Carvedilol to prevent decompensation of liver cirrhosis in patients with clinically significant portal hypertension stratified by novel non-invasive model

Xiaolong Qi¹, Chuan Liu¹, Hong You², Qing-Lei Zeng³, Wong YJ⁴, Bingqiong Wang², Ivica Grgurevic⁵, Bingtian Dong⁶, Wei Gou⁷, Shenghong Ju⁸, Hyung Joon Yim⁹, Qian Yu⁸, Masashi Hirooka¹⁰, H. Enomoto¹¹, Amr Hanafy¹², Zhujun Cao¹³, Xiemin Dong⁷, Young Kul Jung⁹, Tae Hyung Kim¹⁴, Yohei Koizumi¹⁰, Yoichi Hiasa¹⁰, Takashi Nishimura¹¹, Hiroko Iijima¹¹, Chuanjun Xu¹⁵, Xinru Guo¹⁶, XiaoLin Lan¹⁷, Changxiang Lai¹⁸, Shirong Liu¹⁹, Fang Wang¹⁸, Ying Guo²⁰, Jiaojian Lv¹⁷, Jie Li²¹, Liting Zhang²², Yuqing Wang⁸, Erhei Dai¹⁶, Qing Xie¹³, Chuxiao Shao¹⁷, Zhensheng Liu⁷, Federico Ravaoli²³, Antonio Colecchia²³, and Gaojun Teng⁵

¹Southeast University Zhongda Hospital Department of Radiology
²Capital Medical University Affiliated Beijing Friendship Hospital
³The First Affiliated Hospital of Zhengzhou University
⁴Changi General Hospital
⁵Sveuciliste u Zagrebu Medicinski fakultet
⁶First Affiliated Hospital of Anhui Medical University
⁷Qingdao Sixth People’s Hospital
⁸Southeast University Zhongda Hospital
⁹Korea University Ansan Hospital
¹⁰Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu
¹¹Hyogo Ika Daigaku Byoin
¹²Zagazig University Department of Internal Medicine
¹³Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
¹⁴Hallym University Sacred Heart Hospital
¹⁵The Second Affiliated Hospital of Nanjing University of Chinese Medicine
¹⁶North China University of Science and Technology School of Electrical Information and Light Industry
¹⁷Lishui City People’s Hospital
¹⁸Shenzhen Third People’s Hospital
¹⁹Qufu People’s Hospital
²⁰Third People’s Hospital of Taiyuan
²¹Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
²²Lanzhou University First Hospital
²³Orto Botanico Universita di Modena e Reggio Emilia

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Abstract

Objective: To develop a novel non-invasive model for CSPH, and investigate whether carvedilol could reduce the risk of decomposition in patients with high-risk CSPH stratified by the novel model. Methods: International multicenter observational study with a median follow-up time of 38 months. Three cohorts were included in study from 6 countries. In this study, a total of 1,304 patients were fulfilled diagnosis of liver cirrhosis. Patients were treated with carvedilol in longitudinal carvedilol-treating cohort. The primary outcome was the development of the first hepatic decomposition. Results: Six studies from the meta-analysis were involved (n=819), and LSM and platelet count (PLT) were identified as independent risk factors of CSPH, with pooled risk ratios of 1.10 (95% confidence interval [CI] 1.06-1.15) and 0.99 (95% CI 0.98-0.99). A novel model was established. In HVPG cohort (n=151), the areas under the receiver operating characteristic curve (AUC) of the novel model, ANTICIPATE model, and Baveno VII criteria for CSPH were 0.91 (95% CI 0.86-0.95), 0.80 (95% CI 0.73-0.87), and 0.83 (95% CI 0.77-0.89). The novel model narrows down the grey zone to 22.5%, significantly lower than 50.3%, using Baveno VII criteria (p<0.001). In follow-up cohort (n=1,102), the cumulative incidences (1.7% vs 2.5% vs 15.8%) of decompensation events were significantly different by using the novel model cutoff values of >0, 0 to -0.68 (medium-risk), and <0.68 (p<0.001). In the carvedilol-treating cohort, the patients with high-risk CSPH stratified by the novel model (treating cohort, n=51) had significantly lower rates of decomposition than those of NSBBs untreated patients with high-risk CSPH (n=613 before propensity score matching [PSM], n=102 after PSM, all p<0.05). Conclusion: A novel model provides stratification for CSPH and decomposition in patients with liver cirrhosis. Treatment with carvedilol significantly reduces the risk of decomposition among high-risk CSPH patients stratified by the novel model.

Title:
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Authors & Affiliations:
Chuan Liu1,+, Hong You2,+, Qing-Lei Zeng3,+, Yu Jun Wong4,5,+, Bingqiong Wang2,+, Ivica Grgurevic6,+, Bingtian Dong7,+, Wei Gou8,+, Shenghong Ju9,+, Hyung Joon Yim10,+, Qian Yu9, Masashi Hirooka11, Hirayuki Enomoto12, Amr Shaaban Hanafy13, Zhujun Cao14, Xiemin Dong8, Young Kul Jung10, Tae Hyung Kim15, Yohei Koizumi11, Yoichi Hiasa11, Takashi Nishimura12,16, Hiroko Iijima12,16, Chunjun Xu17, Xinru Guo18, XiaoLin Lan19, Changxiang Lai20, Shirong Liu21, Fang Wang20, Ying Guo22, Jiaojian Lv19, Jie Li23, Liting Zhang24, Yuqing Wang25, Erhei Dai18, Qing Xie14, Chuxiao Shao26, Zhensheng Liu8, Federico Ravaioli27,28, Antonio Colecchia27, Gaojun Teng25,26, Xiaolong Qi1,++,*  

1. Center of Portal Hypertension, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China  
2. Liver Research Center, Beijing Key Laboratory of Translational Medicine in Liver Cirrhosis, National Clinical Research Center of Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing, China  
3. Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China  
4. Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore  
5. Duke-NUS Medical School, Singapore  
6. University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry, Zagreb, Croatia  
7. Department of Ultrasound, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China  
8. Qingdao Sixth People’s Hospital, Qingdao, China  
9. Department of Radiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China  
10. Division of Gastroenterology and Hepatology, Korea University Ansan Hospital, Ansan-si, Gyeonggi-do, Republic of Korea  
11. Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Japan
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**Conclusion:** A novel model provides stratification for CSPH and decompensation in patients with liver cirrhosis. Treatment with carvedilol significantly reduces the risk of decompensation among high-risk CSPH patients stratified by the novel model.

**Keywords**
liver cirrhosis; clinically significant portal hypertension; hepatic venous pressure gradient; non-selective beta-blockers; non-invasive model

**Introduction**

Although the hepatic venous pressure gradient (HVPG) is a gold standard, non-invasive tests are capable and widely used to identify clinically significant portal hypertension (CSPH) in patients with liver cirrhosis. According to the latest Baveno VII criteria, a liver stiffness measurement (LSM) value $\geq 15$ kPa is sufficient to rule in CSPH, and LSM $\geq 25$ kPa plus platelets (PLT) $\geq 150 \times 10^9$/L rules out CSPH. For the patients in the grey zone that did not meet the cutoff mentioned above values, a relatively complicated ANTICIPATE model was used, i.e., LSM values between 20-25 kPa plus PLT $< 150 \times 10^9$/L or LSM values between 15-20 kPa plus PLT $< 110 \times 10^9$/L, however, it can only predict CSPH risk of 60% or little higher. Notably, these non-invasive CSPH identification methods are not present as a continuous form that includes all combinations of LSM and PLT; for example, a patient with LSM of 18 kPa (or 10 kPa) plus PLT of $90 \times 10^9$/L (or $100 \times 10^9$/L) does not have a proper diagnostic scale.

More importantly, finding a diagnostic scale with a smaller grey zone is a reasonable and ongoing need. In the current study, we first perform a systemic review and meta-analysis to extract the significantly non-invasive risk factors of CSPH and then generate a novel model for the detection of CSPH. Secondly, the novel CSPH risk model was validated in two international multicenter cohorts containing cirrhotic patients, i.e., the cross-sectional HVPG-performed cohort for validation of diagnosis performance and the longitudinal follow-up cohort for prediction of cumulative decompensation events. Finally, we investigate whether carvedilol therapy could reduce the risk of hepatic decompensation in high-risk CSPH patients stratified by this novel CSPH risk model.

**Methods**

**Model derivation cohort**

The derivation cohort came from a systematic review and meta-analysis of three prospective cohorts and three retrospective cohorts. These six cohorts were identified by searching the electronic databases of MEDLINE, Embase, PubMed, and Web of Science from the time of their inception to December 1, 2022, using a combined text and MeSH heading search strategy with the terms: “liver stiffness”, “chronic liver diseases”, “portal hypertension”, “elastography” and “diagnosis”. All the studies reported odds ratios (ORs) and
corresponding 95% confidence intervals (CIs) for risk factors. A flowchart of the study selection methodology was shown in Figure 1.

**Meta-analysis**

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search, study selection, data extraction, and quality assessment were performed by two independent reviewers (C. Liu and B.T. Dong, Figure 1). A third reviewer (X.L. Qi) adjudicated disagreements between the two authors.

**Data synthesis**

All data were extracted from eligible studies using a standard data extraction checklist. We extracted the ORs with their 95% CIs for each specific initiating independent parameter of CSPH and calculated the pooled ORs and 95% CIs across studies using a random or fixed-effect model depending on heterogeneity. The revised Quality Assessment for Studies of Diagnostic Accuracy tool (QUADAS-2) was used to assess the methodological quality of the included studies.

Heterogeneity was assessed using Cochran’s Q-test (p < 0.1 indicated significant heterogeneity). The inconsistency index $I^2$ was also calculated. A value of $>50\%$ was considered to represent substantial heterogeneity. The funnel plot was not evaluated in this meta-analysis due to the limited number of studies included. Statistical analysis was performed by R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

**CSPH risk model development**

We developed a categorization model according to the method of Jiang et al. Firstly, the risk factors included in CSPH predicting model were selected from the systematic review and meta-analysis described above. Secondly, the $\beta$-coefficient of risk factors was calculated according to the pooled ORs and its corresponding 95% CIs, respectively. Thirdly, the score of different components was calculated by multiplying the value of one component by the $\beta$-coefficient. For example, the score of part of LSM was calculated by multiplying the value of LSM by the $\beta$-coefficient of LSM. Finally, the CSPH risk was calculated by summing the score of all components.

**Model validation cohorts**

A total of 1,304 patients with liver cirrhosis were enrolled in the study. In the international multicenter cross-sectional HVPG cohort, patients were included from China, Croatia, Singapore, and Japan between August 2021 and November 2022. Moreover, in the international multicenter longitudinal follow-up cohort, patients were included in China, Japan, Southern Korea, Egypt, and Singapore between January 2009 and August 2020. Besides, patients under carvedilol treatment based on clinical manifestation were recruited from China between January 2018 and October 2020.

**An international multicenter cross-sectional HVPG cohort**

The enrollment criteria: (1) age above or equal to 18-year-old; (2) fulfilled diagnosis of liver cirrhosis based on LSM, radiological, histological or clinical features; (3) without prior or current decompensating events (e.g., ascites, variceal bleeding, or overt encephalopathy); and (4) with HVPG measurement. The exclusion criteria: (1) received either non-selective beta-blockers (NSBBs) or endoscopic varical ligation for primary prophylaxis of varical bleeding; (2) lactation or pregnancy; (3) suspicious or confirmed hepatocellular carcinoma (HCC); (4) asplenia or splenectomy; (5) incomplete clinical information.

Liver stiffness was detected by Fibroscan® (Echosens, Pairs, France). Liver stiffness was performed as per the manufacturer’s instructions. The final result must be in accordance with the criteria reported in the previous study. HVPG was performed with standard balloon catheter technique by experienced interventional specialists.

**An international multicenter longitudinal follow-up cohort**
The inclusion criteria: (1) adult age above or equal to 18 years old; (2) fulfilled liver cirrhosis diagnosis based on LSM, radiological, histological or clinical features. The exclusion criteria: (1) prior hepatic decompensation; (2) HCC; (3) prior liver transplantation; (4) portal vein thrombosis; (5) ongoing use of antiplatelet or anticoagulation; (6) incomplete follow-up data; (7) with NSBBs treatment.

A longitudinal carvedilol-treating cohort

The inclusion criteria: (1) adult age above or equal to 18 years old; (2) fulfilled liver cirrhosis diagnosis based on LSM, radiological, histological or clinical features; (3) high risk defined by CSPH risk model. The exclusion criteria: (1) prior hepatic decompensation; (2) HCC; (3) prior liver transplantation; (4) portal vein thrombosis; (5) ongoing use of antiplatelet or anticoagulation; (6) incomplete follow-up data.

The primary outcome in two longitudinal follow-up cohorts

In the international multicenter longitudinal follow-up cohort and longitudinal carvedilol-treating cohort, the primary outcome was the development of the first hepatic decompensation. To minimize reporting bias, we only include objective endpoints such as clinically significant ascites, variceal bleeding documented by endoscopy, and hepatic encephalopathy defined as West-Haven grade 3-4 determined by specialists.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (IBM, New York, USA) and the time receiver operating characteristic curve (ROC) package in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided with a 5% significance level. Continuous variables and categorical variables were summarized and compared. Propensity score matching (PSM) is calculated by logistic regression based on baseline characteristics, including age, gender, Child-Pugh score total bilirubin, alanine aminotransferase, aspartate transaminase, albumin, PLT, LSM, etiology and the score of the novel model were applied to achieve a balance between carvedilol and non-NSBBs cohorts. The diagnostic accuracy of the novel model was assessed using the areas under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Comparisons of accuracy were made with the DeLong method between the novel model, ANTICIPATE model and Baveno VII criteria. Moreover, we considered a diagnostic model adequate with NPV \( \geq 90\% \) for ruling out CSPH and PPV \( \geq 90\% \) for ruling in CSPH.

Ethics statement

All the datasets came from studies approved by the Ethical Review Boards of the study sites and performed in accordance with the Declaration of Helsinki. Patients or legal delegates from the participating centers provided informed consent for the medical information to be used for research.

Role of the funding source

No funding sources were involved in study design, data collection, analysis and interpretation of the data, or writing the report or decision to submit for publication.

Results

Characteristics of the model derivation cohort

In total, 819 patients with liver cirrhosis from Europe (Italy, Germany, Belgium, Denmark), the United States, China, Korea, and Australia who had undergone HVPG measurement were included in the derivation cohort. The main etiologies of chronic liver disease were viral (n=295), alcohol (n=214) and non-alcoholic fatty liver disease (n=150). The baseline characteristics of the derivation cohort were shown in sTable 1. The risk of bias and concerns regarding the applicability of the six included studies was low based on QUADAS-2 criteria, as presented in sFigure 2.

Development of the novel model
As the forest plot shown in Figure 1, two risk factors (i.e., LSM and PLT, Table 2) of CSPH were identified in the systematic review and meta-analysis, with the pooled OR of 1.10 (95% CI 1.06-1.15) and 0.99 (95% CI 0.98-0.99), respectively. Furthermore, the β-coefficient of LSM and PLT were 0.095310 and 0.01005, respectively. Finally, a novel non-invasive CSPH risk model was developed as follows: 0.095310 \times \text{LSM (kPa)} - 0.01005 \times \text{PLT (} \times 10^9/L) - 0.11.

Characteristics of one HVPG and two follow-up validation cohorts

A total of 1,304 cirrhotic patients were included from three cohorts (i.e., international HVPG cohort, international follow-up cohort, and carvedilol-treating cohort, Figure 3), which were employed to validate the diagnostic performance to predict cumulative decompensation events and to guide carvedilol therapy by using the novel CSPH risk model, respectively. The mean (±standard deviation [SD]) ages were 55.6 (11.3), 54.8 (11.4), 52.8 (10.1) years, while the LSM values were 16.9, 18.7, and 19.4 kPa, and 58.9%, 75.7%, and 100% were viral hepatitis-related cirrhosis in the international HVPG cohort, international follow-up cohort, and carvedilol-treating cohort, respectively (Tables 1 and Table 3). Notably, the median follow-up durations between the international follow-up cohort and the carvedilol-treating cohort were similar (39.0 [25.2-55.2] months vs 38.0 [23.0-44.0] months) (Tables 1 and Table 3).

Model validation in international HVPG cohort

In the HVPG cohort, the ROC of the novel CSPH risk model was shown in Figure 2. The AUC were 0.91 (95% CI 0.86-0.95), 0.80 (95% CI 0.73-0.87), and 0.83 (95% CI 0.77-0.89) for the CSPH risk model, ANTICIPATE model, and Baveno VII criteria, respectively (Figure 2, Table 2). In addition, the AUC of CSPH risk model for assessing CSPH is 0.86 (0.78-0.94) and 0.96 (0.91-1.00) in viral cohort and non-viral cohort, respectively (Figure 4). According to the NPV and PPV >90%, the cutoff value of >0 (high-risk) and < -0.68 (low-risk) were used to rule in and rule out CSPH, respectively. Notably, the novel model cut off value of >0 (high-risk) with a higher PPV of 0.906 and a specificity of 0.961 rules in 42.3% of patients with high-risk CSPH, which is higher than the 19.2% of Baveno VII criteria (Table 2). Similar performances were also observed for ruling out of patients with low-risk (Table 2). Notably, the novel model narrows down the grey zone to 22.5%, which is significantly lower than 50.3%, using Baveno VII criteria (Table 2).

Model validation of decompensation incidences in the international follow-up cohort

Overall, there were 248 (22.5%), 241 (21.9%), and 613 (55.6%) cirrhotic patients were categorized into low-risk, medium-risk and high-risk CSPH groups based on the novel model. Over a median follow-up of 39.0 (25.2-55.2) months, the 3-year cumulative incidences of decompensation among the follow-up cohort was substantially higher in the high-risk CSPH group (15.8%) as compared to the low-risk CSPH (1.7%) or medium-risk CSPH group (2.5%) without NSBBs treatment (p<0.001) (Figure 3). Moreover, the 3-year and 5-year AUCs of the CSPH risk model were higher than that of ANTICIPATE model and Baveno VII criteria (Figure 5).

Model validation of guiding carvedilol therapy in a longitudinal carvedilol-treating cohort

Among 114 patients receiving carvedilol in the retrospective cohort, 51 (44.7%) were categorized in high-risk CSPH based on the novel model (Figure 3c, Table 3). Compared to high-risk CSPH patients who did not receive NSBBs (n=613), those who received carvedilol were younger and had less advanced liver diseases, as indicated by lower baseline serum albumin and higher LSM (Table 3). After PSM in a 2:1 ratio, the baseline characteristics were well-balanced between cirrhotic patients with carvedilol and without NSBBs. Notably, treatment with carvedilol was associated with a significantly lower cumulative incidence of 3-year decompensation (p=0.02) (Figure 4A). After PSM, the cumulative incidence of decompensation remained significantly lower in cirrhotic patients treated with carvedilol (p=0.03) (Figure 4B). Furthermore, the high-risk CSPH patients treated with carvedilol had significantly lower incidence of ascites than those of NSBBs untreated high-risk CSPH patients before and after PSM (all p<0.05, Figure 6).

Discussion
The Baveno VII criteria is recently validated as a non-invasive tool for detecting CSPH; however, the diagnosis of CSPH grey zone remained suboptimal to identify cirrhotic patients for NSBBs treatment to prevent decompensation. In this study, we developed a novel CSPH risk model to better stratify the CSPH among cirrhotic patients, with a higher AUC than ANTICIPATE model and Baveno VII criteria to identify CSPH. Most importantly, we demonstrated that treatment with carvedilol significantly reduces the 3-year cumulative incidence of decompensation (primarily ascites) among the high-risk CSPH patients, which provided much-needed evidence of using carvedilol in cirrhotic patients with CSPH.

Currently, non-invasive tools for CSPH stratification are the mainstream trend. It is well known that HVPG ≥10 mmHg is the gold standard to determine the presence of CSPH in patients with viral- and alcohol-related cirrhosis. Given that HVPG is an invasive measurement, more and more non-invasive tests have been proven as a surrogate of HVPG for the diagnosis or prediction of CSPH. Among these non-invasive markers, LSM and PLT are the most favorable parameters and were employed by Baveno VII criteria, which defined an LSM of ≥25 kPa to rule in and LSM ≥15 kPa plus PLT ≥150 x 10^9/L to rule out CSPH, respectively. Notably, the meta-analysis of the current study also revealed the significant importance of the non-invasive markers of LSM and PLT. More importantly, based on the results of the meta-analysis, we established a novel CSPH risk model, and additionally, we found that the AUC of this novel model was higher and the grey zone was smaller when compared with the Baveno VII criteria for the CSPH identification.

The role of non-invasive tools in stratifying decompensation events is currently widely studied. Subsequently, given patients with CSPH are at increased risk of decompensation events, the performance of decompensation stratification was an important issue after the development of a non-invasive CSPH diagnosis tool. In the current study, the high-risk CSPH patients stratified by the novel CSPH risk model presented significantly higher rates (15.8%) of decompensation than the CSPH medium (2.5%) and low (1.7%) risk patients in the follow-up cohort. Notably, the CSPH medium and low-risk subgroups had similarly low rates (2.5% vs 1.7%) of decompensation during a mean follow-up duration of 39.0 (25.2-55.2) months, which synergistically indicates the favorable performance of the novel CSPH risk model.

Finally, it is well known that NSBBs (carvedilol is more favorable) treatment can prevent decompensation in patients with CSPH; therefore, NSBBs therapy should be initiated in patients with CSPH; and a favorable non-invasive CSPH stratification tool is expected to fulfill the mission of guiding the response of NSBBs therapy in patients with high-risk CSPH. According to the Baveno VII consensus, assessing the emerging non-invasive methods to diagnose CSPH and determine response to NSBBs is on the research agenda. Meanwhile, and unfortunately, studies are limited in this field, and there is an ongoing need to non-invasively identify patients who may benefit from NSBBs to prevent decompensation. Remarkably and excitingly, in this study, we found that the high-risk CSPH patients stratified by the novel CSPH risk model and treated with carvedilol had significantly lower rates of decompensation than those of NSBBs untreated high-risk CSPH patients. Further analysis revealed that the most common decompensation event decreased by carvedilol was the ascites, which was consistent with previous studies.

We acknowledge that limitations were in our study. Firstly, the sample size of the retrospective cohort of cirrhotic patients treated with carvedilol is rather small. Nevertheless, we demonstrated that treatment with carvedilol was associated with a significantly lower incidence of hepatic decompensation among high-risk CSPH patients. Secondly, we lack granular data in this large cohort of cirrhotic patients concerning alcohol intake and changes in body weight over time. Thirdly, the sample of patient with non-alcoholic steatohepatitis is limited. Lastly, given that our cohort was predominantly viral-related cirrhosis, further validation is required among cirrhotic patients with non-viral etiology.

In conclusion, we developed a novel non-invasive model to better risk-stratify the CSPH and subsequent decompensation events among patients with liver cirrhosis. Treatment with carvedilol among high-risk CSPH patients stratified by the novel model significantly reduces the risk of hepatic decompensation.

Acknowledgement

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and platform support for this study.

**Conflicts of Interest:** The authors declare no competing interests.

**List of Abbreviations**

- AUC: areas under the receiver operating characteristic curve
- CIs: confidence intervals
- CSPH: clinically significant portal hypertension
- HCC: hepatocellular carcinoma
- HVPG: hepatic venous pressure gradient
- LSM: liver stiffness measurement
- NPV: negative predictive value
- ORs: odds ratios
- PLT: platelet count
- PPV: positive predictive value
- PSM: propensity score matching
- ROC: receiver operating characteristic curve
- SD: standard deviation

**References**


Table 1. Baseline characteristics of patients in HVPG cohort and follow-up cohort.

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>HVPG cohort (n=151)</th>
<th>Follow-up cohort (n=1,102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55.6 (11.3)</td>
<td>54.8 (11.4)</td>
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<td>Male, N, %</td>
<td>73 (48.3)</td>
<td>749 (68.0)</td>
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<td>ALT, U/L</td>
<td>42.0 (37.8)</td>
<td>52.3 (58.4)</td>
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<tr>
<td>AST, U/L</td>
<td>45.7 (43.1)</td>
<td>50.5 (52.4)</td>
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<tr>
<td>Albumin, g/L</td>
<td>40.3 (6.6)</td>
<td>40.6 (5.4)</td>
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<td>Τοταλ βιλιρυβιν, μμολ/Λ</td>
<td>19.4 (11.9)</td>
<td>20.5 (20.9)</td>
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<td>LSM, kPa</td>
<td>16.9 (13.0)</td>
<td>18.7 (12.5)</td>
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<tr>
<td>Platelets, × 10⁹/L</td>
<td>145.7 (68.8)</td>
<td>133.7 (67.8)</td>
</tr>
<tr>
<td>HVPG, mmHg</td>
<td>10.4 (6.1)</td>
<td>-</td>
</tr>
<tr>
<td>Follow-up, month, Median (IQR)</td>
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<td>39.0 (25.2-55.2)</td>
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<tr>
<td>Child-Pugh, N, %</td>
<td>A</td>
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<td>Viral</td>
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<td>834 (75.7)</td>
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<td>ALD</td>
<td>28 (18.5)</td>
<td>54 (4.9)</td>
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<tr>
<td>NASH</td>
<td>16 (10.6)</td>
<td>105 (9.5)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (11.9)</td>
<td>109 (9.9)</td>
</tr>
</tbody>
</table>

*Data are presented as the mean (standard deviations), median (IQR), or n (%).

Abbreviations: ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NASH, non-alcoholic steatohepatitis.

Table 2. Performances of different models for ruling in and out CSPH in the HVPG cohort.

<table>
<thead>
<tr>
<th>Model</th>
<th>Cutoff</th>
<th>Patients</th>
<th>HVPG-proved CSPH patients</th>
<th>Performance</th>
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11
### CSPH risk model (n=151)

<table>
<thead>
<tr>
<th>Rule out CSPH risk</th>
<th>53 (35.1%)</th>
<th>5</th>
<th>SE: 93.6% NPV: 90.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey zone</td>
<td>34 (22.5%)</td>
<td>15</td>
<td>50.0% of patients with CSPH</td>
</tr>
<tr>
<td>Rule in CSPH risk</td>
<td>64 (42.3%)</td>
<td>58</td>
<td>SP: 91.8% PPV: 90.6%</td>
</tr>
</tbody>
</table>

| Rule out LSM [?]15 kPa and PLT [?]150×10⁹/L | 46 (30.4%) | 3 | SE: 96.9% NPV: 94.6% |
| Grey zone | 76 (50.3%) | 48| 63.1% of patients with CSPH |
| Rule in LSM [?]25 kPa | 29 (19.2%) | 27| SP: 98.2% PPV: 96.0% |

Data are presented as n or n (%). *p<0.001.

Abbreviations: CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NPV, negative predictive value; SE, sensitivity; SP, specificity.

**Table 1. Baseline characteristics of the six cohorts included in the systematic review and meta-analysis.**

<table>
<thead>
<tr>
<th>First Author/Year/Country or region (continent)</th>
<th>Study design and period</th>
<th>Sample size (N)</th>
<th>Age (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dajti E &amp; Ravaioli F/2022/Italy</td>
<td>Retrospective/2013-2018</td>
<td>195</td>
<td>59 (49-70)</td>
</tr>
<tr>
<td>Banini BA &amp; Patel S/2022/USA</td>
<td>Retrospective/2016-2020</td>
<td>197</td>
<td>55.3 (11.3)</td>
</tr>
<tr>
<td>Jiang F/2021/China</td>
<td>Prospective/2021-2021</td>
<td>82</td>
<td>50.5 (10.4)</td>
</tr>
<tr>
<td>Jasen C &amp; Bogs C/2016/ Europe</td>
<td>Prospective/2013-2015</td>
<td>158</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Kim TY &amp; Jeong WK/2015/ Korea</td>
<td>Retrospective/2010-2012</td>
<td>92</td>
<td>52.5 (11.9)</td>
</tr>
<tr>
<td>Kitson MT/2015/Australia</td>
<td>Prospective/2008-2013</td>
<td>95</td>
<td>56.8 (9.3)</td>
</tr>
</tbody>
</table>

Data are presented as n or n (%).

Abbreviations: ALD, alcohol-associated liver disease; NAFLD, non-alcoholic fatty liver disease.

**Table 2. The independent variables of the six studies in the systematic review and meta-analysis.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dajti E &amp; Ravaioli F/2022/Italy</td>
<td>Liver stiffness measurement by transient elastography</td>
</tr>
<tr>
<td>Dajti E &amp; Ravaioli F/2022/Italy</td>
<td>Spleen stiffness measurement by transient elastography</td>
</tr>
<tr>
<td>Dajti E &amp; Ravaioli F/2022/Italy</td>
<td>Platelets</td>
</tr>
<tr>
<td>Banini BA &amp; Patel S/2022/USA</td>
<td>Liver stiffness measurement by transient elastography</td>
</tr>
<tr>
<td>Banini BA &amp; Patel S/2022/USA</td>
<td>Platelets</td>
</tr>
<tr>
<td>Jiang F/2021/China</td>
<td>Liver stiffness measurement by transient elastography</td>
</tr>
<tr>
<td>Jiang F/2021/China</td>
<td>Platelets</td>
</tr>
<tr>
<td>Jiang F/2021/China</td>
<td>Varices</td>
</tr>
<tr>
<td>Jasen C &amp; Bogs C/2016/ Europe</td>
<td>Liver stiffness measurement by two-dimensional shear wave elastography</td>
</tr>
<tr>
<td>Jasen C &amp; Bogs C/2016/ Europe</td>
<td>Spleen stiffness measurement by two-dimensional shear wave elastography</td>
</tr>
<tr>
<td>Jasen C &amp; Bogs C/2016/ Europe</td>
<td>Platelets</td>
</tr>
<tr>
<td>Kim TY &amp; Jeong WK/2015/ Korea</td>
<td>Liver stiffness measurement by two-dimensional shear wave elastography</td>
</tr>
<tr>
<td>Kim TY &amp; Jeong WK/2015/ Korea</td>
<td>Platelets</td>
</tr>
</tbody>
</table>
Table 3. Baseline characteristics of high-risk CSPH cohort.

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>Patients with high-risk CSPH and treated by carvedilol (n=51)</th>
<th>Patients with high-risk CSPH and without NSBBs before PSM (n=613)</th>
<th>p</th>
<th>Patients with high-risk CSPH and without NSBBs after PSM (n=102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.8 (10.1)</td>
<td>56.5 (11.3)</td>
<td>0.026</td>
<td>52.8 (10.0)</td>
<td>0.986</td>
</tr>
<tr>
<td>Male, N, %</td>
<td>35 (68.6)</td>
<td>396 (64.6)</td>
<td>0.563</td>
<td>68 (66.7)</td>
<td>0.807</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>28.7 (25.1)</td>
<td>51.4 (58.6)</td>
<td>&lt;0.001</td>
<td>28.3 (14.4.2)</td>
<td>0.906</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>32.4 (15.5)</td>
<td>55.2 (57.9)</td>
<td>&lt;0.001</td>
<td>33.0 (15.8)</td>
<td>0.813</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>43.4 (5.1)</td>
<td>39.0 (5.6)</td>
<td>&lt;0.001</td>
<td>43.2 (4.6)</td>
<td>0.776</td>
</tr>
<tr>
<td>Τοταλ βιλιρυβιν, μμολ/Λ</td>
<td>24.1 (15.3)</td>
<td>22.8 (25.3)</td>
<td>0.732</td>
<td>23.3 (14.1)</td>
<td>0.773</td>
</tr>
<tr>
<td>LSM, kPa</td>
<td>19.4 (11.1)</td>
<td>24.9 (13.5)</td>
<td>0.005</td>
<td>19.3 (11.8)</td>
<td>0.983</td>
</tr>
<tr>
<td>Platelets, × 10⁹/L</td>
<td>78.3 (35.2)</td>
<td>99.0 (44.2)</td>
<td>0.001</td>
<td>73.7 (31.8)</td>
<td>0.417</td>
</tr>
<tr>
<td>CSPH risk model</td>
<td>1.06 (0.96)</td>
<td>1.38 (1.26)</td>
<td>0.079</td>
<td>1.09 (1.04)</td>
<td>0.857</td>
</tr>
<tr>
<td>Follow-up, month</td>
<td>38.0 (23.0-44.0)</td>
<td>38.0 (25.0-53.5)</td>
<td>0.149</td>
<td>28.6 (22.7-47.0)</td>
<td>0.542</td>
</tr>
<tr>
<td>Child-Pugh, N, %</td>
<td>0.824</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>48 (94.1)</td>
<td>572 (93.3)</td>
<td>98 (96.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3 (5.9)</td>
<td>41 (6.7)</td>
<td>4 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology, N, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Viral</td>
<td>51 (100.0)</td>
<td>436 (71.1)</td>
<td>102 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD</td>
<td>-</td>
<td>35 (5.7)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td>-</td>
<td>68 (11.1)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>-</td>
<td>74 (12.1)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as the means (standard deviations), median (IQR), or n (%).

Abbreviations: ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate transaminase; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; PSM, propensity score matching.

Supplementary Figure 1. Flow chart of the study selection methodology.

Supplementary Figure 2. Risk of bias and concerns regarding the applicability of the included studies based on QUADAS-2 criteria.

Supplementary Figure 3. Flowchart of patient recruitment in the different cohorts.
**Supplementary Figure 4.** Performance of CSPH risk model for detection of clinically significant portal hypertension in viral cohort and non-viral cohort.

**Supplementary Figure 5.** Performance of CSPH risk model, ANTICIPATE model and Baveno VII criteria in follow-up cohort.

**Supplementary Figure 6.** Ascites according to treatment group. A: cumulative incidence of ascites before propensity score matching (PSM); B: cumulative incidence of ascites after PSM.

**Supplementary materials**

**Inclusion and exclusion criteria of the study**

Included studies were required to satisfy each of the following criteria: (1) the study examined the independent parameters (including liver stiffness measured by transient elastography and/or platelet count) of clinically significant portal hypertension (CSPH) and reported the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of these independent parameters; (2) measurement of the hepatic venous pressure gradient (HVPG) was used as the reference method; and (3) the study design was a prospective or retrospective cohort design.

The exclusion criteria were as follows: (1) reviews, editorials, conference abstracts, and letters; (2) studies unrelated to the topic; (3) data incomplete or no HVPG. Supplementary Figure 1. displays the study flow diagram.

**PubMed/MEDLINE Search strategy.**

#1 "Hypertension, Portal"[Mesh]
#2 portal hypertension[Title/Abstract]
#3 #1 OR #2
#4 "Elasticity Imaging Techniques"[Mesh]
#5 Elasticity Imaging Techniques[Title/Abstract]
#6 elastography[Title/Abstract]
#7 elastograph[Title/Abstract]
#8 FibroScan[Title/Abstract]
#9 transient elastography[Title/Abstract]
#10 TE[Title/Abstract]
#11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12 #3 AND #11
#13 liver stiffness[Title/Abstract]
#14 #3 AND #13
#15 PLT[Title/Abstract]
#16 platelet[Title/Abstract]
#17 #15 OR #16
#18 #3 AND #17
#19 #12 OR #14 OR #18

**Search results**

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A total of 2,935 records were retrieved using our search method. After removing 871 duplicates, 2,064 records were retained and initially screened. Following the titles and abstract screening, 37 studies were considered potentially relevant for further inspection. By reading the full text, 6 studies were finally included for the systematic review and meta-analysis.
**Figure 1:** Pooled risk ratios and their corresponding 95% confidence intervals of liver stiffness measurement (A) and platelets (B) for predicting clinically significant portal hypertension.
Figure 2: Performance of different models for diagnosis of clinically significant portal hypertension.
Figure 3. The cumulative incidence of liver decompensation in follow-up cohort.
Figure 4. Decompensation according to treatment group. A: cumulative incidence of decompensation before PSM; B: cumulative incidence of decompensation after PSM;