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

Xiaolong Qi[1], Chuan Liu[1], Hong You[2], Qing-Lei Zeng[3], Wong YJ[4], Bingqiong Wang[2], Ivica Grgurevic[5], Bingtian Dong[6], Wei Gou[7], Shenghong Ju[8], Hyung Joon Yim[9], Qian Yu[8], Masashi Hirooka[10], H. Enomoto[11], Amr Hanafy[12], Zhujun Cao[13], Xiemin Dong[7], Young Kul Jung[9], Tae Hyung Kim[14], Yohei Koizumi[10], Yoichi Hiasa[10], Takashi Nishimura[11], Hiroko Iijima[11], Chuanjun Xu[15], Xinru Guo[16], XiaoLin Lan[17], Changxiang Lai[18], Shirong Liu[19], Fang Wang[18], Ying Guo[20], Jiaojian Lv[17], Jie Li[21], Liting Zhang[22], Yuqing Wang[8], Erhei Dai[16], Qing Xie[13], Chuxiao Shao[17], Zhensheng Liu[7], Federico Ravaioli[23], Antonio Colecchia[23], and Gaojun Teng[8]

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

Title:

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

Authors & Affiliations:

Chuan Liu[1,+], Hong You[2,+], Qing-Lei Zeng[3,+], Yu Jun Wong[4,5,+], Bingqiong Wang[2,+], Ivica Grgurevic[6,+], Bingtian Dong[7,+], Wei Gou[8,+], Shenghong Ju[9,+], Hyung Joon Yim[10,+], Qian Yu[9], Masashi Hirooka[11], Hirayuki Enomoto[12], Amr Shaaban Hanafy[13], Zhujun Cao[14], Xiemin Dong[8], Young Kul Jung[10], Tae Hyung Kim [15], Yohei Koizumi[11], Yoichi Hiasa[11], Takashi Nishimura[12,16], Hiroko Iijima[12,16], Chuanjun Xu[17], Xinru Guo[18], XiaoLin Lan[19], Changxiang Lai[20], Shirong Liu[21], Fang Wang[20], Ying Guo[22], Jiaojian Lv[19], Jie Li[23], Liting Zhang[24], Yuqing Wang[25], Erhei Dai[18], Qing Xie[14], Chuxiao Shao[26], Zhensheng Liu[8], Federico Ravaioli[27,28], Antonio Colecchia[27], Gaojun Teng[25,++], Xiaolong Qi[1,++,*]

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

12. Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo Medical University, Nishinomiya, Hyogo, Japan
13. Division of Gastroenterology, Hepatology and Endoscopy, Internal Medicine, Zagazig University Faculty of Medicine, Egypt
14. Department of Infectious Disease, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
15. Division of Gastroenterology and Hepatology, Hallym University Sacred Heart Hospital, Republic of Korea
16. Ultrasound Imaging Center, Hyogo Medical University, Nishinomiya, Hyogo, Japan
17. Department of Radiology, The Second Hospital of Nanjing, Nanjing University of Chinese Medicine, Nanjing, China
18. Division of Liver Diseases, The Fifth Hospital of Shijiazhuang, North China University of Science and Technology, Shijiazhuang, China
19. Department of Infectious Diseases, Lishui People's Hospital, Lishui, China
20. Shenzhen Third People's Hospital, Shenzhen, China
21. Department of Infectious Diseases, Qufu People's Hospital, Qufu, China
22. Department of Hepatology, The Third People's Hospital of Taiyuan, Taiyuan, China
23. Department of Infectious Diseases, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China
24. Department of Infectious Diseases, The First Hospital of Lanzhou University, Lanzhou, China
25. Center of Interventional Radiology and Vascular Surgery, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
26. Lishui People's Hospital, Lishui, China
27. Gastroenterology Unit, University Hospital of Modena, Department of Medical Specialities, University of Modena & Reggio Emilia, Modena, Italy
28. Department of Medical and Surgical Sciences (DIMEC), IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

+ These authors contributed equally

Corresponding authors

++ Co-senior authors

Corresponding Author:

Professor Xiaolong Qi, MD, PhD

Founder & Chair, Portal Hypertension Alliance in China (CHESS)

Center of Portal Hypertension, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing 210009, China

Email: qixiaolong@vip.163.com

ORCID: 0000-0002-3559-5855

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Abstract

Objective: To develop a novel non-invasive model for CSPH, and investigate whether carvedilol could reduce the risk of decompensation 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

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diagnosis of liver cirrhosis. Patients were treated with carvedilol in longitudinal carvedilol-treating cohort. The primary outcome was the development of the first hepatic decompensation .

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 decompensation 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 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.[1-3] According to the latest Baveno VII criteria, a liver stiffness measurement (LSM) value [?]25 kPa is sufficient to rule in CSPH, and LSM [?]15 kPa plus platelets (PLT) [?]150×10^9/L rules out CSPH.[1] 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 $<150\times10^9$/L or LSM values between 15-20 kPa plus PLT $<110\times10^9$/L, however, it can only predict CSPH risk of 60% or little higher.[1,4] 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 160×10^9/L (or 90×10^9/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.[5-10] 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 sFigure 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, 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.[12]

Heterogeneity was assessed using Cochran's Q-test ($p<0.1$ indicated significant heterogeneity).[13] The inconsistency index I^2 was also calculated. A value of [?]50% was considered to represent substantial heterogeneity.[13] 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.[14] Firstly, the risk factors included in CSPH predicting model were selected from the systematic review and meta-analysis described above. Secondly, the β-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 β-coefficient. For example, the score of part of LSM was calculated by multiplying the value of LSM by the β-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 variceal ligation for primary prophylaxis of variceal 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.[15,16] HVPG was performed with standard balloon catheter technique by experienced interventional specialists.[17]

An international multicenter longitudinal follow-up cohort

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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 [?]90% for ruling out CSPH and PPV [?]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

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As the forest plot shown in Figure 1, two risk factors (i.e., LSM and PLT, sTable 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 × LSM (kPa) - 0.01005 × 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, sFigure 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 sTable 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 sTable 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 (sFigure 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 0.918 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 (sFigure 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 (sFigure 3c, sTable 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 (sTable 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, sFigure 6).

Discussion

The Baveno VII criteria is recently validated as a non-invasive tool for detecting CSPH;[18] however, the diagnosis of CSPH grey zone remained suboptimal to identify cirrhotic patients for NSBBs treatment to prevent decompensation.[18] 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.[2,4-9,19-21] 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 [?]150x10^9/L to rule out CSPH, respectively.[1] 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, [1,22] the performance of decompensation stratification was an important issue after the development of a non-invasive CSPH diagnosis tool.[4,15,16,23-26] 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[1,27,28]; and a favorable non-invasive CSPH stratification tool is expected to fulfil 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.[1] 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.[29] 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.[3,30]

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.

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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

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

Parameters*	**HVPG cohort (n=151)**	**Follow-up cohort (n=1,102)**
Age, years	55.6 (11.3)	54.8 (11.4)
Male, N, %	73 (48.3)	749 (68.0)
ALT, U/L	42.0 (37.8)	52.3 (58.4)
AST, U/L	45.7 (43.1)	50.5 (52.4)
Albumin, g/L	40.3 (6.6)	40.6 (5.4)
Τοταλ βιλιρυβιν, μμολ/Λ	19.4 (11.9)	20.5 (20.9)
LSM, kPa	16.9 (13.0)	18.7 (12.5)
Platelets, $\times$ 10^9/L	145.7 (68.8)	133.7 (67.8)
HVPG, mmHg	10.4 (6.1)	-
Follow-up, month, Median (IQR)	-	39.0 (25.2-55.2)
Child-Pugh, N, %		
A	138 (91.4)	1050 (95.3)
B	13 (8.6)	52 (4.7)
Etiology, N, %		
Viral	89 (58.9)	834 (75.7)
ALD	28 (18.5)	54 (4.9)
NASH	16 (10.6)	105 (9.5)
Other	18 (11.9)	109 (9.9)

*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.

Model	**Cutoff**	**Patients**	**HVPG-proved CSPH patients**	**Performance**

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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 [?]150×10^9/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 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.

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

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

Data are presented as n or n (%).

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

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

Study	Variable
Dajti E & Ravaioli F /2022/Italy	Liver stiffness measurement by transient elastography
Dajti E & Ravaioli F /2022/Italy	Spleen stiffness measurement by transient elastography
Dajti E & Ravaioli F /2022/Italy	Platelets
Banini BA & Patel S/2022/USA	Liver stiffness measurement by transient elastography
Banini BA & Patel S/2022/USA	Platelets
Jiang F/2021/China	Liver stiffness measurement by transient elastography
Jiang F/2021/China	Platelets
Jiang F/2021/China	Varices
Jasen C & Bogs C/2016/ Europe	Liver stiffness measurement by two-dimensional shear wave elastography
Jasen C & Bogs C/2016/ Europe	Spleen stiffness measurement by two-dimensional shear wave elastography
Jasen C & Bogs C/2016/ Europe	Platelets
Kim TY & Jeong WK/2015/ Korea	Liver stiffness measurement by two-dimensional shear wave elastography
Kim TY & Jeong WK/2015/ Korea	Platelets

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Kitson MT/2015/Australia	Liver stiffness measurement by transient elastography
Kitson MT/2015/Australia	International normalised ratio

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sTable 3. Baseline characteristics of high-risk CSPH cohort.

Parameters*	**Patients with high-risk CSPH and treated by carvedilol (n=51)**	**Patients with high-risk CSPH and without NSBBs before PSM (n=613)**	**p**	**Patients with high-risk CSPH and without NSBBs after PSM (n=102)**	**p**
Age, years	52.8 (10.1)	56.5 (11.3)	0.026	52.8 (10.0)	0.986
Male, N, %	35 (68.6)	396 (64.6)	0.563	68 (66.7)	0.807
ALT, U/L	28.7 (25.1)	51.4 (58.6)	<0.001	28.3 (14.4.2)	0.906
AST, U/L	32.4 (15.5)	55.2 (57.9)	<0.001	33.0 (15.8)	0.813
Albumin, g/L	43.4 (5.1)	39.0 (5.6)	<0.001	43.2 (4.6)	0.776
Τοταλ βιλιρυβιν, μμολ/Λ	24.1 (15.3)	22.8 (25.3)	0.732	23.3 (14.1)	0.773
LSM, kPa	19.4 (11.1)	24.9 (13.5)	0.005	19.3 (11.8)	0.983
Platelets, $\times 10^9$/L	78.3 (35.2)	99.0 (44.2)	0.001	73.7 (31.8)	0.417
CSPH risk model	1.06 (0.96)	1.38 (1.26)	0.079	1.09 (1.04)	0.857
Follow-up, month	38.0 (23.0-44.0)	38.0 (25.0-53.5)	0.149	28.6 (22.7-47.0)	0.542
Child-Pugh, N, %			0.824		0.584
A	48 (94.1)	572 (93.3)		98 (96.1)	
B	3 (5.9)	41 (6.7)		4 (3.9)	
Etiology, N, %			<0.001		1.000
Viral	51 (100.0)	436 (71.1)		102 (100.0)	
ALD	-	35 (5.7)		-	
NAFLD	-	68 (11.1)		-	
other	-	74 (12.1)		-	

*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.

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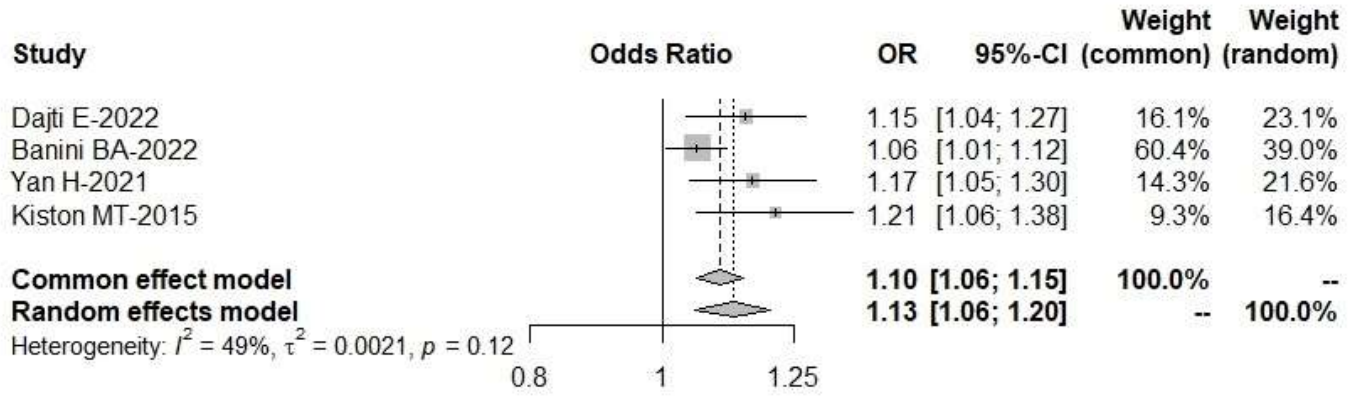
A



B

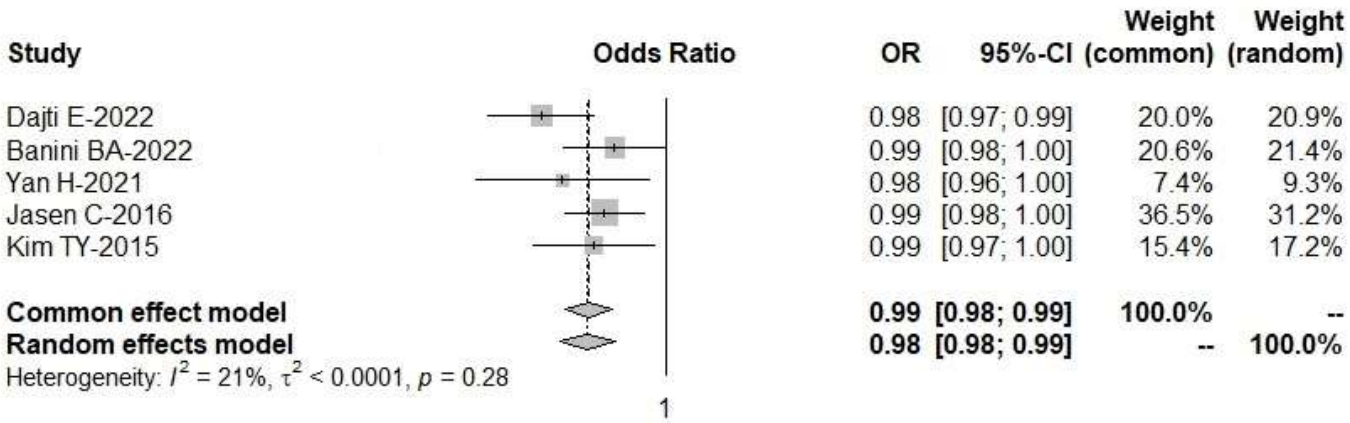


Figure 1: Pooled risk ratios and their corresponding 95% confidence intervals of liver stiffness measurement (A) and platelets (B) for predicting clinically significant portal hypertension.

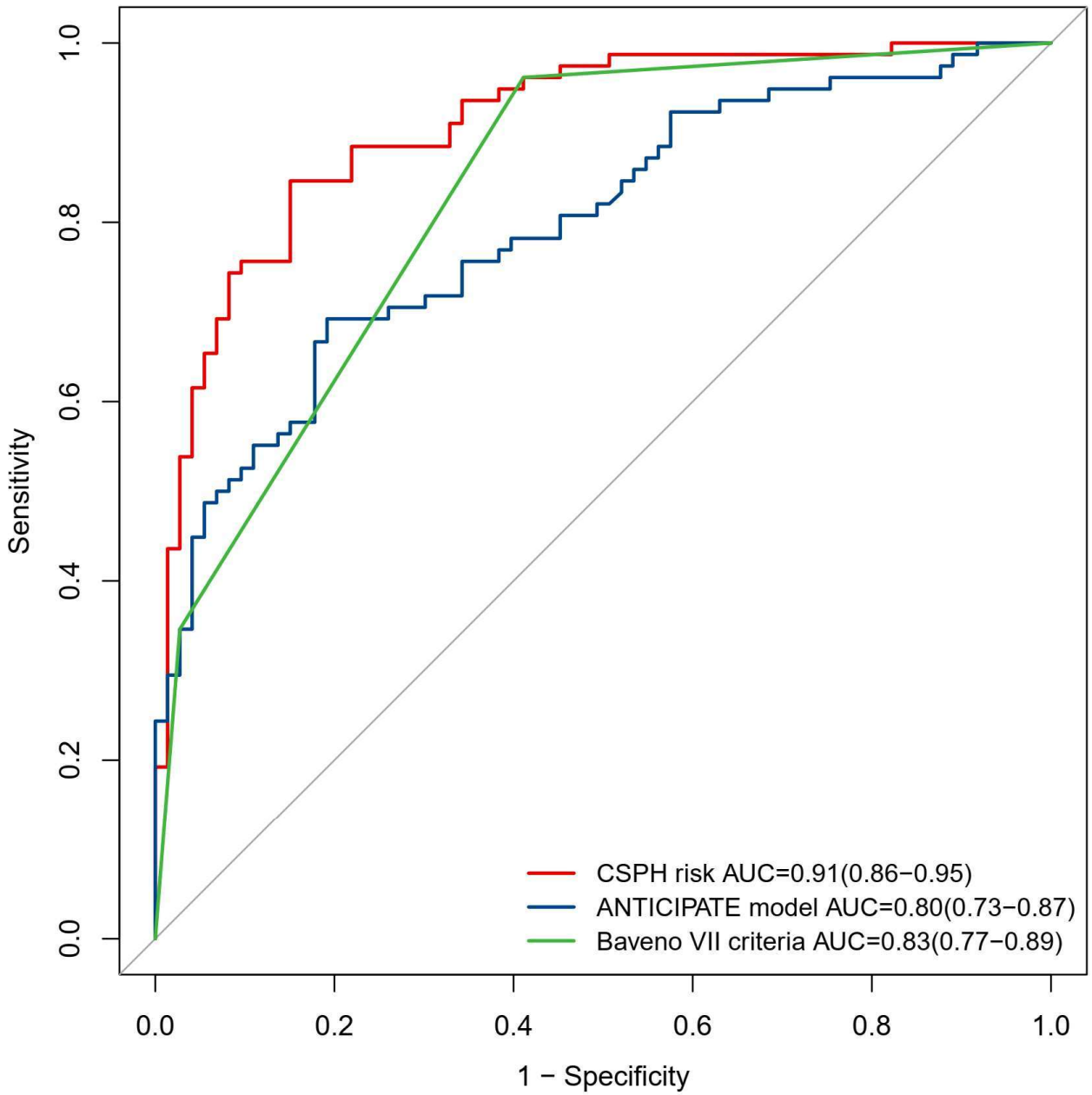
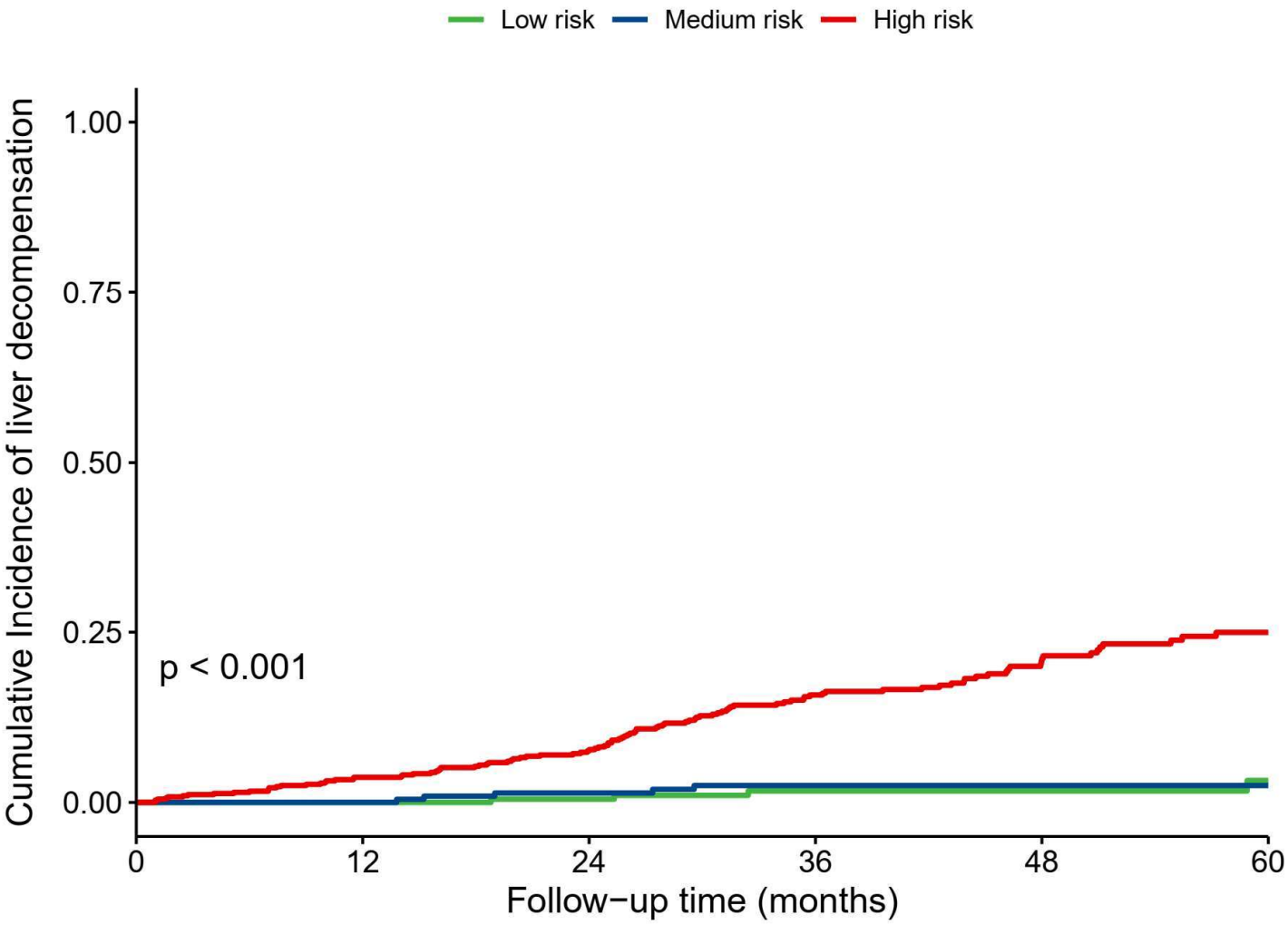


Figure 2: Performance of difference models for diagnosis of clinically significant portal hypertension.



Number at risk

248	226	187	142	96	62
241	222	195	149	97	58
613	555	471	328	204	122

Figure 3. The cumulative incidence of liver decompensation in follow-up cohort.

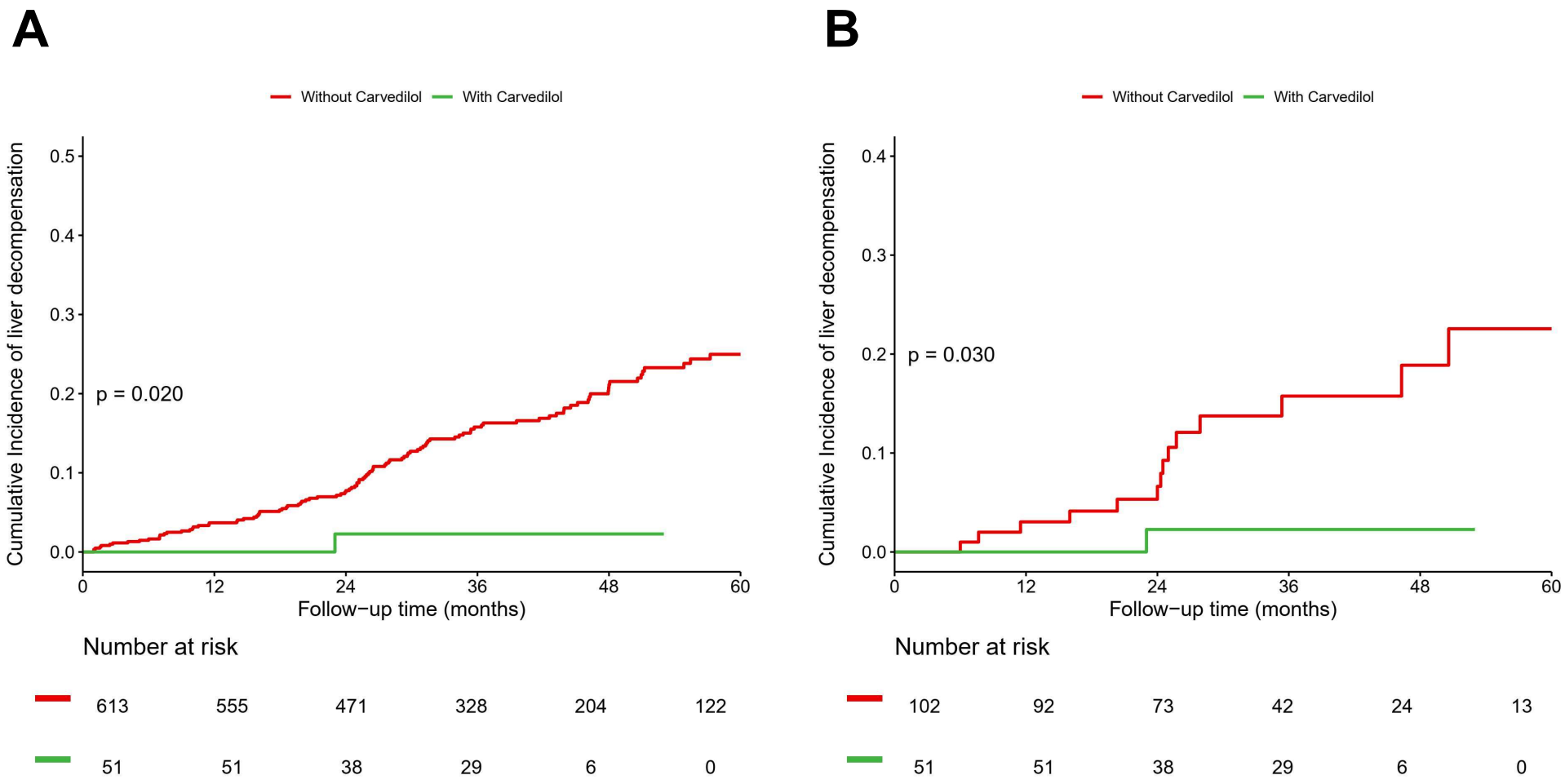


Figure 4. Decompensation according to treatment group. A: cumulative incidence of decompensation before PSM; B: cumulative incidence of decompensation after PSM;