 10 mm stents at the time of TIPS creation, to 8 mm for example, is a utilized technique to decrease HE incidence, but this technique has not proven to be long-lasting [10–12]. Riggio et al. were the first to compare TIPS placement with 8 mm and 10 mm stents, showing that 8 mm stents lead to significantly less efficient control of portal hypertension with recurrence or persistence of portal hypertension complications in the majority of patients [13]. Another study comparing small-diameter (majority of 8 mm) TIPS with the standard treatment for prevention of variceal rebleeding revealed a significant lower incidence of rebleeding in the 8 mm group, with just a slightly higher prevalence of HE [14]. Other prospective and retrospective studies comparing 8 mm and 10 mm stents in relation to HE, rebleeding, ascites, and survival have shown mixed results in favor of 8 mm or 10 mm stents [15, 16]. Given this controversy, this study is aimed at providing meta-analysis-based evidence regarding the efficacy of 8 mm vs. 10 mm stents during TIPS placement on HE incidence, control of portal hypertension, and overall survival (OS).

2. Materials and Methods

2.1. Search Method and Selection of Studies. PubMed, Embase, Cochrane Library, and Web of Science were searched for eligible studies from 1988 (the initial year in which metal stent TIPS procedures were performed) to January 2020. The Web of Science search engine was also used for peer-reviewed publications and conference papers or abstracts to ensure full coverage of information to reduce selection bias. The following keywords were included: "transjugular intrahepatic portosystemic shunt", "TIPS", "diameter", "shunt", "8-mm", and "10-mm". The cited references of original studies and reviews were also searched. The following criteria were employed for study selection: (1) study with full text in English; (2) study design: randomized controlled trial (RCT) or retrospective observational study; (3) study participants: cirrhotic patients receiving TIPS for variceal bleeding and/or refractory ascites; (4) study interventions: TIPS with different stent diameters including 8 mm and 10 mm; and (5) at least one of the following outcomes reported: overall survival (OS), number or prevalence of post-TIPS HE, number or rate of post-TIPS rebleeding, number or rate of post-TIPS failure to control ascites or paracentesis, and number or rate of post-TIPS stent dysfunction. Exclusion criteria included the following: (1) noncirrhotic portal hypertension, (2) Budd-Chiari syndrome or hepatic veno-occlusive diseases, and (3) case series studies. This study has been registered at the International Prospective Register of Systematic Reviews (registration number: CRD42020168695).

2.2. Outcome Definitions. We acknowledge that the endpoint and adverse event reporting metrics might not be uniform across studies and often include rates or time-to-event results. Given this, the outcomes utilized in this meta-analysis were based on the results of data extraction. The study outcome includes the prevalence of HE or time to HE, the prevalence of rebleeding or the need for paracentesis, time to rebleeding or the need for paracentesis, mortality, or OS. The prevalence of HE was defined as the number of patients who presented with encephalopathy symptoms during follow-up after TIPS. The rebleeding rate was defined as the number of cases who presented with variceal bleeding during follow-up after TIPS. The need for paracentesis was defined as the number of patients with refractory ascites who still required paracentesis during follow-up after TIPS. The rebleeding prevalence and need for paracentesis were combined to create the category of "rebleeding/paracentesis." OS was defined as the length of time that the patients were still alive after the date of TIPS or to the endpoint of study. Mortality was defined as the number of patients who died from any reason during follow-up after TIPS.

2.3. Risk of Bias Assessment. Two investigators (JL and EWK) independently assigned an overall evaluation of quality and bias for each study with the "revised Cochrane risk of bias tool for randomized trials" (RoB 2.0) [17] or the "risk of bias in non-randomized studies of interventions" (ROBINS-I) for observational cohort studies [18]. The RoB 2.0 tool evaluated the randomization process, deviation from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results with the overall risk-of-bias judgment as "low risk of bias," "some concerns," and "high risk of bias." The overall evaluation with ROBINS-I criteria was "low," "moderate," "serious," "critical," and "no information" based on the seven domains evaluated. Any differences in evaluation were resolved with a consensus between the two investigators.

2.4. Data Extraction. The trial eligibility determination and extraction of data were performed independently by the two investigators. Agreements were made through consensus discussion. Data were extracted with study features and clinical information levels, respectively. Study feature information included the following: study year, study design, sample size and allocation, stent type, mean follow-up time, and bias risk score. Clinical information included the following: treatment group, age, gender, etiology of cirrhosis, history of HE, ascites, Child-Pugh score or class, portosystemic pressure gradient (PSG) before and after TIPS, and indication of TIPS placement. The time-event information in each study was pooled if accessible. The hazard ratio (HR) and its standard error (SE) were pooled directly if they were reported in the publication. Another method for calculation was to use the data available in the report and back-calculate the values with the Mantel-Haenszel method [19]. For outcomes with binary variables, the numbers of observed events were extracted directly or based on the information reported or, if necessary, by contacting the authors for possible data. The risk ratio (RR) was used to evaluate the pooled effect of binary outcomes.

2.5. Statistical Analysis. Heterogeneity was assessed by the I^2 index. Data was pooled with a fixed effects model if $I^2 \leq 50\%$, indicating insignificant heterogeneity. Otherwise, the results of both the fixed effects and random effects models were reported. The visualization of publication bias of the included studies was evaluated using the funnel plot if the sample size was over 10. The Z-test was performed to evaluate the significance of the combined HR or RR estimate. Subgroup analysis was conducted based on TIPS indication (variceal bleeding or refractory ascites). A p value of 0.05 was set as the threshold for statistical significance. All analyses were performed using the free software R (R Foundation for Statistical Computing, Vienna, Austria) with the "meta" and "dmetar" packages.

3. Results

Utilizing the described search strategy, we identified a total of 113 publications. 108 of the identified papers were abandoned with the preset inclusion and exclusion criteria. Five studies including 2 RCTs [13, 16] and 3 retrospective cohort studies [15, 20, 21] from 2010 to 2019 were included into the meta-analysis. Figure 1 provides the flow diagram of publication retrieval, screening, and resulting study selection. Data from Trebicka et al. [20] was retrieved based on a multicenter RCT and propensity score matching for known confounders, so this study was categorized as having an observational feature [20]. The total number of patients reported in the five studies was 489.

3.1. Study Characteristics. The five included studies are summarized in Table 1. The two arms for treatment comparisons in all five studies were defined as TIPS placement with 8 mm vs. 10 mm stents. All studies used self-expandable PTFE-covered stents (VIATORR, Gore, Newark, DE, or FLUENCY, Becton Dickinson, East Rutherford, NJ). The indications for TIPS were variceal bleeding in two studies [16, 21], refractory ascites (RA) in one study [15], and both variceal bleeding and RA in two studies [13, 20]. Rebleeding was reported as the probability of remaining free of recurrence and/or persistence of complications due to portal hypertension in one study [13] and as the cumulative incidence of variceal rebleeding in two studies [16, 21]. One study reported the cumulative probability of remaining free from paracentesis for RA [15]. Time-event analysis of HE was reported in four studies [13, 15, 16, 21]. Survival analysis with the log-rank test was reported in three studies [13, 16, 21]. Information on OS was accessed by contacting the authors of [15]. The HR and the corresponding standard error were calculated based on information retrieved in the context of Trebicka et al. [20], where two arms of data were retrieved with the subgroup of 8 mm vs. 10 mm stents (fully dilated plus underdilated). In all the 3 studies with observational features [15, 20, 21], propensity score matching (PSM) was applied to reduce the bias due to confounding variables that could be found in nonrandomized trials. The two RCTs [13, 16] were evaluated with the RoB 2.0 tool, and the three observational cohort studies [15, 20, 21] were evaluated with the ROBINS-I criteria. The bias risk assessment information is summarized in Table 1.

3.2. Patient Characteristics. Table 2 summarizes the characteristics of the patients in the five studies. Most of the baseline variables were balanced between the 8 mm and 10 mm groups. Patient age in one study [16] had a slight statistical difference between the two groups (49.4 in 8 mm vs. 52.0 years in 10 mm, $p < 0.001$). In Trebicka et al. [20], the presence of ascites (no/yes; 22/19 in 8 mm vs. 6/35 in 10 mm, $p < 0.01$), Child-Pugh class (A/B/C; 19/18/4 in 8 mm vs. 3/27/11 in 10 mm, $p < 0.01$), and indication for TIPS (bleeding/RA; 29/12 in 8 mm vs. 6/35 in 10 mm, $p < 0.01$) had a statistical difference.

3.3. Technical Results. The technical success rate was reported as 100% in all the studies except for Riggio et al. [13], in which an incorrect placement of a stent was subsequently corrected with a second stent. Of all the studies, significant reduction of portal-systemic gradient (PSG) was observed in both the 8 mm and 10 mm stent groups. In Riggio et al. [13], the post-TIPS PSG of the 10 mm group was lower than that of the 8 mm group (6.5 ± 2.7 vs. 8.9 ± 2.7 mmHg, p value: 0.0007). Percentages of HE, rebleeding/paracentesis, and mortality were calculated based on the data available in the corresponding studies. The prevalence of post-TIPS HE was between 35.9% and 48.9%, with prevalence of 25%-50% in the 8 mm group and 46.9%-50% in the 10 mm group. The prevalence of rebleeding/paracentesis ranged from 18.1% to 33.3%, with prevalence of 20.3%-54.5% in the 8 mm group and 8.7%-15.5% in the 10 mm group. The mortality rate during follow-up was from 17.8% to 40.2%, with a rate of 20.3%-22.7% in the 8 mm group and 13.0%-27% in the 10 mm group.

3.4. Meta-Analysis. According to the heterogeneity analysis, I^2 of both HE and rebleeding/paracentesis was less than 50%. The HR of time to HE or rebleeding/paracentesis amongst the studies was combined with the fixed effects model. The pooled HR of post-TIPS HE was significantly lower in patients in the 8 mm stent group than in the 10 mm stent group (HR: 0.68, 95% CI: 0.51~0.92, p value < 0.0001) (Figure 2). The 8 mm stent group had a 32% decreased risk in HE compared to the 10 mm stent group. Compared to the 10 mm stent group, the HR of HE in the 8 mm stent group for four of the studies was between 0.51 and 1.34. Two studies had a statistically significant difference [16, 21], and the other two studies [13, 15] did not show significant differences.

The pooled HR of post-TIPS rebleeding/paracentesis was significantly higher in the 8 mm stent compared with the 10 mm stent (HR: 1.76, CI: 1.22~2.55, p value < 0.0001), with the 8 mm stent group having a 76% increased risk in rebleeding/paracentesis compared to the 10 mm stent group (Figure 3). Compared with the 10 mm stent group, the HR of rebleeding/paracentesis in the 8 mm stent group was between 1.21 and 3.10, with only Riggio et al. [13] showing a statistically significant difference in favor of the 10 mm group.

I^2 of the HR for OS was above 50% between studies, so the HR was reported with both fixed and random effects models, and the latter was preferred as the final impression. The pooled HR of OS between the 8 mm and 10 mm stent groups in the included five studies was 0.98 (95% CI: 0.76~1.26, p value: 0.859) with the fixed effects model and

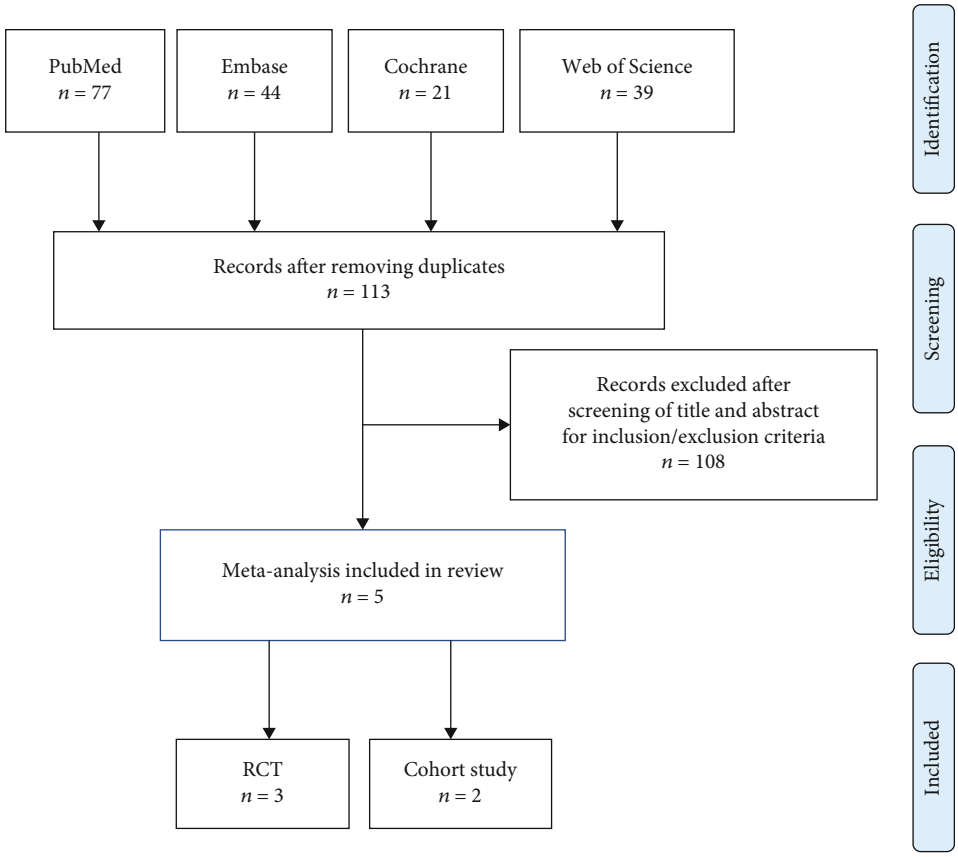

Figure 1: Flow diagram of the meta-analysis study selection process.

Table 1: Study characteristics.

Reference	Year	Study design	Sample size (8 mm/10 mm)	Stent type (PTFE-covered)	Mean follow-up time in months (8 mm/10 mm)	Bias risk evaluation**
Riggio et al. [13]	2010	Randomized control trial	22/23	VIATORR, Gore	12/15.7	Some concerns
Miraglia et al. [15]	2017	Retrospective cohort study	111/60	VIATORR, Gore	71.7/74.8	Moderate risk
Wang et al. [16]	2017	Randomized control trial	64/63	FLUENCY, Bard	26.9*	Low risk
Trebicka et al. [20]	2019	Retrospective cohort study#	41/41	VIATORR, Gore	NA	Serious risk
Luo et al. [21]	2019	Retrospective cohort study	32/32	FLUENCY, Bard	38.7/22.5	Moderate risk

#Subgroup cohort data within a randomized controlled trial. *Reported with overall follow-up time. **RCTs were evaluated with RoB 2.0; cohort studies were evaluated with ROBINS-I.

0.81 (95% CI: 0.49~1.34, p value: 0.411) with the random effects model. There was no statistically significant difference in the risk of death between the 8 mm and 10 mm stent groups (Figure 4). The HR of the 5 studies was between 0.44 and 1.51 with only Trebicka et al. [20] showing a statistically significant difference in survival (HR: 0.44, p value: 0.025) in favor of the 8 mm stent group.

Of the 5 studies included in the meta-analysis, Riggio et al. [13] and Trebicka et al. [20] included both variceal bleeding and refractory ascites, Wang et al. [16] and Luo et al. [21] included only variceal bleeding, and Miraglia et al. [15] focused only on refractory ascites patients. The outcome information corresponding specifically to bleeding or refractory ascites patients is limited. Given this, subgroup analysis was conducted within studies recruiting either variceal bleeding or refractory ascites patients [15, 16, 21]. Results demonstrated that the pooled risk of HE was statistically lower (HR: 0.62, CI: 0.45-0.85) in the 8 mm stent group compared with the 10 mm stent group in the three studies. In the variceal bleeding subgroup, the pooled risk of HE was

Table 2: Patient characteristics.

Reference	Treatment group	Age (years)	Gender (male/female)	Etiology (viral/nonviral)	History of HE (yes/no)	Ascites (yes/no)	Child-Pugh class (A/B/C)	PSG baseline (mmHg)	Post-TIPS PSG (mmHg)	TIPS indication (bleeding/RA)
Riggio et al. [13]	8 mm	53.1 ± 11.3	15/7	13/9[#]	6/16	15/7	5/10/7	21.3 ± 4.9	8.9 ± 2.7*	12/10
	10 mm	57.1 ± 9.9	13/10	14/9[#]	3/20	18/5	5/15/3	22.1 ± 7.1	6.5 ± 2.7*	9/14
Miraglia et al. [15]	8 mm	58.6 ± 10.6	76/35	63/51	36/75	111/0	0/71/40	16.1 ± 3.7	7.5 ± 2.6	0/111
	10 mm	59.0 ± 10.0	36/24	40/20	20/40	60/0	0/35/25	17.0 ± 4.2	6.5 ± 3.4	0/60
Wang et al. [16]	8 mm	49.4 ± 11.0*	41/23	54/10	NA	32/32	36/25/3	26.2 ± 4.3	8.2 ± 3.0	64/0
	10 mm	52.0 ± 9.7*	37/26	47/16	NA	35/28	35/25/3	24.9 ± 4.3	7.4 ± 3.0	63/0
Trebicka et al. [20]	8 mm	56 (33~81)**	29/12	25/16	11/30	19/22*	19/18/4*	NA	NA	29/12*
	10 mm	56 (41~71)**	29/12	31/10	14/27	35/6*	3/27/11*	NA	NA	6/35*
Luo et al. [21]	8 mm	52 ± 12	20/12	25/7	0/32	21/11	10/18/4	23.9 ± 6.3	9.2 ± 3.5	32/0
	10 mm	51 ± 11	20/12	23/9	0/32	21/11	12/16/4	24.6 ± 7.3	7.4 ± 3.7	32/0

[#]Reported as alcoholic/nonalcoholic. *Variables of 8 mm vs. 10 mm groups with significant difference. **Expressed as median (range).

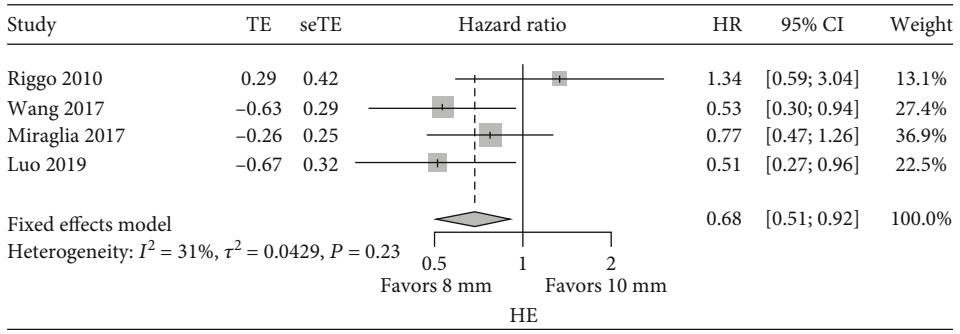

Figure 2: Meta-analysis of HR of HE: 8 mm vs. 10 mm.

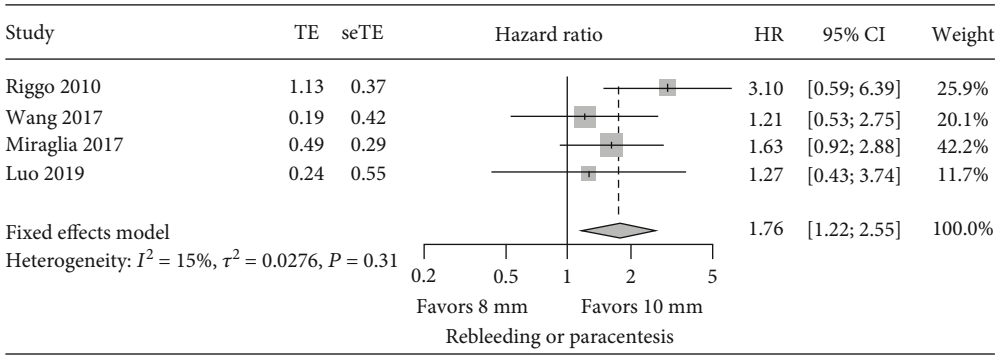

Figure 3: Meta-analysis of HR of rebleeding or paracentesis: 8 mm vs. 10 mm stent TIPS.

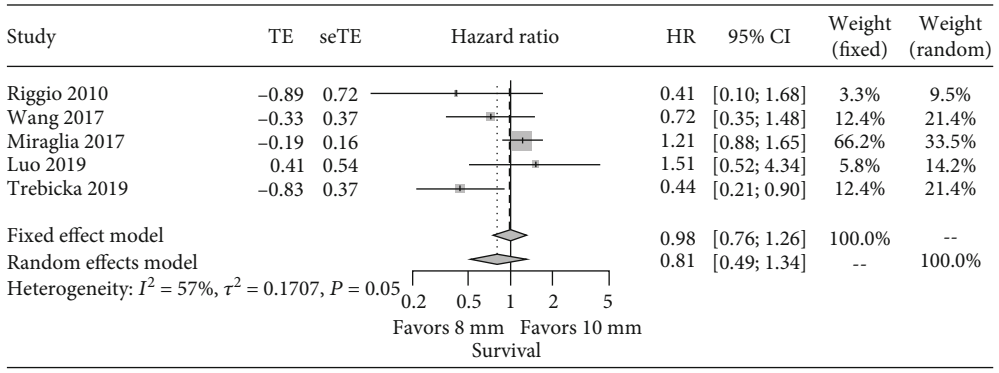

Figure 4: Meta-analysis of HR of survival: 8 mm vs. 10 mm.

also statistically lower (HR: 0.52, CI: 0.34-0.80) in the 8 mm stent group compared with the 10 mm stent group. There was only one study with refractory ascites [15]. It did not demonstrate a significant difference of risk of HE between 8 mm and 10 mm stent use (Figure 5). The pooled risk of both rebleeding/paracentesis and survival was not statistically significant between the 8 mm stent and 10 mm stent groups in the subgroup analysis (Figures 6 and 7). The risk of the need for paracentesis with the 8 mm stent group compared to the 10 mm stent group in Miraglia et al. [15] demonstrated marginal significance (HR: 1.63, CI: 0.92-2.88).

4. Discussion

The primary result of this meta-analysis shows that the incidence of post-TIPS HE is significantly lower in patients with 8 mm versus 10 mm stents. The 8 mm stent group had a 32% decreased risk of HE compared to the 10 mm stent group. This was in concordance with both Wang et al. and Luo et al. [16, 21], which had statistically significant lower incidences of HE in 8 mm stents, with a HR of 0.53 and 0.51, respectively [16, 21]. Early studies suggested that a stent diameter greater than 12 mm resulted in excessive risk of

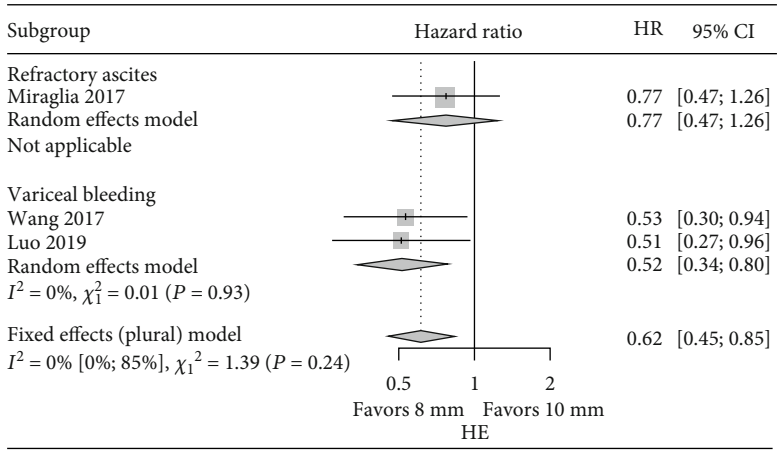

Figure 5: Subgroup meta-analysis of HR of HE in variceal bleeding and refractory ascites: 8 mm vs. 10 mm.

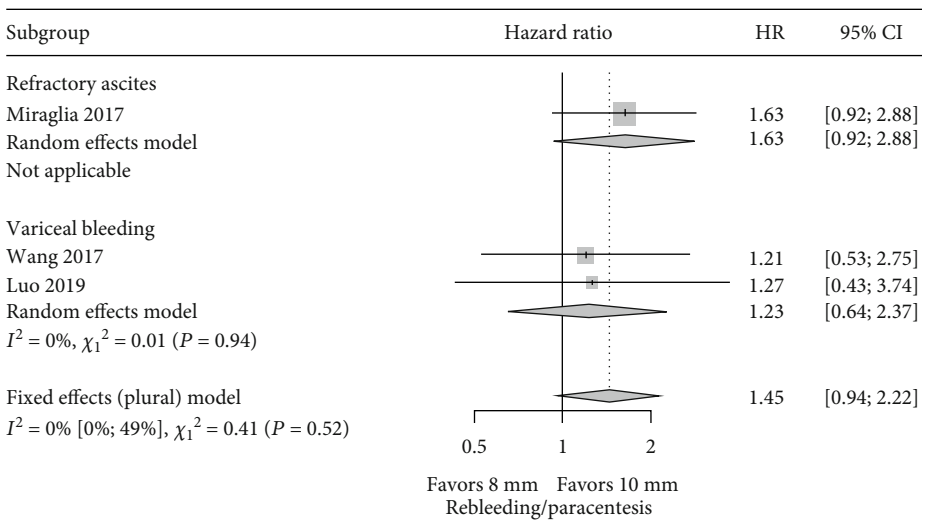

Figure 6: Subgroup meta-analysis of HR of rebleeding or paracentesis in variceal bleeding and refractory ascites groups: 8 mm vs. 10 mm. #The HR of paracentesis was reported in the refractory ascites group. The HR of rebleeding was compared in the subgroup of variceal bleeding.

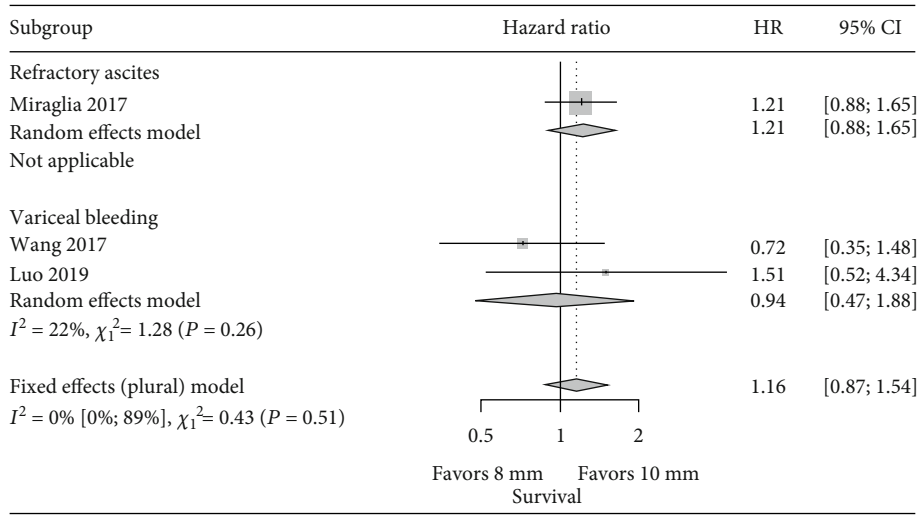

Figure 7: Subgroup meta-analysis of HR of survival in variceal bleeding and refractory ascites groups.

HE, without additional portal decompression benefits. Further studies established the superiority of 10 mm to 12 mm stents for TIPS procedures in various clinical outcomes, including HE [22]. Meanwhile, a relationship between a smaller shunt diameter and lower incidence of HE has been documented with surgical shunts [23]. In subgroup analysis, the risk of HE in 8 mm stents compared to 10 mm stents remained significant in the variceal bleeding subgroup. Miraglia et al. [15] focused on refractory ascites and did not show a statistical difference between 8 mm and 10 mm stents. To date, there is no definitive statement on the overall superiority of 8 mm versus 10 mm shunts. The challenge in identifying the optimal diameter relates to individual patient characteristics, including the need to balance the necessity of absolute portal pressure reduction against HE risk. What we can report from our present analysis is the superiority of 8 mm stents to 10 mm stents in decreasing post-TIPS HE in portal hypertension-related complications.

Post-TIPS PSG is a critical determinant for the occurrence of HE [24]. In this study, the post-TIPS PSG as well as the extent of decreasing pre-TIPS PSG was comparable between each group in all the recruited studies except for Miraglia et al. [15]. In that study, the post-TIPS PSG was 7.5 ± 2.6 in the 8 mm group vs. 6.5 ± 3.4 mmHg in the 10 mm group ($p = 0.039$). The decrease in PSG was 8.7 mm $\pm$ 3.5 mmHg in the 8 mm group vs. 10.4 ± 4.2 mmHg in the 10 mm group ($p = 0.004$). Like most of the recruited studies, previous studies comparing 12 mm and 10 mm stents have not shown a difference in post-TIPS PSG between the two groups [22]. This may be because the subtle decreases in the diameter may not cause remarkable differences in pressure gradient between the portal and hepatic veins. In other words, the pressure gradient might not linearly decrease with an increased shunt diameter after a certain threshold, and the TIPS has reached its maximum effect of decreasing portal pressure. Further increasing the stent diameter may not enhance this effect.

With comparable pressure gradients, a 10 mm stent will receive more portal flow compared to an 8 mm stent, and more unfiltered portal blood will flow directly into the systemic circulation, resulting in an increased risk of HE. In fact, despite the quality of life detriment reported in patients with HE [25], it has been reported as inversely associated with chance of survival [26]. The use of the 8 mm stent in the present analysis leads to decreased incidence of HE. A recent single-arm study [27] of a new controlled expansion stent revealed that most of patients (92%) reached the PSG target (<12 mmHg) with the diameter of 8 mm. With the emerging application of new controlled expansion stents, the choice between 8 mm and 10 mm diameters may be more flexible during TIPS procedures [27, 28] and chosen on a case-by-case basis. However, an 8 mm shunt can be considered when the aim of a PSG of 12 mmHg or a 20% reduction in PSG [29, 30] is satisfactory for clinical indications.

Our study demonstrated a significant difference in risk of rebleeding/paracentesis between the two groups. The 8 mm stent group had a higher risk of rebleeding or the need for subsequent paracentesis. Riggio et al. [13] reported a higher rebleeding rate in patients from the 8 mm stent group, which had a higher post-TIPS PSG than the 10 mm stent patients at the onset of the rebleeding event. Interestingly, the other three studies also reported a trend to higher risk of rebleeding or refractory ascites in the 8 mm stent group with a HR of 1.21-1.63, although without statistical significance. The post-TIPS PSG were similar between both groups, and both were below the recommended threshold of 12 mmHg in the three studies. In Riggio et al. [13], most cases with recurrence and/or persistence of portal hypertension in the 8 mm stent group did not have obvious stenoses on venography, but with an obvious elevated PSG (17.5 ± 5.4 mmHg) compared to immediate TIPS placement. Although the information of PSG was not mentioned in the 10 mm stent group, all cases with recurrence and/or persistence of portal hypertension were shown to have restenosis. The higher rebleeding rate or need for paracentesis of the combined studies in the 8 mm group might not be related directly to the immediate post-TIPS PSG but may represent failure of long-term persistence of decreased portal pressure.

The RCT conducted by Wang et al. [16] demonstrated that TIPS with 8 mm covered stents did not compromise shunt patency compared with 10 mm stents in patients with variceal bleeding. Accordingly, in our subgroup analysis of variceal bleeding indication, the pooled risk of rebleeding did not show a significant difference between 8 mm and 10 mm stents. Miraglia et al., focusing on refractory ascites, did reveal a marginal significance of increased risk of paracentesis requirements in the 8 mm stent group compared with the 10 mm stent group. This suggests that an 8 mm stent does not compromise shunt patency in patients with variceal bleeding but may not be satisfactory for patients with refractory ascites. In fact, the clinical requirements of appropriate post-TIPS PSG may be different between recurrent variceal bleeding and refractory ascites [31, 32] indications, which in turn might have different optimal stent diameters. Although the selection of patients might explain the reason for increased rebleeding or RA incidence in the 8 mm group, it is not definitive.

All-cause mortality is a tangible and clinically relevant outcome. Although different endpoints were reported in the studies, we preferred to combine the time-to-event information between them. The combined HR of OS between the 8 mm stent and 10 mm stent groups was 0.81 and did not reach statistical significance. The heterogeneity of HR for OS within the recruited studies is high. This may be the result of wide confidence intervals in each study, indicating that the pooled result of HR is associated with high uncertainty.

We acknowledge some study limitations. The first is the small sample sizes (5 studies). This might weaken the statistical power of the meta-analysis. Secondly, all three retrospective observational studies have conducted propensity score matching (PSM), by which most of the known baseline characteristics in the studies were matched between groups and balanced. But unlike RCT, it may not eliminate the potential bias that arises from any unknown confounders. Due to their study designs, the risk of bias remains moderate to severe in the three studies. A third limitation is the subgroup analysis, which was conducted with only 3 studies recruiting either variceal bleeding or refractory ascites due

to specific outcome information inaccessibility. This weakens the persuasive power of the results. Fourth, all the retrieved studies used covered stents, which limits the generalizability of the conclusion. Although bare stents are used much less for TIPS in the era of covered stents, this should be noted because the difference between covered and bare stents is popularly regarded as significant [33]. Lastly, post-TIPS HE is often associated with multiple factors including age, prior HE, and liver function [34]. The shunt diameter should only be included into consideration amongst other important factors that influence the post-TIPS HE.

In conclusion, this meta-analysis demonstrated that 8 mm stents during TIPS placement are associated with a significantly lower risk of HE, but a higher risk of rebleeding and/or uncontrolled refractory ascites when compared to 10 mm stents. The OS between 8 mm and 10 mm stent patients is similar. Based on the limited information in the present analysis, we deduce conservatively that the indication of TIPS may indicate specific selection of the shunt diameter, with variceal bleeding being prone to 8 mm stent placement and refractory ascites to 10 mm stent placement. Furthermore, well-designed clinical trials with subgroup TIPS indications should be encouraged to further reveal the optimal choice of 8 mm or 10 mm stents in clinical practice.

Conflicts of Interest

All authors of the study declared no potential sources of conflict of interest.

Acknowledgments

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Research Article

Correlation of Serum Cardiac Markers with Acute Decompensating Events in Liver Cirrhosis

Miaomiao Li,[1,2] Zeqi Guo,[1] Dan Zhang,[3] Xiangbo Xu,[1,4] Fernando Gomes Romeiro,[5] Andrea Mancuso,[6] Jingqiao Zhang,[1,4] Ruirui Feng,[1] Xinmiao Zhou,[1] Cen Hong,[1] and Xingshun Qi[1]

[1]*Liver Cirrhosis Group, Department of Gastroenterology, General Hospital of Northern Theater Command (Formerly General Hospital of Shenyang Military Area), Shenyang, China*
[2]*Department of Clinical Laboratory, The First Hospital of Lanzhou University, Lanzhou, China*
[3]*Department of General Surgery, General Hospital of Northern Theater Command (Formerly General Hospital of Shenyang Military Area), Shenyang, China*
[4]*Department of Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang, China*
[5]*Faculdade de Medicina de Botucatu UNESP, Campus de Botucatu, S/N, Botucatu, SP, Brazil*
[6]*Department of Internal Medicine, ARNAS Civico, Palermo, Italy*

Correspondence should be addressed to Xingshun Qi; xingshunqi@126.com

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Background and Aim. Liver cirrhosis is often accompanied by insidious cardiac dysfunction. This retrospective cross-sectional study is aimed at exploring the correlation between serum cardiac markers and decompensating events in liver cirrhosis. *Methods*. Cirrhotic patients who were consecutively hospitalized between January 2016 and March 2019 were screened. Serum cardiac biomarkers at admission, including N-Terminal pro-B-type natriuretic peptide (NT-pro BNP), high-sensitivity cardiac troponin T (hs-cTnT), creatine kinase (CK), creatine kinase MB (CK-MB), and lactate dehydrogenase (LDH), were collected. Acute decompensating events at admission, primarily including ascites, acute gastrointestinal hemorrhage, and acute-on-chronic liver failure (ACLF), were recorded. *Results*. The NT-pro BNP level was significantly higher in cirrhotic patients with acute decompensating events than in those without any decompensating events (median: 140.75 pg/mL versus 41.86 pg/mL, $P < 0.001$). The NT-pro BNP level significantly correlated with ascites, acute gastrointestinal hemorrhage, and ACLF. The hs-cTnT level was significantly higher in cirrhotic patients with acute decompensating events than in those without decompensating events (median: 0.008 ng/mL versus 0.006 ng/mL, $P = 0.007$). The hs-cTnT level significantly correlated with acute gastrointestinal hemorrhage, but not ascites or ACLF. LDH (185.0 U/L versus 173.5 U/L, $P = 0.281$), CK (71 U/L versus 84 U/L, $P = 0.157$), and CK-MB (29.5 U/L versus 33.0 U/L, $P = 0.604$) levels were not significantly different between cirrhotic patients with and without acute decompensating events. *Conclusion*. The elevated NT-pro BNP level seems to be closely related to the development of acute decompensating events in liver cirrhosis.

1. Introduction

Liver cirrhosis is a state of systemic hyperdynamic circulation characterized by increased cardiac output and decreased peripheral resistance, especially in the presence of decompensating events [1]. This disease activates the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), which further increases the myocardial tension and ultimately results in chronic cardiac dysfunction [2–4]. Consequently, the levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and troponin I (TnI) are increased [5]. Such chronic cardiac dysfunction in liver cirrhosis presenting with systolic dysfunction, diastolic dysfunction, and electrophysiological changes is known as "cirrhotic cardiomyopathy" [4]. An interaction between liver cirrhosis and cardiac dysfunction suggests that serum cardiac

markers may be valuable in evaluating the disease state of liver cirrhosis.

BNP and N-Terminal pro-B-type natriuretic peptide (NT-pro BNP) are secreted in response to increased myocardial stress [6–8]. The NT-pro BNP level is significantly increased in liver cirrhosis, which may be related to cardiac dysfunction [9–11]. Also, the NT-pro BNP level significantly correlates with the severity of liver dysfunction and prognosis of cirrhotic patients [7, 12]. On the other hand, high-sensitivity cardiac troponin T (hs-cTnT), another highly specific and sensitive marker of myocardial injury, is also significantly increased in patients with liver cirrhosis. Thus, NT-pro BNP as well as hs-cTnT may be valuable for prognostic assessment of liver cirrhosis [12]. However, their correlation with acute decompensating events in liver cirrhosis has never been explored yet. Additionally, the clinical significance of other biomarkers of cardiac injury, such as creatine kinase (CK), creatine kinase MB (CK-MB), and lactate dehydrogenase (LDH), in liver cirrhosis remains unclear.

Therefore, this study is aimed at exploring the relationship between these cardiac markers and decompensating events in cirrhosis.

2. Methods

2.1. Patients. We have prospectively collected the demographic, clinical, and laboratory data of cirrhotic patients who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area) and treated by an attending physician (XQ) since January 1, 2016. Until March 31, 2019, there were a total of 761 admissions. We retrospectively screened the patients who had undergone the evaluation of laboratory data regarding serum cardiac markers during the hospitalizations. Exclusion criteria were as follows: (1) confirmed or suspected diagnosis of malignancy, (2) severe renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2), (3) cardiac diseases (i.e., heart failure, coronary atherosclerotic heart disease, and atrial fibrillation), (4) ischemic stroke, and (5) absence of data regarding serum cardiac markers detected during the hospitalizations. Repeated admissions of the same patient were not deliberately excluded, because this study focused on the in-hospital outcome and decompensating events during the hospitalizations, but not on long-term follow-up outcomes. If a patient had multiple measurements of serum cardiac markers during the same hospitalization, we selected the data obtained at the first time of blood collection. The study protocol was approved by the Medical Ethics Committee of our hospital. We primarily collected demographic data, etiology of liver cirrhosis, decompensating events at admissions, and laboratory tests including serum cardiac markers.

2.2. Definitions and Diagnosis. Acute gastrointestinal hemorrhage was defined as previously described [13, 14]. The Child-Pugh score was calculated [15]. Model for end-stage liver disease (MELD) and MELD with sodium (MELD-Na) scores were calculated according to an equation updated by the OPTN/UNOS (American Organ Acquisition and Transplantation Network/Organ Resource Sharing Network) in 2016 [16], as follows:

$$\begin{aligned} MELD\,(i) &= 9.57 \times \ln\ (\text{creatinine mg/dL}) + 3.78 \\ &\quad \times \ln\ (\text{bilirubin mg/dL}) + 11.2 \\ &\quad \times \ln\ (\text{INR}) + 6.43, \end{aligned}$$

$$\begin{aligned} MELD\text{-}Na &= MELD\,(i) + 1.32 \times (137\text{-}Na) \\ &\quad - [0.033 \times MELD\,(i) \times (137\text{-}Na). \end{aligned} \tag{1}$$

If $Na^+ < 125$ mmol/L, it is set to 125; if $Na^+ > 137$, it is set to 137.

The grade of ascites was defined according to the consensus of the International Ascites Club [17]. Patients with acute-on-chronic liver failure (ACLF) were identified by the recommendations of the Asian Pacific Association for the Study of the Liver (APASL) consensus [18, 19]. Severe renal insufficiency was defined as eGFR < 30 mL/min/1.73 m^2 [20]. The eGFR was calculated using the simplified equation [21], as follows:

$$\begin{aligned} &e\text{GFR}\left(\text{mL/min per } 1.73\ m^2\right) \\ &\quad = 186.3 \times \text{serum creatinine} \\ &\qquad \text{concentration (mg/dL)}\,(\exp\ [-1.154]) \\ &\qquad \times age\,(\exp\ [-0.203]) \times (0.742 \text{ if } female) \\ &\qquad \times (1.212 \text{ if } black). \end{aligned} \tag{2}$$

2.3. Groups. We divided cirrhotic patients into 5 groups: (1) cirrhotic patients without acute decompensating events, (2) cirrhotic patients with acute decompensating events, (3) cirrhotic patients with ascites, (4) cirrhotic patients with acute gastrointestinal hemorrhage, and (5) cirrhotic patients with ACLF.

2.4. Measurement of Serum Cardiac Markers. All serum cardiac markers were measured at the Department of Laboratory of our hospital. They included NT-pro BNP detected by enzyme-linked immunosorbent assay (ELISA) (double antibody sandwich method) with a normal range of 0-125 pg/mL, hs-cTnT by ELISA (double antibody sandwich method) with a normal range of 0-0.05 ng/mL, CK by coupled-enzyme assay with a normal range of 38-174 U/L, CK-MB by immune inhibition assay with a normal range of 0-24 U/L, LDH by the spectrophotometric method with a normal range of 109-245 U/L, and hs-CRP by latex immune turbidimetry with a normal range of 0-3 mg/L. Only the data obtained at the first time of measurement were selected, thus avoiding the influence of drugs used during hospitalization.

2.5. Statistical Analyses. Continuous data were expressed as mean ± standard deviation and median (quartiles) and were compared by using the Wilcoxon rank-sum test. Categorical data were expressed as frequency (percentage) and were compared by using the chi-square test. Considering that age and gender are important factors influencing serum NT-

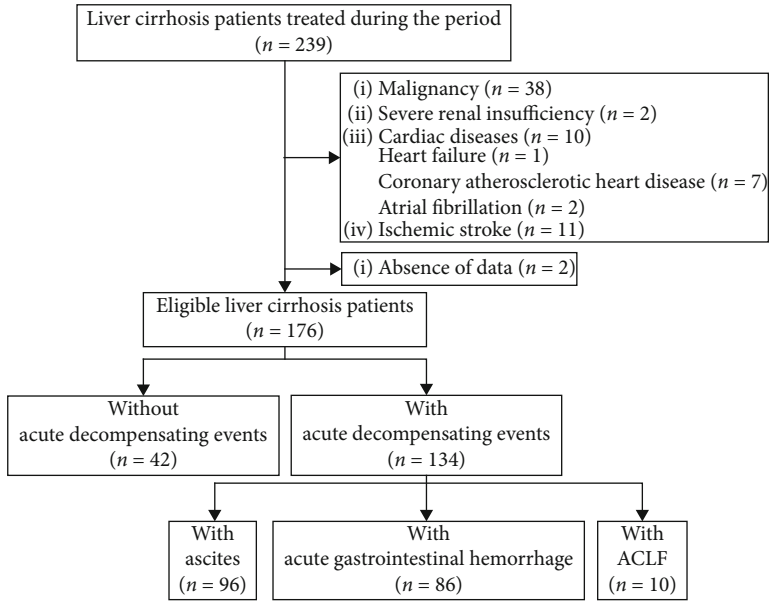


Figure 1: A flow chart of patient selection.

pro BNP and hs-cTnT levels [22–26], partial correlation analysis was adjusted for age and gender to analyze the correlation of serum NT-pro BNP and hs-cTnT with liver disease conditions. Pearson or Spearman tests were performed to analyze the correlation between disease conditions and other serological cardiac markers, such as CK, CK-MB, and LDH. Multivariate linear regression analysis was performed to analyze the correlation of serological cardiac markers with categorical variables. A two-sided $P < 0.05$ was considered to be statistically significant. SPSS statistics software version R23.0.0.0 was employed to perform all statistical analyses.

3. Results

3.1. Patients. Overall, 176 patients with liver cirrhosis were included (Figure 1), of whom 42 (23.86%) did not have any decompensating events but conducted regular follow-up and/or prophylactic endoscopic variceal treatment and 134 (76.14%) had acute decompensating events, including ascites ($n = 96$, 71.64%), acute gastrointestinal hemorrhage ($n = 86$, 64.18%), and ACLF ($n = 10$, 7.46%).

3.2. Comparison between Cirrhotic Patients with and without Decompensating Events. Cirrhotic patients with decompensating events had significantly higher levels of NT-pro BNP ($P < 0.001$) and hs-cTnT ($P = 0.007$) than those without decompensating events (Figure 2), but the differences in the levels of CK, CK-MB, and LDH were not significant between them (Table 1).

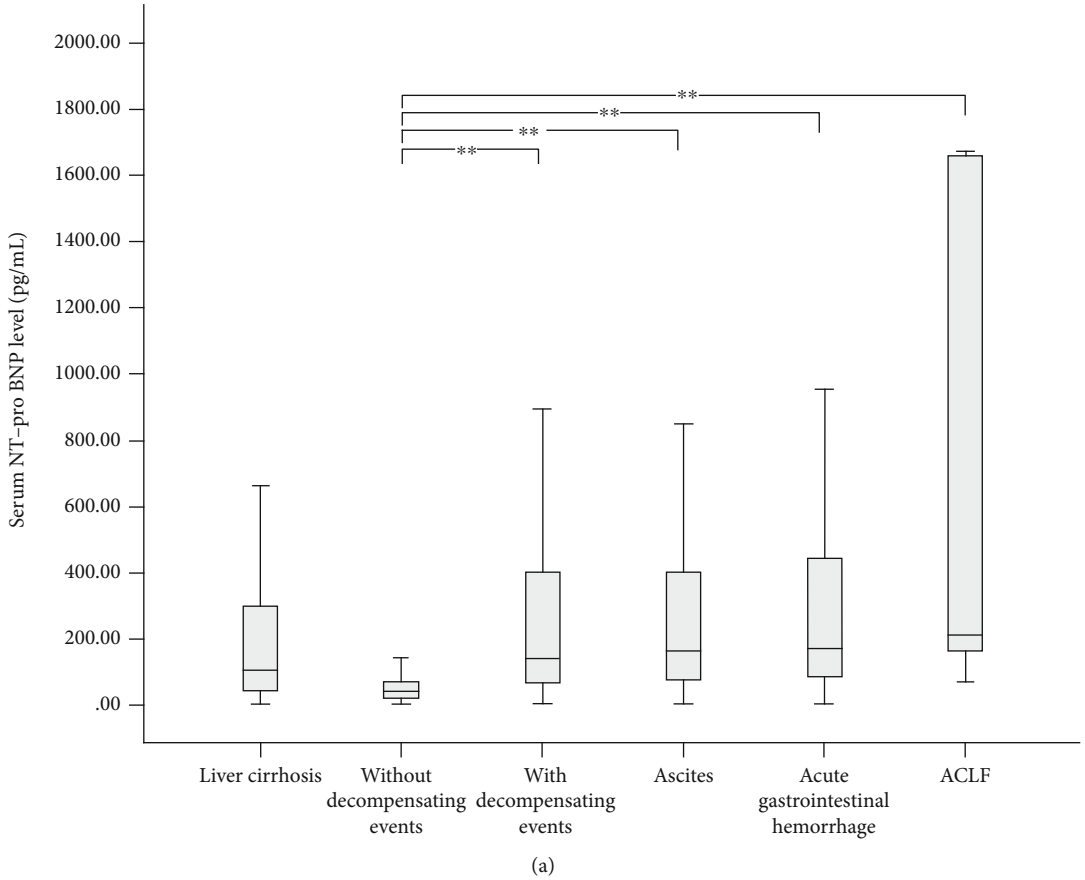
Cirrhotic patients with ascites had significantly higher levels of NT-pro BNP ($P < 0.001$) and hs-cTnT ($P = 0.002$) than those without decompensating events (Figure 2), but the differences in the levels of CK, CK-MB, and LDH were not significant between them (Table 2).

Cirrhotic patients with acute gastrointestinal hemorrhage had significantly higher levels of NT-pro BNP ($P < 0.001$) and hs-cTnT ($P = 0.003$) than those without decompensating events (Figure 2), but the differences in the levels of CK, CK-MB, and LDH were not significant between them (Table 2).

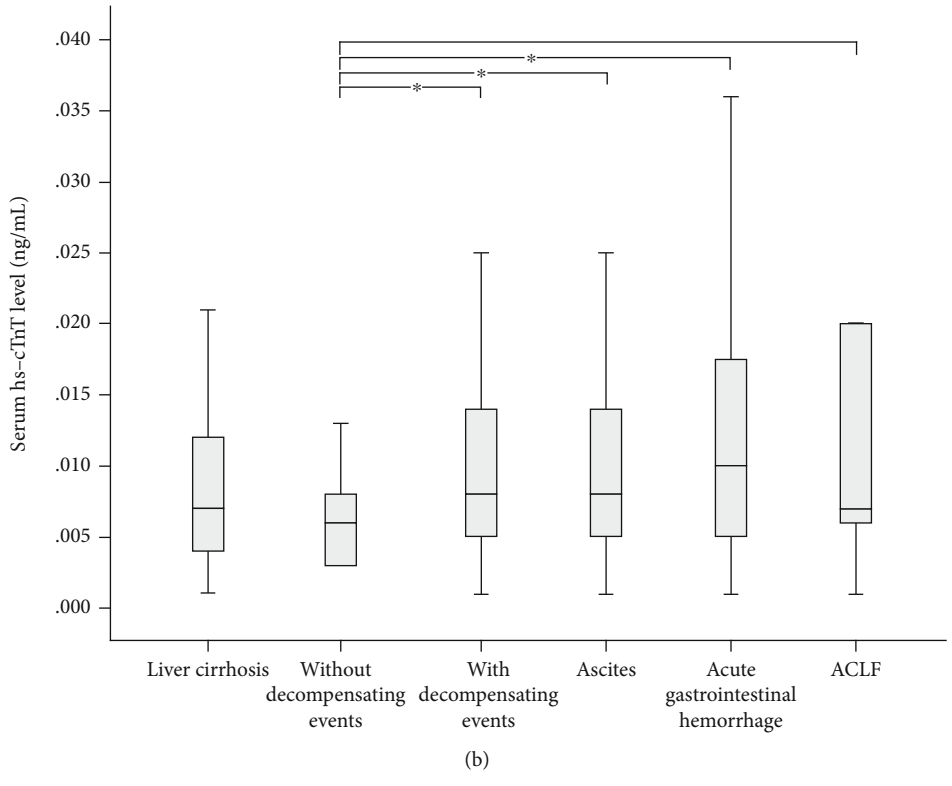
Cirrhotic patients with ACLF had a significantly higher level of NT-pro BNP ($P < 0.001$) than those without decompensating events (Figure 2), but the differences in the levels of CK, CK-MB, and LDH were not significant between them (Table 2).

3.3. Correlation of Serum Cardiac Markers with Child-Pugh and MELD Scores in Patients with Liver Cirrhosis. Partial correlation analyses demonstrated that the NT-pro BNP level significantly correlated with Child-Pugh and MELD scores. These correlations were observed in all the cirrhotic patients and in those with decompensating events, but not in those without decompensating events (Table 3). Partial correlation analyses demonstrated that the hs-cTnT level had no significant correlation with Child-Pugh and MELD scores in cirrhotic patients regardless of the presence of decompensating events (Supplementary Table 1). Correlation analyses demonstrated that CK (Supplementary Table 2) and CK-MB (Supplementary Table 3) levels did not significantly correlate with Child-Pugh and MELD scores in cirrhotic patients. On the other hand, the LDH level significantly correlated with Child-Pugh and MELD scores in cirrhotic patients (Supplementary Table 4).

3.4. Correlation between Serum Cardiac Markers and Decompensating Events in Cirrhotic Patients. Age- or gender-adjusted multivariate linear regression analyses demonstrated that the NT-pro BNP level significantly correlated with overall acute decompensating events, ascites, acute gastrointestinal hemorrhage, and ACLF (Table 4); the hs-cTnT level significantly correlated with overall acute decompensating events and acute gastrointestinal hemorrhage, but not ascites or ACLF (Supplementary Table 5); CK and

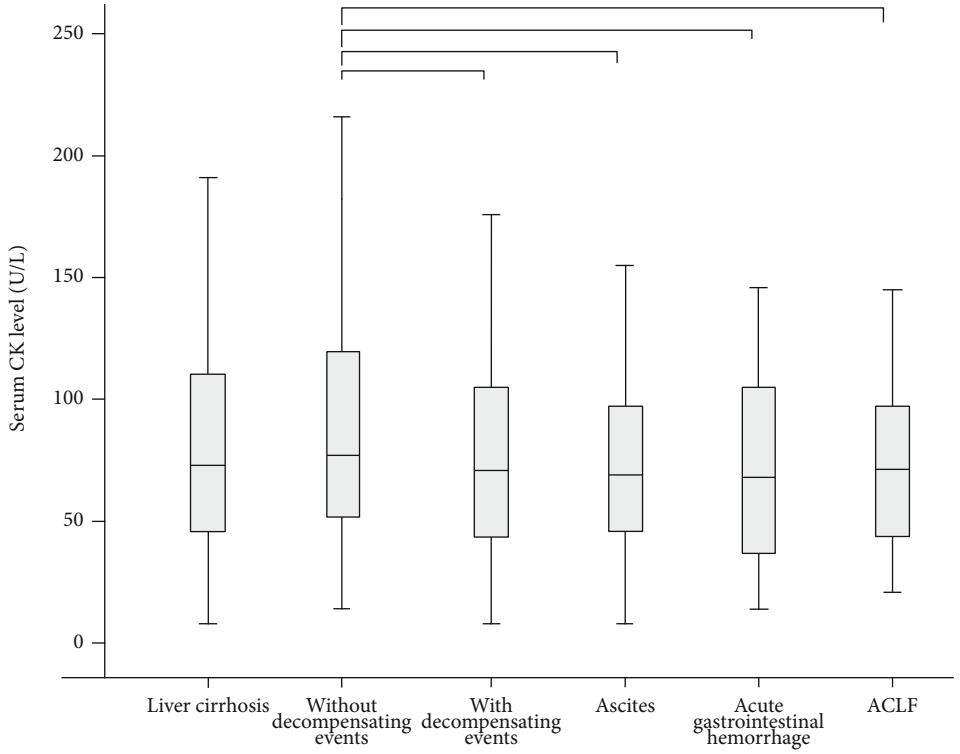


(a)



(b)

Figure 2: Continued.



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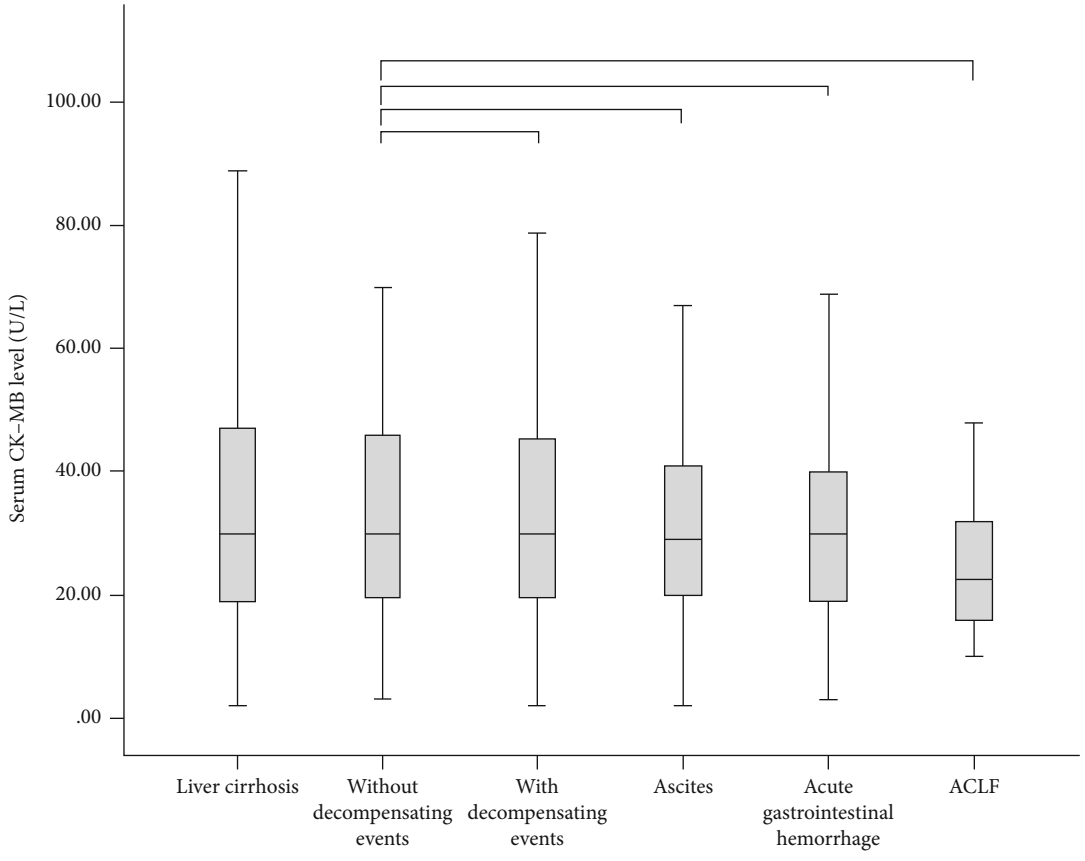

(d)

Figure 2: Continued.

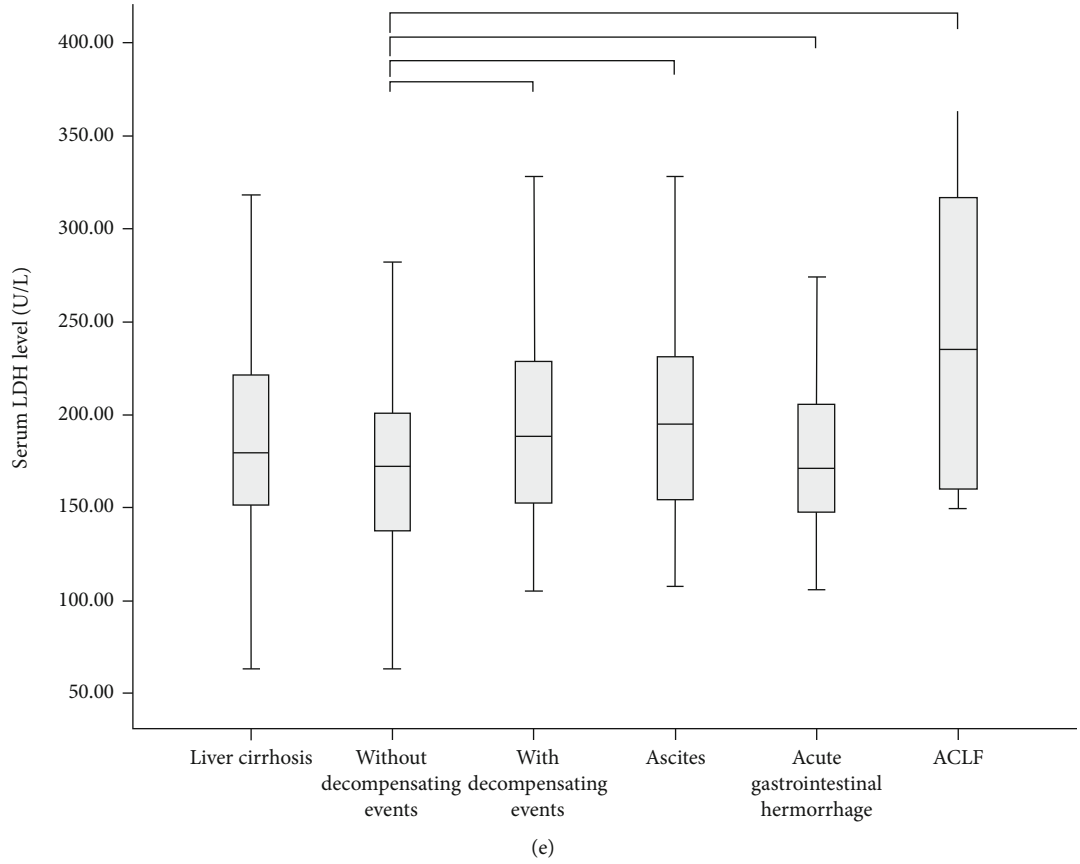

Figure 2: Box plots showing the concentrations of serum NT-pro BNP (a), hs-cTnT (b), CK (c), CK-MB (d), and LDH (e) in general cirrhotic patients, cirrhotic patients with and without decompensating events, cirrhotic patients with ascites, cirrhotic patients with acute gastrointestinal hemorrhage, and cirrhotic patients with ACLF. Notes: $^{**}P < 0.001$ and $^{*}P < 0.05$.

CK-MB levels did not significantly correlate with overall acute decompensating events, ascites, acute gastrointestinal hemorrhage, or ACLF; the LDH level significantly correlated with ascites, acute gastrointestinal hemorrhage, and ACLF, but not overall acute decompensating events (Supplementary Table 6).

4. Discussion

In this retrospective observational study, we rigorously screened the participants by excluding the confounding factors, which makes our statistical results more reliable. Additionally, we included a relatively large number of cirrhotic patients, which makes our conclusions more representative. The major findings are as follows: (i) the NT-pro BNP level was significantly higher in decompensated cirrhosis. (ii) The NT-pro BNP level also significantly correlated with Child-Pugh and MELD scores in cirrhosis with acute decompensation, but not in those without decompensation. (iii) The hs-cTnT level was elevated in cirrhosis with acute decompensation but was unrelated to the liver disease severity. (iv) The LDH level significantly correlated with Child-Pugh and MELD scores in cirrhosis, but was unrelated to decompensating events. (v) CK and CK-MB levels were neither significantly increased in cirrhosis with decompensation nor correlated with Child-Pugh and MELD scores.

4.1. NT-pro BNP. NT-pro BNP, a prohormone of BNP, is secreted into the systemic circulation by cardiac ventricles in response to myocardial hypertrophy and is involved in the regulation of cardiac volume homeostasis [27–29]. Thus, the NT-pro BNP level is often considered as an effective and useful marker for screening of early stages of cardiac dysfunction [30]. As we know, cirrhotic cardiomyopathy is a chronic cardiac systolic and diastolic dysfunction in cirrhotic patients in the absence of prior heart disease [31, 32]. There is no obvious abnormal change of cardiac function in the resting state; besides, a decreased afterload in cirrhosis often results in normal or even increased left ventricular ejection fraction [31]. Thus, noninvasive cardiac biomarkers are potentially useful to reflect the slight change of pressure state of end-diastolic wall stress and intracardiac filling pressures.

The serum NT-pro BNP level is significantly higher in patients with liver cirrhosis [7, 9, 10, 12, 33], probably because it is often associated with hyperdynamic circulation, such as increased heart rate and cardiac output, thereby impairing cardiac contractility [34–36]. Our study for the first time found that the serum NT-pro BNP level was significantly higher in cirrhotic patients who suffer an acute decompensation, such as ascites, gastrointestinal hemorrhage, and ACLF, when the values were compared to those without decompensation. Interestingly, we also found that the NT-pro BNP level significantly correlated with Child-

Table 1: Comparison of characteristics of cirrhotic patients without and with decompensating events.

Variables	Without decompensation		With decompensation		P value
	No. Pts	Mean ± SD; median (range) or frequency (percentage)	No. Pts	Mean ± SD; median (range) or frequency (percentage)	
Sex (male/female), *n* (%)	42	35 (83.33%)/7 (16.67%)	134	89 (66.42%)/45 (33.58%)	0.051
Age (years)	42	52.74 ± 11.03; 52.5 (46.50-62.25)	134	56.36 ± 12.16; 55.00 (47.00-65.00)	0.130
Causes of liver diseases, *n* (%)	42		134		
Hepatitis B virus alone	14	14 (33.33%)	48	48 (35.82%)	/
Hepatitis C virus alone	4	4 (9.52%)	9	9 (6.72%)	/
Alcohol alone	12	12 (28.57%)	29	29 (21.64%)	/
Hepatitis B virus+alcohol	1	1 (2.38%)	4	4 (2.99%)	/
Autoimmune	1	1 (2.38%)	16	16 (11.94%)	/
Drug	1	1 (2.38%)	6	6 (4.48%)	/
Others	1	1 (2.38%)	0	0 (0%)	/
Red blood cell (10^{12}/L)	42	3.99 ± 0.64; 4.05 (3.62-4.57)	134	3.16 ± 0.79; 3.10 (2.56-3.76)	**<0.001**
Hemoglobin (g/L)	42	117.07 ± 23.75; 123.00 (108.00-131.25)	134	93.48 ± 27.35; 91.50 (70.00-115.00)	**<0.001**
Hematocrit (%)	42	35.65 ± 6.58; 36.60 (32.88-39.63)	134	28.49 ± 7.88; 28.20 (21.90-34.73)	**<0.001**
White blood cell (10^9/L)	42	3.83 ± 1.97; 3.35 (2.45-4.65)	134	4.71 ± 3.14; 3.70 (2.60-6.03)	0.155
Platelet count (10^9/L)	42	87.67 ± 57.48; 71.00 (48.50-104.75)	134	97.04 ± 74.17; 76.00 (53.50-107.50)	0.433
Total bilirubin (μmol/L)	42	32.22 ± 34.77; 22.90 (16.15-32.45)	134	43.84 ± 60.88; 23.15 (15.15-45.13)	0.682
Direct bilirubin (μmol/L)	42	16.32 ± 24.77; 9.90 (6.25-13.75)	134	25.94 ± 45.74; 10.50 (6.08-20.73)	0.351
Alanine aminotransferase (U/L)	42	68.38 ± 216.68; 26.29 (17.86-37.58)	134	31.96 ± 30.04; 23.43 (15.80-38.64)	0.391
Aspartate aminotransferase (U/L)	42	62.81 ± 130.73; 32.73 (24.25-50.47)	134	49.40 ± 44.79; 32.71 (23.91-59.55)	0.753
Alkaline phosphatase (U/L)	42	126.48 ± 121.34; 96.34 (77.34-139.58)	134	121.54 ± 97.12; 95.93 (67.99-143.13)	0.612
Gamma-glutamyl transpeptidase (U/L)	42	120.56 ± 274.49; 49.94 (27.53-83.88)	134	91.17 ± 154.74; 41.56 (19.87-93.42)	0.429
Albumin (g/L)	42	36.69 ± 5.40; 37.35 (32.38-41.03)	134	30.87 ± 6.58; 30.80 (25.60-35.80)	**<0.001**
Blood urea nitrogen (mmol/L)	42	5.15 ± 1.75; 4.87 (3.79-6.19)	134	6.69 ± 3.49; 6.05 (4.39-7.87)	**0.007**
Creatinine (μmol/L)	42	65.47 ± 14.14; 64.68 (56.02-74.81)	134	69.58 ± 23.03; 65.20 (53.53-78.15)	0.694
eGFR (mL/min/1.73 m^2)	42	119.18 ± 30.56; 118.40 (97.75-133.97)	134	109.63 ± 36.25; 106.52 (84.22-133.52)	0.068
Na (mmol/L)	42	139.02 ± 2.52; 139.45 (137.80-140.43)	134	138.10 ± 4.67; 138.45 (136.00-141.00)	0.226
Prothrombin time (second)	42	16.22 ± 2.05; 16.05 (15.03-16.88)	134	17.48 ± 3.47; 16.70 (15.10-18.90)	**0.033**
Activated partial thromboplastin time (second)	42	42.41 ± 5.47; 41.60 (38.98-45.53)	134	41.68 ± 7.40; 40.15 (37.10-44.30)	0.149
International normalized ratio	42	1.31 ± 0.21; 1.28 (1.19-1.38)	134	1.44 ± 0.37; 1.36 (1.20-1.58)	**0.040**
D-dimer (mg/L)	41	1.19 ± 1.68; 0.60 (0.29-1.27)	131	3.07 ± 3.73; 1.81 (0.72-4.41)	**<0.001**
High-sensitivity C-reactive protein (mg/L)	41	5.39 ± 8.05; 2.20 (0.90-6.60)	133	15.25 ± 27.70; 5.70 (1.35-14.10)	**0.016**
MELD score	42	11.20 ± 3.10; 10.26 (9.04-13.06)	134	13.40 ± 5.75; 11.32 (9.22-16.56)	0.093
Child-Pugh score	42	5.90 ± 1.10; 6.00 (5.00-6.00)	134	7.82 ± 2.18; 7.00 (6.00-9.00)	**<0.001**
Child-Pugh class	42		134		

Table 1: Continued.

Variables	Without decompensation		With decompensation		*P* value
	No. Pts	Mean ± SD; median (range) or frequency (percentage)	No. Pts	Mean ± SD; median (range) or frequency (percentage)	
A, *n* (%)	33	33 (78.57%)	44	44 (32.84%)	**<0.001**
B, *n* (%)	9	9 (21.43%)	58	58 (43.28%)	**<0.001**
C, *n* (%)	0	0 (0%)	32	32 (23.88%)	**<0.001**
NT-pro BNP (pg/mL)	38	58.20 ± 56.57; 41.86 (20.36-69.16)	120	402.32 ± 1013.60; 140.75 (62.34-401.33)	**<0.001**
High-sensitivity cardiac troponin T (ng/mL)	42	0.007 ± 0.005; 0.006 (0.003-0.008)	128	0.017 ± 0.045; 0.008 (0.015-0.003)	**0.007**
Creatine kinase (U/L)	42	93.93 ± 50.81; 84.00 (53.50-123.75)	132	98.88 ± 103.56; 71.00 (44.00-105.50)	0.157
Creatine kinase MB (U/L)	42	35.90 ± 21.51; 33.00 (19.00-47.25)	132	33.62 ± 18.93; 29.5 (19.25-46.25)	0.604
Lactate dehydrogenase (U/L)	42	184.00 ± 55.87; 173.50 (137.50-211.50)	132	194.17 ± 58.30; 185.00 (152.00-226.75)	0.281

Bold font indicates statistically significant *P* values. Abbreviations: eGFR: the estimated glomerular filtration rate; MELD: model for end-stage liver disease; NT-pro BNP: N-Terminal pro-B-type natriuretic peptide.

Table 2: Comparison of characteristics of cirrhotic patients with ascites, acute gastrointestinal hemorrhage, ACLF, and without decompensating events.

Variables	With ascites			With acute gastrointestinal hemorrhage			With ACLF		
	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value
Sex (male/female), *n* (%)	96	64 (66.67%)/32 (33.33%)	0.064	86	56 (65.12%)/30 (34.88%)	**0.039**	10	8 (80%)/2 (20%)	0.558
Age (years)	96	58.17 ± 11.88; 60.00 (48.00-65.75)	**0.027**	86	53.72 ± 11.37; 54.00 (45.00-63.25)	0.692	10	53.20 ± 14.85; 48.00 (45.00-57.00)	0.429
Red blood cell (10^{12}/L)	96	3.15 ± 0.77; 3.08 (2.57-3.83)	**<0.001**	86	2.95 ± 0.76; 2.75 (2.39-3.35)	**<0.001**	10	2.59 ± 0.85; 2.60 (1.78-3.45)	**<0.001**
Hemoglobin (g/L)	96	93.27 ± 27.38; 93.00 (70.00-113.75)	**<0.001**	86	83.74 ± 25.01; 76.00 (66.00-99.00)	**<0.001**	10	92.60 ± 28.50; 98.50 (65.25-117.25)	0.018
Hematocrit (%)	96	28.41 ± 7.78; 28.40 (21.38-34.33)	**<0.001**	86	25.69 ± 7.34; 23.15 (20.33-30.20)	**<0.001**	10	27.09 ± 8.27; 28.80 (18.58-34.75)	0.004
White blood cell (10^9/L)	96	4.89 ± 3.41; 3.85 (2.73-6.18)	0.119	86	4.80 ± 3.57; 3.60 (2.38-6.30)	0.390	10	6.21 ± 3.02; 6.15 (4.43-8.25)	0.021
Platelet count (10^9/L)	96	98.94 ± 78.63; 78.00 (54.00-106.75)	0.384	86	96.03 ± 77.77; 72.50 (51.00-103.75)	0.755	10	73.60 ± 45.68; 64.50 (39.00-97.25)	0.562
Total bilirubin (μmol/L)	96	52.38 ± 69.82; 28.90 (15.38-63.15)	0.186	86	33.63 ± 47.34; 19.55 (13.20-32.20)	0.292	10	199.84 ± 121.74; 166.20 (121.25-223.50)	**<0.001**
Direct bilirubin (μmol/L)	96	32.73 ± 52.48; 13.45 (6.43-37.53)	**0.039**	86	19.02 ± 37.59; 8.45 (5.40-16.23)	0.582	10	141.24 ± 97.61; 105.10 (82.08-184.23)	**<0.001**
Alanine aminotransferase (U/L)	96	33.89 ± 33.87; 23.09 (16.25-39.37)	0.517	86	29.02 ± 26.62; 20.92 (14.62-36.63)	0.132	10	64.24 ± 61.31; 51.43 (23.77-63.76)	0.012
Aspartate aminotransferase (U/L)	96	55.35 ± 50.57; 34.56 (24.01-68.95)	0.404	86	41.78 ± 40.40; 27.45 (20.43-48.41)	0.232	10	109.25 ± 70.69; 93.55 (65.65-128.31)	**<0.001**
Alkaline phosphatase (U/L)	96	132.01 ± 106.30; 101.99 (75.12-149.67)	0.621	86	98.19 ± 61.17; 81.09 (59.99-110.37)	**0.019**	10	132.94 ± 51.66; 137.08 (84.14-169.98)	0.202
Gamma-glutamyl transpeptidase (U/L)	96	94.49 ± 133.18; 46.21 (21.10-108.21)	0.901	86	70.20 ± 144.14; 29.01 (16.74-57.98)	**0.032**	10	75.11 ± 44.44; 67.05 (37.05-97.91)	0.218
Albumin (g/L)	96	29.70 ± 6.34; 29.65 (25.10-33.40)	**<0.001**	86	31.31 ± 6.18; 31.10 (25.68-36.18)	**<0.001**	10	23.52 ± 4.40; 22.80 (19.95-26.98)	**<0.001**
Blood urea nitrogen (mmol/L)	96	6.78 ± 3.64; 6.05 (4.42-7.86)	**0.007**	86	7.18 ± 3.95; 6.25 (4.39-8.46)	**0.003**	10	8.13 ± 5.06; 6.26 (4.78-11.15)	0.070
Creatinine (μmol/L)	96	71.20 ± 25.69; 63.55 (53.23-82.68)	0.686	86	68.14 ± 22.75; 65.86 (52.78-75.94)	0.895	10	74.36 ± 28.63; 61.15 (52.53-101.95)	0.763
eGFR (mL/min/1.73 m^2)	96	108.05 ± 38.74; 104.38 (77.60-133.84)	**0.047**	86	112.93 ± 37.30; 108.07 (86.83-138.32)	0.247	10	110.64 ± 43.03; 107.84 (73.24-137.83)	0.403
Na (mmol/L)	96	137.54 ± 5.13; 137.75 (134.93-140.95)	**0.041**	86	138.66 ± 4.80; 139.35 (136.55-141.03)	0.741	10	135.05 ± 5.57; 135.20 (131.55-139.15)	0.021
Prothrombin time (second)	96	18.17 ± 3.74; 17.15 (15.60-20.45)	**0.001**	86	17.69 ± 3.55; 16.90 (15.20-19.10)	**0.026**	10	24.30 ± 4.63; 22.85 (20.65-27.95)	**<0.001**
Activated partial thromboplastin time (second)	96	43.11 ± 7.89; 41.90 (37.73-47.28)	0.987	86	41.37 ± 7.12; 39.70 (36.98-43.98)	0.064	10	52.95 ± 8.64; 52.85 (46.63-55.95)	**<0.001**
International normalized ratio	96	1.52 ± 0.40; 1.40 (1.25-1.75)	**0.001**	86	1.47 ± 0.38; 1.37 (1.21-1.60)	**0.031**	10	2.18 ± 0.53; 1.99 (1.77-2.59)	**<0.001**

Table 2: Continued.

Variables	With ascites			With acute gastrointestinal hemorrhage			With ACLF		
	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value	No. Pts	Mean ± SD; median (range) or frequency (percentage)	*P* value
D-dimer (mg/L)	95	3.53 ± 4.04; 2.28 (0.93-4.64)	**<0.001**	83	2.31 ± 2.30; 1.43 (0.58-3.57)	**0.001**	9	7.79 ± 8.54; 4.51 (3.41-9.02)	**<0.001**
High-sensitivity C-reactive protein (mg/L)	95	18.93 ± 31.44; 6.90 (2.20-20.30)	**0.001**	85	13.88 ± 26.58; 4.50 (1.20-11.55)	0.071	10	44.50 ± 36.88; 30.65 (11.35-75.35)	**<0.001**
MELD score	96	14.79 ± 6.10; 13.50 (10.07-18.23)	**0.001**	86	12.68 ± 5.29; 10.65 (9.13-14.42)	0.343	10	25.81 ± 4.68; 28.14 (21.24-30.04)	**<0.001**
Child-Pugh score	96	8.57 ± 2.04; 8.00 (7.00-10.00)	**<0.001**	86	7.29 ± 2.07; 7.00 (6.00-8.00)	**<0.001**	10	12.10 ± 1.10; 12.00 (11.75-13.00)	**<0.001**
NT-pro BNP (pg/mL)	87	458.09 ± 1167.73; 165.20 (71.06-415.80)	**<0.001**	78	459.77 ± 1208.86; 144.95 (60.82-443.93)	**<0.001**	10	1511.39 ± 3188.84; 212.30 (150.70-1662.75)	**<0.001**
High-sensitivity cardiac troponin T (ng/mL)	92	0.015 ± 0.018; 0.008 (0.005-0.014)	**0.002**	81	0.020 ± 0.055; 0.009 (0.005-0.014)	**0.003**	9	0.024 ± 0.033; 0.007 (0.005-0.035)	0.157
Creatine kinase (U/L)	95	90.65 ± 83.30; 69.00 (45.00-97.00)	0.099	84	101.63 ± 117.93; 69.00 (40.50-105.50)	0.117	10	99.30 ± 98.38; 71.50 (41.25-109.00)	0.501
Creatine kinase MB (U/L)	95	32.72 ± 18.73; 29.00 (20.00-42.00)	0.463	84	33.13 ± 18.40; 29.50 (19.00-43.75)	0.552	10	29.60 ± 24.40; 22.50 (14.50-36.00)	0.163
Lactate dehydrogenase (U/L)	95	201.85 ± 57.99; 195.00 (154.00-232.00)	0.076	84	181.51 ± 58.43; 171.00 (140.00-206.25)	0.727	10	238.30 ± 80.65; 235.00 (157.50-317.25)	0.050

Bold font indicates statistically significant *P* values. Abbreviations: ACLF: acute-on-chronic liver failure; eGFR: the estimated glomerular filtration rate; MELD: model for end-stage liver disease; NT-pro BNP: N-Terminal pro-B-type natriuretic peptide.

Table 3: Partial correlation analysis of the NT-pro BNP level in cirrhosis.

Variables	All liver cirrhosis			Liver cirrhosis without decompensation			Liver cirrhosis with decompensation		
	No. Pts	*P* value	Correlation coefficient	No. Pts	*P* value	Correlation coefficient	No. Pts	*P* value	Correlation coefficient
Age (years)	/	Controlling	/	/	Controlling	/	/	Controlling	/
Sex (male/female), *n* (%)	/	Controlling	/	/	Controlling	/	/	Controlling	/
Red blood cell (10^{12}/L)	154	**<0.001**	-0.322	34	**0.023**	-0.379	116	**0.001**	-0.313
Hemoglobin (g/L)	154	**0.004**	-0.229	34	**0.001**	-0.540	116	**0.025**	-0.207
Hematocrit (%)	154	**0.001**	-0.254	34	**0.001**	-0.523	116	**0.011**	-0.234
White blood cell (10^9/L)	154	**0.027**	0.177	34	0.093	-0.284	116	0.058	0.175
Platelet count (10^9/L)	154	0.894	-0.011	34	0.201	-0.218	116	0.842	-0.018
Total bilirubin (μmol/L)	154	**0.027**	0.178	34	0.755	-0.054	116	0.054	0.178
Direct bilirubin (μmol/L)	154	0.063	0.149	34	0.661	-0.076	116	0.113	0.146
Alanine aminotransferase (U/L)	154	0.715	-0.029	34	0.534	-0.107	116	0.609	-0.048
Aspartate aminotransferase (U/L)	154	0.694	-0.032	34	0.493	-0.118	116	0.687	-0.037
Alkaline phosphatase (U/L)	154	0.534	-0.050	34	0.071	-0.304	116	0.623	-0.046
Gamma-glutamyl transpeptidase (U/L)	154	0.983	-0.002	34	0.206	-0.216	116	0.794	0.024
Albumin (g/L)	154	**0.006**	-0.219	34	0.263	-0.192	116	**0.042**	-0.188
Blood urea nitrogen (mmol/L)	154	**0.022**	0.183	34	0.099	0.279	116	0.074	0.165
Creatinine (μmol/L)	154	0.692	-0.032	34	0.755	-0.054	116	0.547	-0.056
eGFR (mL/min/1.73 m^2)	154	0.073	0.144	34	0.823	0.039	116	0.058	0.175
Sodium (mmol/L)	154	**0.039**	-0.165	34	0.586	0.094	116	0.082	-0.161
Prothrombin time (second)	154	**<0.001**	0.416	34	0.480	0.122	116	**<0.001**	0.419
Activated partial thromboplastin time (second)	154	**0.023**	0.182	34	0.406	0.143	116	**0.030**	0.200
International normalized ratio	154	**<0.001**	0.436	34	0.380	0.151	116	**<0.001**	0.439
D-dimer (mg/L)	153	**0.003**	0.241	34	0.125	0.260	115	**0.040**	0.190
High-sensitivity C-reactive protein (mg/L)	153	**<0.001**	0.285	33	0.576	0.098	116	**0.003**	0.270
MELD score	154	**<0.001**	0.302	34	0.701	0.066	116	**0.001**	0.296
Child-Pugh score	154	**<0.001**	0.346	34	0.279	0.185	116	**<0.001**	0.325
High-sensitivity cardiac troponin T (ng/mL)	151	**0.004**	0.229	34	0.062	-0.315	113	**0.026**	0.208
Creatine kinase (U/L)	154	0.653	-0.036	34	0.567	0.099	116	0.588	-0.050
Creatine kinase MB (U/L)	154	0.209	-0.101	34	0.744	-0.056	116	0.217	-0.115
Lactate dehydrogenase (U/L)	154	0.622	-0.040	34	0.985	-0.003	116	0.586	-0.051

Bold font indicates statistically significant *P* values. Abbreviations: NT-pro BNP: N-Terminal pro-B-type natriuretic peptide; eGFR: the estimated glomerular filtration rate; MELD: model for end-stage liver disease.

Pugh and MELD scores in cirrhotic patients with acute decompensating events, but not in those without decompensation, which would suggest that NT-pro BNP can reflect the insidious change of cardiac dysfunction in advanced cirrhosis with cardiac dysfunction.

In addition, BNP is a natriuretic hormone released from myocardial cells in response to volume expansion, end-diastolic wall stress, and possibly increased intracardiac filling pressures [8, 37]. Hypertrophy of the left ventricle, left-atrial dilatation, and increased end-diastolic and end-systolic left-ventricular volume are frequently observed in liver cirrhosis [1, 32, 38, 39], which are potentially the main causes for an increase of NT-pro BNP.

4.2. hs-cTnT. hs-cTnT, a protein complex regulating the contraction of striated muscle, is released when myocardial ischemia induces nonreversible injury of myocardial tissue [40]. hs-cTnT is a specific and sensitive biomarker of myocardial damage and is being widely used for clinical screening in patients with suspected acute myocardial infarction [41, 42], but not for evaluating the change of myocardial contractility. The hs-cTnT level can be also elevated in some

Table 4: Multivariate linear regression analysis of factors associated with the NT-pro BNP level.

Factors	No. Pts	Age-adjusted *B*-coefficient (SE)	*P* value
Age	158	0.302 (0.008)	**<0.001**
Gender	158	0.106 (0.214)	0.137
Acute decompensating events	158	0.432 (0.229)	**<0.001**
Ascites	158	0.175 (0.195)	**0.014**
Acute gastrointestinal hemorrhage	158	0.309 (0.183)	**<0.001**
ACLF	158	0.218 (0.384)	**<0.001**

Bold font indicates statistically significant *P* values. Serum NT-pro BNP concentrations were $\log_{10}$-transformed in order to normalize their distribution. Abbreviations: NT-pro BNP: N-Terminal pro-B-type natriuretic peptide; SE: standard error; ACLF: acute-on-chronic liver failure.

cardiac and noncardiac conditions, such as severe renal insufficiency [43–46], tachycardia, pericarditis, vigorous exercise [47], and atrial fibrillation [48–50]. The present study has rigorously excluded these conditions. The hs-cTnT level seems to be related to the severity and survival of cirrhotic patients [12, 14]. Our results also showed that the hs-cTnT level was significantly higher in decompensated cirrhotic patients than those without decompensation. This association was mainly attributed to the effect of acute gastrointestinal hemorrhage, but not to ascites or ACLF (Supplementary Table 5). A possible explanation for this finding could be that acute gastrointestinal bleeding in cirrhotic patients may lead to hypovolemic hypotension, which is a significant risk factor for myocardial damage [51–53], thereby increasing the levels of myocardial damage biomarkers [54]. The pathophysiological link of the association remains unexplained, and it needs further research to clarify its mechanism.

4.3. CK and CK-MB. We did not find any significant difference in CK and CK-MB levels, comparing compensated and decompensated cirrhotic patients. Moreover, there was no correlation of CK and CK-MB levels with Child-Pugh and MELD scores in cirrhosis. These analyses were performed in the groups with and without decompensating events. Traditionally, CK-MB is helpful for estimating the infarct size in acute myocardial infarction and is highly specific to heart tissue [55, 56] while CK is used for assessing myocardial damage in acute myocardial infarction [57]. None of them is a good indicator of cardiac volume overload. Our study suggested that CK and CK-MB levels did not correlate with the severity of cirrhosis.

4.4. LDH. LDH, a cytoplasmic enzyme, exists in a wide range of tissues and is elevated when cells are damaged. LDH is not specific for the diagnosis of a disease. There are five types of serum LDH isoenzymes. Among them, LDH1 is mainly derived from the heart and LDH5 from the liver [58]. However, LDH5 have lower specificity and sensitivity than ALT for diagnosing and evaluating liver diseases [59]. LDH significantly correlated with Child-Pugh and MELD scores in cirrhotic patients. However, there was no significant difference in LDH levels between cirrhotic patients with and without decompensation. These results indicate that LDH might not be sensitive to early cardiac dysfunction caused by cirrhosis.

4.5. Limitations. First, the number of patients with ACLF was small in our cohort and the relationship between serum cardiac markers and ACLF needs further clarification. Second, a reasonable and convenient approach for quantifying blood loss volume during acute gastrointestinal hemorrhage and volume of ascites was unavailable. Third, healthy controls may make the results more comprehensive. Further studies should further consider the effects of the severity of such decompensating events on the long-term prognosis.

5. Conclusion

An elevated NT-pro BNP level might be useful to identify the cardiac volume overload caused by acute decompensating events in advanced cirrhosis. Additionally, the hs-cTnT level was elevated in cirrhosis with acute decompensating events.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

The abstract was published in the Asian Pacific Association for the Study of the Liver (APASL) 2020 Conference as a poster presentation. Please see the following link: https://link.springer.com/content/pdf/10.1007/s12072-020-10030-4.pdf.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Miaomiao Li reviewed the literature, wrote the study protocol, collected the data, performed the statistical analyses, and drafted the manuscript; Zeqi Guo, Dan Zhang, Xiangbo Xu, Fernando Gomes Romeiro, Andrea Mancuso, Jingqiao Zhang, Ruirui Feng, Xinmiao Zhou, and Cen Hong collected the data, checked the data, and gave critical comments; Xingshun Qi conceived the study, reviewed the literature, wrote the study protocol, treated the patients, checked the data, gave critical comments, and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission. Miaomiao Li, Zeqi Guo, Dan Zhang, and Xiangbo Xu are co-first authors.

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Supplementary Materials

Supplementary Table 1: a table showing partial correlation analysis of the hs-cTnT level in cirrhotic patients, cirrhotic patients with and without decompensation using *P* value, correlation coefficient parameter. Supplementary Table 2: a table showing partial correlation analysis of the CK level in cirrhotic patients using *P* value, correlation coefficient parameter. Supplementary Table 3: a table showing partial correlation analysis of the CK-MB level in cirrhotic patients using *P* value, correlation coefficient parameter. Supplementary Table 4: a table showing partial correlation analysis of the LDH level in cirrhotic patients using *P* value, correlation coefficient parameter. Supplementary Table 5: a table showing multivariate linear regression analysis of factors, such as age, gender, acute decompensation, ascites, acute gastrointestinal hemorrhage, and ACLF, associated with the hs-cTnT level in cirrhotic patients using *P* value, *B*-coefficient parameter. Supplementary Table 6: a table showing multivariate linear regression analysis of factors, such as age, gender, acute decompensation, ascites, acute gastrointestinal hemorrhage, and ACLF, associated with CK, CK-MB, and LDH levels in cirrhotic patients using *P* value, *B*-coefficient parameter. *(Supplementary Materials)*

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