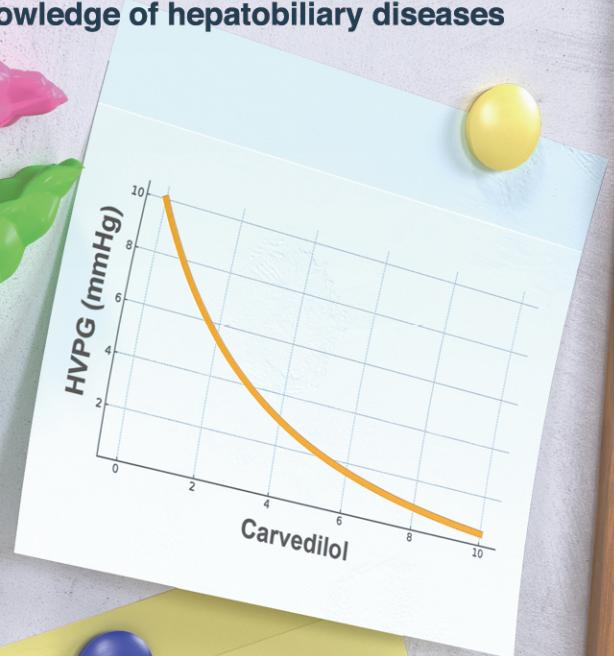


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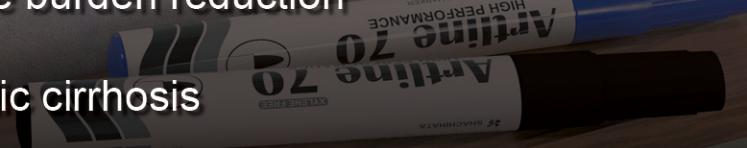
Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT

HCV self-testing and disease burden reduction

MASLD and microbiota

Bariatric surgery for metabolic cirrhosis



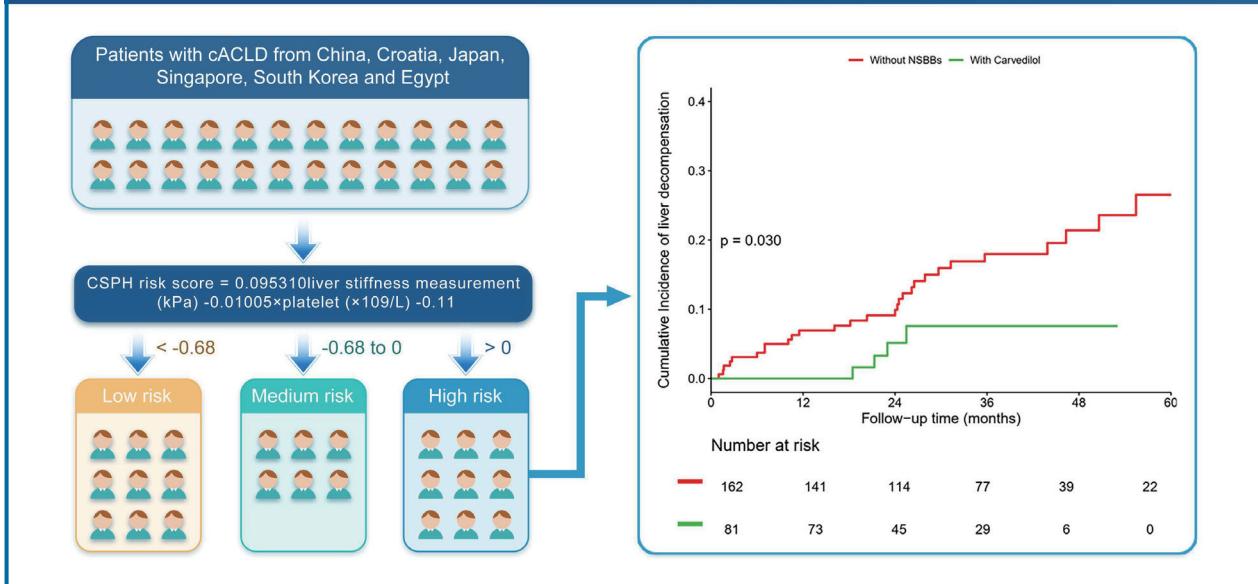
Carvedilol to prevent hepatic decompensation of cirrhosis in patients with clinically significant portal hypertension stratified by new non-invasive model (CHESS2306)

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Graphical Abstract

Carvedilol to prevent hepatic decompensation in patients with CSPH stratified by new non-invasive model



Study Highlights

- NSBBs significantly reduce the risk of hepatic decompensation in patients with liver cirrhosis and CSPH. Non-invasive models to stratify CSPH, predict hepatic decompensation, and guide NSBB therapy in patients with cirrhosis are limited. A new non-invasive model was developed and validated to better risk-stratify the CSPH and subsequent decompensation events in patients with cirrhosis. Treatment with carvedilol among patients with high-risk CSPH, as stratified using the new model, significantly reduces the risk of hepatic decompensation.

Backgrounds/Aims: Non-invasive models stratifying clinically significant portal hypertension (CSPH) are limited. Herein, we developed a new non-invasive model for predicting CSPH in patients with compensated cirrhosis and investigated whether carvedilol can prevent hepatic decompensation in patients with high-risk CSPH stratified using the new model.

Methods: Non-invasive risk factors of CSPH were identified via systematic review and meta-analysis of studies involving patients with hepatic venous pressure gradient (HVPG). A new non-invasive model was validated for various performance aspects in three cohorts, i.e., a multicenter HVPG cohort, a follow-up cohort, and a carvedilol-treating cohort.

Results: In the meta-analysis with six studies (n=819), liver stiffness measurement and platelet count were identified as independent risk factors for CSPH and were used to develop the new “CSPH risk” model. In the HVPG cohort (n=151), the new model accurately predicted CSPH with cutoff values of 0 and -0.68 for ruling in and out CSPH, respectively. In the follow-up cohort (n=1,102), the cumulative incidences of decompensation events significantly differed using the cutoff values of <-0.68 (low-risk), -0.68 to 0 (medium-risk), and >0 (high-risk). In the carvedilol-treated cohort, patients with high-risk CSPH treated with carvedilol (n=81) had lower rates of decompensation events than non-selective beta-blockers untreated patients with high-risk CSPH (n=613 before propensity score matching [PSM], n=162 after PSM).

Conclusions: Treatment with carvedilol significantly reduces the risk of hepatic decompensation in patients with high-risk CSPH stratified by the new model. (*Clin Mol Hepatol* 2025;31:105-118)

Keywords: Cirrhosis; Portal hypertension; Hepatitis B; Carvedilol

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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

INTRODUCTION

Although the hepatic venous pressure gradient (HVPG) is the gold standard, non-invasive tests are widely used to identify clinically significant portal hypertension (CSPH) in patients with compensated cirrhosis.¹⁻³ According to the latest Baveno VII criteria, a liver stiffness measurement (LSM) ≥ 25 kPa can rule in CSPH, whereas a LSM ≤ 15 kPa plus platelet count (PLT) $\geq 150 \times 10^9/L$ can rule out CSPH.¹ For patients in the grey zone not meeting these cutoffs, the more 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 $< 110 \times 10^9/L$, which predicts a CSPH risk of 60% or marginally higher.^{1,4} Notably, these non-invasive CSPH identification methods do not provide a continuous scale that includes all combinations of LSM and PLT. For example, a patient with LSM of 18 kPa (or 10 kPa) plus PLT of $160 \times 10^9/L$ (or $90 \times 10^9/L$) does not fit into an existing diagnostic framework.

Notably, finding a diagnostic scale with a smaller grey zone is a reasonable and ongoing need. In this study, we first conducted a systematic review and meta-analysis to identify the significantly non-invasive risk factors of CSPH and subsequently generated a new model for the detection of CSPH. Second, the new CSPH risk model was validated in two international multicenter cohorts containing patients with compensated cirrhosis, i.e., a cross-sectional HVPG-performed cohort to validate diagnostic performance and a longitudinal follow-up cohort for to predict cumulative decompensation events. Finally, we investigated whether carvedilol therapy could reduce the risk of hepatic decompensation in patients with high-risk CSPH stratified by this new CSPH risk model.

MATERIALS AND METHODS

Model derivation cohort

The derivation cohort came from a systematic review and meta-analysis of three prospective cohorts and three retrospective cohorts.⁵⁻¹⁰ These cohorts were identified via a comprehensive search of electronic databases including MEDLINE, Embase, PubMed, and Web of Science, from inception to December 1, 2022. The search strategy used

combined text and MeSH heading terms such as: “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 is shown in Supplementary Figure 1.

Meta-analysis

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ The literature search, study selection, data extraction, and quality assessment were performed by two independent reviewers (C. Liu and B.T. Dong, Fig. 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 independent parameter associated with CSPH, and calculated pooled ORs and 95% CIs across studies. Depending on the heterogeneity observed, we used either a random- or fixed-effects model for the meta-analysis. The revised Quality Assessment for Studies of Diagnostic Accuracy tool (QUADAS-2) was used to assess the methodological quality of the included studies.¹²

Heterogeneity was assessed using Cochran's Q-test with $P < 0.1$ indicating significant heterogeneity.¹³ The inconsistency index (I^2) was also calculated, with a value of $\geq 50\%$ considered to represent substantial heterogeneity.¹³ Owing to the limited number of studies included, a funnel plot was not evaluated in this meta-analysis. Statistical analysis was performed using 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.¹⁴ First, the risk factors included in the CSPH predicting model were selected from the systematic review and meta-analysis described above. Second, the β -coefficient of each risk factor was calculated based on the

pooled ORs and their corresponding 95% CIs. Third, the score for each component was calculated by multiplying the value of that component by its β -coefficient. For example, the score for the LSM component was calculated by multiplying the LSM value by its β -coefficient of LSM. Finally, the CSPH risk was calculated by summing the scores of all components.

Model validation cohorts

A total of 1,396 patients 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. Additionally, in the international multicenter longitudinal follow-up cohort, patients were included from China, Japan, South Korea, Egypt, and Singapore between January 2009 and August 2020. Furthermore, patients undergoing carvedilol treatment based on clinical manifestation were recruited from China between January 2018 and March 2021.

An international multicenter cross-sectional HVPG cohort

The enrollment criteria were: (1) age above or equal to 18 years old; (2) fulfilled diagnosis of cirrhosis based on LSM, radiological, histological or clinical features; (3) no prior or current decompensating events (e.g., ascites, variceal bleeding, or overt encephalopathy); and (4) availability of HVPG measurement. The exclusion criteria were: (1) prior treatment with non-selective beta-blockers (NSBBs) or endoscopic variceal ligation for primary prophylaxis of variceal bleeding; (2) lactation or pregnancy; (3) suspected or confirmed hepatocellular carcinoma (HCC); (4) asplenia or splenectomy; and (5) incomplete clinical information.

Liver stiffness was detected using Fibroscan® (Echosens, Pairs, France) according to manufacturer's instructions. The final results were required to meet the criteria reported in the previous studies.^{15,16} HVPG was measured using the standard balloon catheter technique by experienced interventional specialists.^{17,18}

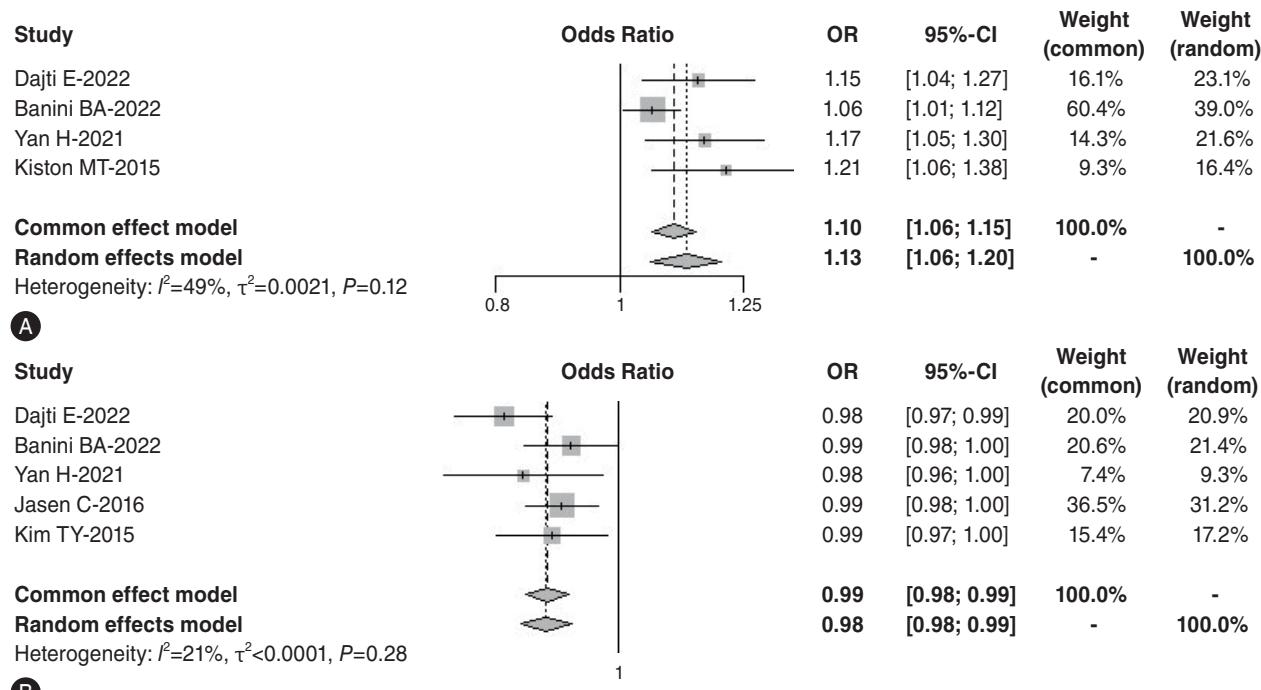


Figure 1. Pooled risk ratios and their corresponding 95% confidence intervals of liver stiffness measurement (A) and platelet counts (B) for predicting clinically significant portal hypertension.

An international multicenter longitudinal follow-up cohort

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

A longitudinal carvedilol-treating cohort

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

The primary outcome in two longitudinal follow-up cohorts

In the international multicenter longitudinal follow-up cohort and the longitudinal carvedilol-treating cohort, the primary outcome was the development of the first hepatic decompensation. To minimize reporting bias, we included only 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, Armonk, NY, USA) and the time receiver operating characteristic curve (ROC) package in R version 4.2.1 (R Foundation for Statistical Computing). All statistical tests were two-sided with a 5% significance level. Continuous variables and categorical variables were summarized and compared. Propensity score matching (PSM) was calculated via logistic regression based on baseline characteristics, including age, gender, Child-Pugh score total bilirubin, alanine aminotransferase, aspartate transaminase, albumin, PLT, LSM, and etiology to achieve balance between

the carvedilol and non-NSBBs cohorts. The diagnostic accuracy of the new 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 new 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 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 their legal representatives from the participating centers provided written informed consent for their medical information to be used for research.

RESULTS

Characteristics of the model derivation cohort

In total, 819 patients with compensated cirrhosis from Europe (Italy, Germany, Belgium, and 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 metabolic dysfunction-associated steatotic liver disease (n=150). The baseline characteristics of the derivation cohort were shown in Supplementary Table 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 Supplementary Figure 2.

Development of the new model

As shown in the forest plot in Figure 1, two risk factors (i.e., LSM and PLT, Supplementary Table 2) of CSPH were identified in the systematic review and meta-analysis, with the pooled ORs 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. Consequently, a new non-invasive CSPH risk model was developed as follows: $0.095310 \times \text{LSM} \text{ (kPa)} - 0.01005 \times \text{PLT} (\times 10^9/\text{L}) - 0.11$.

Characteristics of one HVPG and two follow-up validation cohorts

A total of 1,396 patients with compensated cirrhosis were included from three cohorts (i.e., international HVPG cohort, international follow-up cohort, and carvedilol-treating cohort, Supplementary Fig. 3), which were employed to validate the diagnostic performance to predict cumulative decompensation events and to guide carvedilol therapy by using the new CSPH risk model, respectively. The mean (\pm standard deviation [SD]) ages were 55.6 (11.3), 54.8 (11.4), and 52.5 (10.5) years old across the cohorts. The LSM values were 16.9, 18.7, and 14.8 kPa, respectively. Viral hepatitis-related cirrhosis accounted for 58.9%, 75.7%, and 100% in the international HVPG cohort, international

follow-up cohort, and carvedilol-treating cohort, respectively (Table 1). Detailed baseline characteristics were listed in Table 1 and Table 2.

Model validation in international HVPG cohort

In the HVPG cohort, the ROC of the new 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 (Fig. 2, Table 3). Additionally, 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 (Supplementary Fig. 4). Based on NPV and PPV criteria $>90\%$, cutoff values of >0 (high-risk), and <-0.68 (low-risk) were used to rule in and rule out CSPH, respectively. Notably, the new model's cut off value of >0 (high-risk) demonstrated a higher PPV of 0.906 and a specificity of 0.918, identifying 42.3% of patients with high-risk CSPH, which is higher than the 19.2%

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

Parameters	HVPG cohort (n=151)	Follow-up cohort (n=1,102)	Carvedilol cohort (n=143)
Age, years	55.6 (11.3)	54.8 (11.4)	52.5 (10.5)
Male, n (%)	73 (48.3)	749 (68.0)	107 (74.8)
ALT, U/L	42.0 (37.8)	52.3 (58.4)	27.1 (17.2)
AST, U/L	45.7 (43.1)	50.5 (52.4)	29.1 (13.6)
Albumin, g/L	40.3 (6.6)	40.6 (5.4)	44.8 (5.0)
Total bilirubin, $\mu\text{mol/L}$	19.4 (11.9)	20.5 (20.9)	21.9 (11.6)
LSM, kPa	16.9 (13.0)	18.7 (12.5)	14.8 (9.7)
Platelet count, $\times 10^9/\text{L}$	145.7 (68.8)	133.7 (67.8)	111.3 (59.4)
HVPG, mmHg	10.4 (6.1)	-	-
Follow-up, month, median (IQR)	-	39.0 (25.2–55.2)	31.0 (22.5–41.0)
Child-Pugh, n (%)			
A	138 (91.4)	1050 (95.3)	134 (93.7)
B	13 (8.6)	52 (4.7)	9 (6.3)
Etiology, n (%)			
Viral	89 (58.9)	834 (75.7)	143 (100)
ALD	28 (18.5)	54 (4.9)	
MASH	16 (10.6)	105 (9.5)	
Other	18 (11.9)	109 (9.9)	

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

ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; IQR, interquartile range.

Table 2. Baseline characteristics of high-risk CSPH cohort

Parameters	Patients with high-risk CSPH and treated by carvedilol (n=81)		Patients with high-risk CSPH and without NSBBs before PSM (n=613)		Patients with high-risk CSPH and without NSBBs after PSM (n=162)		Standardized mean difference	P-value
				P-value				
Age, years	54.5 (10.1)	56.5 (11.3)	0.135	54.3 (10.2)	0.02	0.862		
Male, n (%)	55 (67.9)	396 (64.6)	0.558	104 (64.2)	0.08	0.567		
ALT, U/L	28.5 (21.7)	51.4 (58.6)	<0.001	29.1 (16.9)	-0.03	0.816		
AST, U/L	32.8 (16.1)	55.2 (57.9)	<0.001	33.9 (13.7)	-0.07	0.567		
Albumin, g/L	42.5 (5.1)	39.0 (5.6)	<0.001	41.9 (5.5)	0.13	0.375		
Total bilirubin, µmol/L	25.3 (13.5)	22.8 (25.3)	0.396	23.9 (16.0)	0.10	0.522		
LSM, kPa	19.7 (10.3)	24.9 (13.5)	0.005	20.7 (11.3)	-0.09	0.522		
Platelet count, $\times 10^9$ /L	72.6 (32.7)	99.0 (44.2)	<0.001	75.6 (34.5)	-0.09	0.515		
Follow-up, month	25.0 (19.2–0–39.5)	38.0 (25.0–53.5)	<0.001	33.5 (20.3–47.1)	-	0.010		
Child-Pugh, n (%)			0.148					
A	72 (88.9)	572 (93.3)		150 (92.6)				
B	9 (11.1)	41 (6.7)		12 (7.4)				
Etiology, n (%)			<0.001					
Viral	81 (100.0)	436 (71.1)		162 (100.0)				
ALD	-	35 (5.7)		-				
MASLD	-	68 (11.1)		-				
other	-	74 (12.1)		-				

Data are presented as the means (standard deviations), median (IQR), or number (%).
ALD, alcohol-associated liver disease; AST, aspartate transaminase; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; PSM, propensity score matching; IQR, interquartile range.

identified by the Baveno VII criteria (Table 3). Similar performances were observed for ruling out patients with low risk (Table 3). Notably, the new model narrowed down the grey zone to 22.5%, which is significantly lower than the 50.3% grey zone observed with the Baveno VII criteria (Table 3).

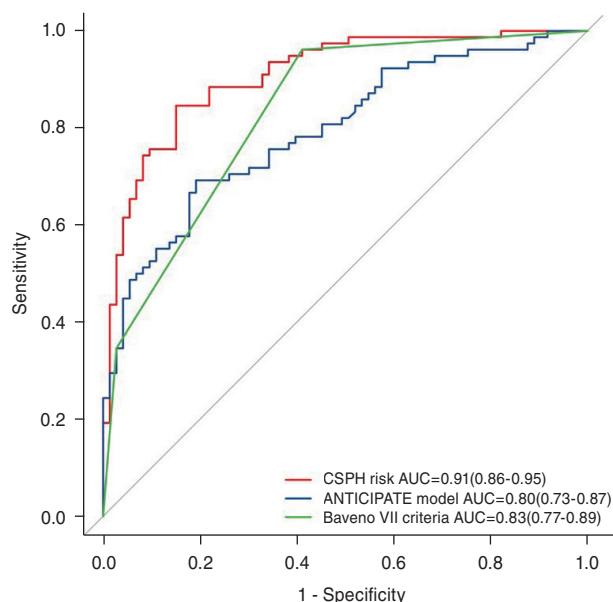


Figure 2. Performance of different models for diagnosis of clinically significant portal hypertension.

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

Overall, 248 (22.5%), 241 (21.9%), and 613 (55.6%) patients with compensated cirrhosis were categorized into low-, medium- and high-risk CSPH groups based on the new 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 were substantially higher in the high-risk CSPH group (15.8%) than those in the low-risk CSPH (1.7%) or medium-risk CSPH group (2.5%) without NSBBs treatment ($P<0.001$) (Fig. 3). Moreover, the 3- and 5-year AUCs of the CSPH risk model were higher than those of the ANTICIPATE model and Baveno VII criteria (Supplementary Fig. 5).

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

Among 143 patients receiving carvedilol in the retrospective cohort, 62 (43.4%) were categorized in low- and medium-risk CSPH, and 81 (56.6%) in high-risk CSPH based on the new model (Supplementary Fig. 3C, Tables 1, 2). No significant difference was observed in the cumulative incidence of 3-year decompensation between patients treated with carvedilol and those without NSBBs in low- and medium-risk CSPH group ($P=0.3$, Supplementary Fig. 6).

Table 3. Performances of different models for ruling in and out CSPH in the HVPG cohort

Model	Cutoff	Patients	HVPG-proved CSPH patients	Performance
CSPH risk model (n=151)	Rule out CSPH risk <-0.68	53 (35.1%)	5	SE: 93.6% NPV: 90.6%
	Grey zone	34 (22.5%)*	15	50.0% of patients with CSPH
	Rule in CSPH risk >0	64 (42.3%)	58	SP: 91.8% PPV: 90.6%
Baveno VII criteria (n=151)	Rule out LSM ≤ 15 kPa and PLT $\geq 150 \times 10^9/L$	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 number or number (%).

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

* $P<0.001$.

Compared to patients with high-risk CSPH who did not receive NSBBs (n=613), the 81 patients who received carvedilol were younger and had less advanced liver diseases, as evidenced by lower baseline serum albumin levels and higher LSM (Table 2). After PSM in a 2:1 ratio, the baseline characteristics were well-balanced between patients with carvedilol and without NSBBs. Treatment with carvedilol was associated with a lower cumulative inci-

dence of 3-year decompensation (4.9% vs. 13.2%, $P=0.08$, Fig. 4A). After PSM, the cumulative incidence of decompensation remained significantly lower in patients treated with carvedilol (4.9% vs. 17.3%, $P=0.04$, Fig. 4B). Notably, patients with high-risk CSPH treated with carvedilol had significantly lower incidence of ascites than those of NSBBs untreated with high-risk CSPH before and after PSM (all $P<0.05$, Fig. 5).

DISCUSSION

The Baveno VII criteria, recently validated as a non-invasive tool for detecting CSPH,¹⁹ still have a suboptimal grey zone for identifying patients with compensated cirrhosis who could benefit from NSBBs treatment to prevent decompensation.¹⁹ In this study, we developed a new CSPH risk model to better stratify CSPH in patients with compensated cirrhosis, achieving a higher AUC than the ANTICIPATE model and Baveno VII criteria. Notably, we demonstrated that treatment with carvedilol significantly reduces the 3-year cumulative incidence of decompensation (primarily ascites) in patients with high-risk CSPH, providing much-needed evidence for using carvedilol in patients with compensated cirrhosis and CSPH.

Currently, non-invasive tools for CSPH stratification are

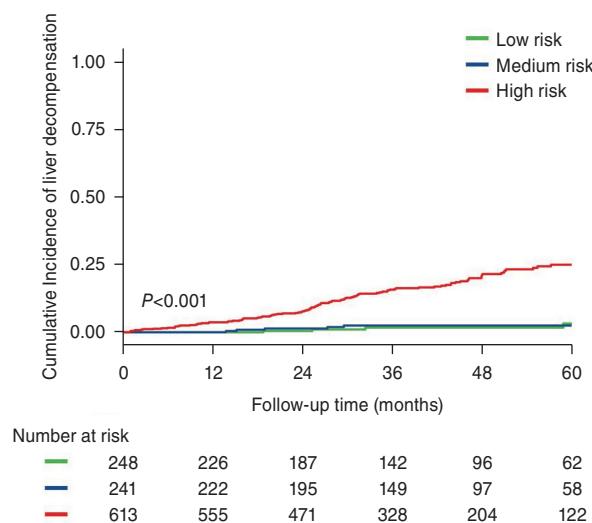
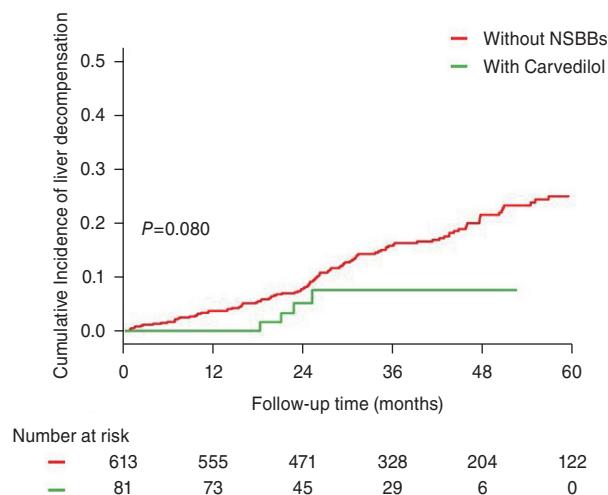
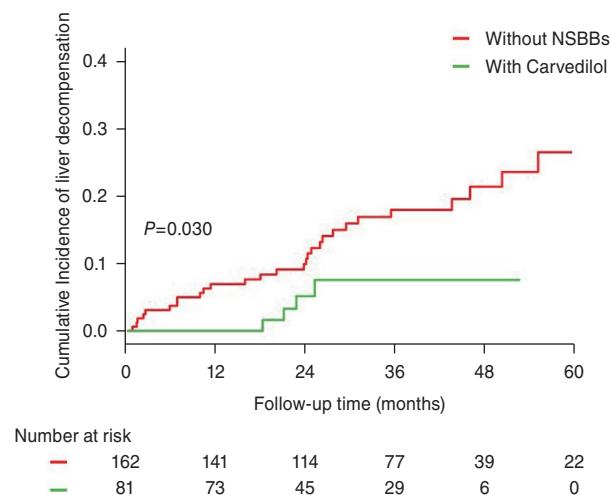


Figure 3. Cumulative incidence of hepatic decompensation in follow-up cohort.



A

Figure 4. Hepatic decompensation according to treatment group in patients with high-risk CSPH. (A) Cumulative incidence of decompensation before propensity score matching (PSM); (B) Cumulative incidence of decompensation after PSM. CSPH, clinically significant portal hypertension.



B

the mainstream trend.²⁰ HVPG ≥ 10 mmHg is the gold standard for determining CSPH in patients with viral- and alcohol-related cirrhosis. However, owing to the invasive nature of HVPG, non-invasive tests are increasingly being used as surrogates for diagnosing or predicting CSPH.^{2,4-9,21-23} Among these non-invasive markers, LSM and PLT are the most favorable parameters and are employed by Baveno VII criteria, which define LSM ≥ 25 kPa to rule in and LSM ≤ 15 kPa plus PLT $\geq 150 \times 10^9/L$ to rule out CSPH.¹ Our meta-analysis also highlighted the significance of LSM and PLT as non-invasive markers. More importantly, we established a new CSPH risk model based on the meta-analysis results, which additionally demonstrated a higher AUC and a smaller grey zone than the Baveno VII criteria for CSPH identification.

The role of non-invasive tools in stratifying decompensation events is widely studied. Given that patients with CSPH are at increased risk of decompensation events,^{1,24} the performance of decompensation stratification is a crucial issue following the development of a non-invasive CSPH diagnosis tool.^{4,15,16,25-28} In the current study, the patients with high-risk CSPH stratified by the new CSPH risk model had significantly higher rates (15.8%) of decompensation than CSPH medium- (2.5%) and low-risk (1.7%) 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, indicating the favorable performance of the new CSPH risk model.

NSBBs, particularly carvedilol, can prevent decompensation in patients with CSPH; therefore, NSBBs therapy should be initiated in these patients with CSPH.^{1,29,30} A favorable non-invasive CSPH stratification tool is needed to guide the response of NSBBs therapy in patients with high-risk CSPH. According to the Baveno VII consensus, assessing emerging non-invasive methods to diagnose CSPH and determine response to NSBBs is on the research agenda.¹ However, studies in this field are limited, highlighting the need to non-invasively identify patients who may benefit from NSBBs to prevent decompensation.³¹ Notably, in this study, we found that the patients with high-risk CSPH stratified by the new CSPH risk model and treated with carvedilol had significantly lower rates of decompensation than those of NSBBs untreated high-risk patients with CSPH. Further analysis revealed that the most common decompensation event decreased by carvedilol treatment was ascites, consistent with previous studies.^{3,32,33}

This study had several limitations. First, the sample size of the retrospective cohort of patients treated with carvedilol was rather small. Nevertheless, we demonstrated that carvedilol treatment was associated with a significantly lower incidence of hepatic decompensation among patients with high-risk CSPH. Second, we lacked granular

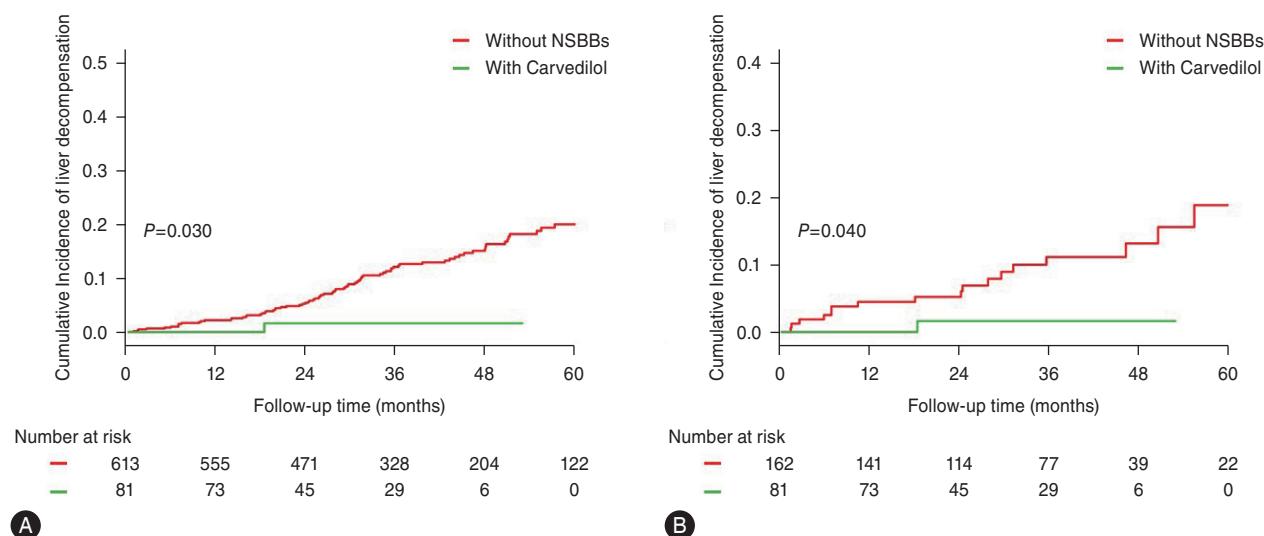


Figure 5. Ascites according to treatment group in patients with high-risk CSPH. (A) Cumulative incidence of ascites before propensity score matching (PSM); (B) Cumulative incidence of ascites after PSM. CSPH, clinically significant portal hypertension.

data in this large cohort of patients with compensated cirrhosis concerning alcohol intake and changes in body weight over time. Third, the sample of patients with metabolic dysfunction-associated steatohepatitis was limited. Fourth, individual participant data was not acquired. Fifth, given that our cohort predominantly consisted of patients with viral-related cirrhosis, further validation is required among patients with cirrhosis with non-viral etiologies. Sixth, the influence of different covariates in calculating pooling ORs was not considered. In meta-analysis, the inconsistency index I^2 of PLT and LSM was less than 50%, indicating that the influence of different covariates is limited. Last, significant differences exist in baseline characteristics between patients treated with carvedilol and those without NSBBs in high-risk group. We plan to conduct a large sample prospective study to confirm the results.

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

Authors' contribution

Guarantor of article: Xiaolong Qi. Study design: Xiaolong Qi, Chuan Liu. Data collection: All authors. Data analysis: Chuan Liu, Bingtian Dong. Drafting of the article: Qing-Lei Zeng, Chuan Liu, Bingtian Dong. Critical reviewed of the manuscript: Xiaolong Qi, Yu Jun Wong, Federico Ravaioli, Antonio Colecchia, Gaojun Teng. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (<http://www.e-cmh.org>).

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