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MASLD risk stratification according to KASL algorithm

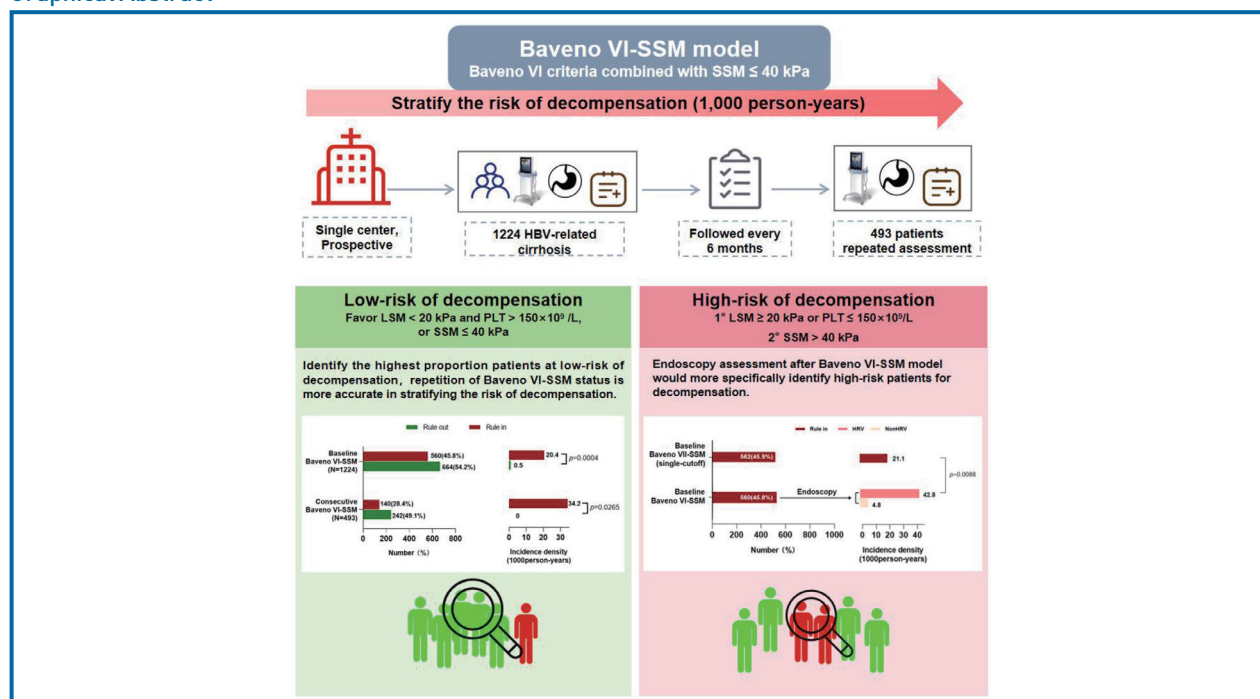
Switching TDF to besifovir
DAA therapy for HCC patients
Baveno VII algorithm stratifies prognostic risk
FIB-4plus score for high-risk varix in compensated cirrhosis

Baveno VI-SSM stratifies the risk of portal hypertension-related events in patients with HBV-related cirrhosis

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Graphical Abstract



Study Highlights

- With the addition of the SSM to the Baveno VI criteria (LSM <20 kPa and platelet count >150/μL), the Baveno VI-SSM (Baveno VI criteria combined with SSM ≤40 kPa) can identify more HBV-related cirrhosis patients at very low risk of decompensation (<1.0 per 1,000 person-years) than other non-invasive models. Reassessment of Baveno VI-SSM is more accurate in stratifying patients at low risk of EV progression and decompensation.
- Endoscopy assessment after Baveno VI-SSM model would more specifically identify high-risk patients for decompensation compared with other non-invasive models.

Background/Aims: Cirrhotic patients with liver stiffness measurement (LSM) <20 kPa and platelet count $\geq 150 \times 10^9/L$ (Baveno VI criteria), otherwise spleen stiffness measurement (SSM) ≤ 40 kPa (Baveno VI-SSM criteria) can avoid endoscopy screening; however, no prospective data for their hepatic outcomes.

Methods: Compensated cirrhosis with HBV were prospectively enrolled from April 2019 to April 2022 and followed until July 2023. All patients underwent LSM, SSM and esophagogastroduodenoscopy assessment.

Results: Among 1,224 patients enrolled with median follow-up of 30 months (interquartile range, 21–42), the incidence of decompensation was greater in 560 patients with unfavored Baveno VI criteria (0.5 vs. 20.4 per 1,000 person-years, $P=0.0004$) than that in 664 patients with favored Baveno VI-SSM criteria. The Baveno VI-SSM model identified more patients (54.2%) as low-risk for decompensation than Baveno VII-SSM model (single cutoff) (48.4%, $P=0.004$) and than Baveno VI criteria (34.6%, $P<0.0001$) did. Patients with high-risk varices diagnosed via endoscopy following Baveno VI-SSM model assessment had greater probability of decompensation compared to those identified by the Baveno VII-SSM model (single cutoff) (42.8 vs. 21.1 per 1,000 person-years, $P=0.0088$). Additionally, among the 493 patients who underwent endoscopic re-assessment, 242 patients with favored Baveno VI-SSM criteria had much lower incidence of EV progression (2.6 vs. 99.5 per 1,000 person-years, $P=0.0004$) and lower risk of decompensation compared to 140 patients with unfavored Baveno VI-SSM model (0 vs. 34.2 per 1,000 person-years, $P=0.0256$).

Conclusions: Baveno VI-SSM model could identify HBV-related cirrhosis patients at low risk of decompensation, which was greatly improved upon Baveno VI-SSM reassessment. (*Clin Mol Hepatol* 2025;31:866-880)

Keywords: Liver cirrhosis; Baveno VI-SSM; Portal hypertension; Decompensation; Chronic hepatitis B

INTRODUCTION

The Baveno VI consensus has recommended that patients with a liver stiffness measurement (LSM) <20 kPa and platelet count (PLT) $>150 \times 10^9/L$ (Baveno VI criteria) are very unlikely to have high-risk varices (HRVs) in compensated liver cirrhosis or advanced chronic liver disease

(ACLD),¹ which has been validated by dozens of cross-sectional studies.²⁻⁷ Further studies have validated that the Baveno VI criteria are able to avoid esophagogastroduodenoscopy (EGD) surveillance²⁻⁴ and differentiate the risk of decompensated events in patients with compensated viral liver cirrhosis or ACLD patients.⁸ The Baveno VII consensus recommends repeated elastography assessment an-

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Abbreviations:

ACLD, advanced chronic liver disease; BMI, body mass index; CSPH, clinically significant portal hypertension; EGD, esophagogastroduodenoscopy; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HRV, high-risk varices; HVPG, hepatic venous pressure gradient; IQR, interquartile range; LSM, liver stiffness measurement; NSBB, nonselective beta blockers; PH, portal hypertension; PLT, platelet count; SSM, spleen stiffness measurement; TE, transient elastography

nually in compensated ACLD patients.⁹

Spleen stiffness measurement (SSM) has emerged as an accurate diagnostic tool to assess portal hypertension (PH) and esophageal varices (EVs), alone or in combination with the Baveno VI criteria.^{3,5,10} Currently, the Baveno VII consensus recommends that the Baveno VI criteria combined with SSM ≤ 40 kPa (the Baveno VI-SSM model) can be used to identify subjects with a low probability of HRVs and that EGD can be avoided.⁹ An increasing number of patients with liver cirrhosis undergo this noninvasive screening to avoid EGD screening. Our timely data have validated that the Baveno VI-SSM model can safely avoid more than half of the EGDs screening in hepatitis B virus (HBV)-related cirrhosis patients, regardless of their antiviral status.¹¹ However, whether the Baveno VI-SSM model is appropriate for avoiding EGD surveillance in liver cirrhosis patients, or to stratify the risks of PH-related events, including varices progression and decompensation events (ascites, variceal bleeding or hepatic encephalopathy), needs prospective data. Encouragingly, other SSM-based models have shown good performance for diagnosing clinically significant portal hypertension (CSPH)¹² and stratifying the risk of hepatic decompensation¹³ in patients with compensated ACLD.

With a prospective cohort of HBV-related cirrhosis patients undergoing regular follow-up, the present study aimed (1) to evaluate the correlation between the baseline Baveno VI-SSM or other noninvasive models and portal hypertension-related events (including varices progression and decompensation events); and (2) to investigate the relevance of repetition of the Baveno VI-SSM or other noninvasive model assessments in stratifying EV progression and decompensation.

MATERIALS AND METHODS

Study population and design

The present study was a prospective cohort study that enrolled consecutive patients with cirrhosis willing to participate in our investigation at the hepatology unit of Nanfang Hospital, China. According to the approved study protocol (Clinical Trials.gov: NCT04123509; NCT04890730), all patients underwent LSM, SSM, and EGD at enrolment.

The study protocol was performed in accordance with the ethical guidelines of the Declaration of Helsinki (2013) and was approved by the Institutional Review Boards of Nanfang Hospital (NFEC-201901-K14 for the index approval; NFEC-202009-K6 for approval of the updated protocol). Written informed consent was obtained from all study patients.

Patient selection and follow-up

Patients were enrolled from April 2019 to April 2022 and were followed every 6 months until July 2023. Cirrhotic patients aged between 18 years and 75 years with evidence of cirrhosis diagnosis based on imaging evidence or histological evaluation with liver biopsy¹⁴ were considered for inclusion. The main exclusion criteria for this current analysis were: previous or present decompensation, Child-Turcotte-Pugh C or those with mild ascites, noncirrhotic patients, acute or chronic portal vein thrombosis, splenectomy, past or current hepatocellular carcinoma (HCC) and those who had undergone the transjugular intrahepatic portosystemic shunt procedures. Additionally, patients with chronic liver disease etiology except for hepatitis B were also excluded.

Patients were regularly monitored at the clinic every 6 months to systematically evaluate their condition, and individuals who missed their appointments were contacted by telephone. Liver-related events, including decompensation events (development of clinically significant ascites, bleeding due to portal hypertensive sources, or overt hepatic encephalopathy), HCC development and death, were documented. Patients with ongoing antiviral therapy were evaluated for their antiviral responses, as previously described.⁵

Transient elastography assessment and esophagogastroduodenoscopy

All enrolled patients underwent transient elastography (TE) and EGD at baseline. LSM and SSM were assessed via TE (FibroScan® 502 apparatus with a 50 Hz 'M' probe; Echosens, Paris, France). The reliable criteria for LSM and SSM assessment were consistent with those of previous study.⁵

Upper endoscopic examinations (Evis Lucera CV-290; Olympus, Tokyo, Japan) were performed by skilled endos-

copists during this study period. The EGD findings were recorded in a standard format and the EVs were graded according to the international guidelines.⁹ The median time interval between EGD and TE monitoring was 0 days (range, 0–2 days).

Esophageal varices progression

During follow-up, patients will be monitored for EVs by TE and PLT according to the Baveno VII consensus,⁹ and some patients will also be monitored by EGD due to their condition. EV progression was defined as the occurrence of grade 2 or 3 EV in patients with no prior EV or grade 1 EV or the occurrence of grade 3 EV in patients with initial grade 2 EV.⁴

Baveno VI-SSM model and other non-invasive models

Baveno VI criteria were defined as LSM <20 kPa and PLT $\geq 150 \times 10^9/L$ to rule out HRV;¹ and combined Baveno VI-SSM model was defined as subjects who favor Baveno VI criteria could avoid EGD, otherwise, subjects with SSM ≤ 40 kPa could also avoid EGD assessment.^{9,11}

The Baveno VII model was defined as LSM ≤ 15 kPa and PLT $\geq 150 \times 10^9/L$ to rule out CSPH and LSM ≥ 25 kPa to rule in CSPH; In the combined Baveno VII-SSM dual cutoff model (21–50 kPa), CSPH was ruled out if at least two of the following criteria were present: LSM ≤ 15 kPa, PLT $\geq 150 \times 10^9/L$, and SSM <21 kPa; and it was ruled in if at least two of the following criteria were present: LSM ≥ 25 kPa, PLT $< 150 \times 10^9/L$, and SSM > 50 kPa;^{12,13} In the combined Baveno VII-SSM single cutoff model (40 kPa), CSPH was ruled out if at least two of the following criteria were present: LSM ≤ 15 kPa, PLT $\geq 150 \times 10^9/L$, and SSM ≤ 40 kPa; and it was ruled in if at least two of the following criteria were present: LSM ≥ 25 kPa, PLT $< 150 \times 10^9/L$, and SSM > 40 kPa.¹² We applied these models to rule out CSPH, if CSPH could be neither ruled in nor ruled out, patients were considered to be in the grey zone.

Further performance reassessment of the non-invasive models was conducted in patients with consecutive measurements of EGD, LSM, and SSM.

Statistical analyses

For baseline characteristics, continuous variables are presented as medians and 25% and 75% percentiles, whereas categorical variables are expressed as numbers (%). The characteristics were compared between 2 different patient groups via Student's *t*-test or the Wilcoxon rank sum test for continuous variables. Categorical variables were compared via χ^2 test or Fisher's exact test, if necessary. Features or factors associated with the onset of an EV progression were assessed via the Cox proportional hazards regression method. All factors associated with the risk of the studied outcome at the $P < 0.20$ level according to the univariate analysis were included in the multivariate model. A forward stepwise procedure was then applied to retain features with significance at the $P < 0.05$ level in the final model. The occurrence of hepatic decompensation at 1, 2, and 3 years of follow-up was assessed by calculating the cumulative incidence and compared using Gray's test, considering HCC, death, and liver transplantation as competing events. The intensity of interested events, including EV progression and decompensation events during follow up, was presented as per 1,000 person-years. The incidence density was compared using Poisson regression analysis. All *P*-values were 2-sided, and $P < 0.05$ was considered significant for all tests. All the statistical analyses were conducted using IBM SPSS version 22.0 (IBM, Armonk, NY, USA), GraphPad 8.0 (GraphPad Software, La Jolla, CA, USA), and R version 4.3.1.

RESULTS

Patient baseline characteristics

During the study period, 2,141 patients with liver cirrhosis were screened between April 2019 and April 2022; 885 patients were excluded according to the protocol's exclusion criteria. Considering the nature of long-term treatment that is typically required for chronic hepatitis B, which is distinctly different from hepatitis C, alcoholic related liver disease or metabolic dysfunction-associated steatotic liver disease, we excluded patients with non-hepatitis B in order to maintain patient homogeneity. Additionally, patients with Child-Pugh class C or mild ascites were excluded, and 32

patients were lost to follow-up (Fig. 1). Ultimately, a total of 1,224 patients with HBV-related compensated cirrhosis were included in the current analysis. The median follow-up duration was 30 months (interquartile range [IQR], 21–42) for these patients. Among all the HBV-related liver cirrhosis patients, 81.6% (n=932) had achieved viral suppression under continuous antiviral therapy (Table 1).

The EGD follow-up subcohort included 493 patients who underwent a second EGD and TE assessment over a median follow-up of 17 months (IQR 12–23). Most patients underwent endoscopy and TE on the same day; for those who did not, the maximum interval between the two procedures was no more than one week. Table 1 shows the baseline characteristics of these patients with EGD reassessment, and those without a second EGD assessment are shown in Supplementary Table 1.

Single Baveno VI-SSM assessment could identify patients at low risk of decompensation

Among the 1,224 patients included in the current analysis, 30 patients (2.5%) experienced decompensation episodes during the follow-up period (Supplementary Tables 2, 3), with an incidence intensity of 9.4 per 1,000 person-

years. Among these patients, 15 (46.9%) developed variceal bleeding, 17 (53.1%) developed ascites, and 5 (15.6%) experienced hepatic encephalopathy. Some of these patients had more than one decompensation event. There were 58 patients who received prophylactic therapy including 57 on nonselective beta blocker (NSBB) and 1 with variceal ligation, among whom 6 patients had decompensation events during the study period.

On the basis of the baseline Baveno VI criteria, 424 patients (34.6%) were identified as having a low probability for HRV and could safely avoid EGD. None of these patients experienced decompensation events during follow-up. In contrast, all 30 patients who experienced decompensation were among the remaining 800 patients (65.4%), resulting in an incidence rate of decompensation events of 14.5 per 1,000 person-years, which was significantly higher than that in the low-risk group ($P=0.015$) (Fig. 2A). Under the baseline Baveno VI-SSM, 664 patients (54.2%) were identified as having a low risk for HRV, could avoid EGD screening and had only one decompensation event at 0.5 per 1,000 person-years (Fig. 2A). Conversely, endoscopy screening was considered necessary in 560 patients (45.8%), who had 29 decompensation events at 20.4 per 1,000 person-years, which was significantly greater than

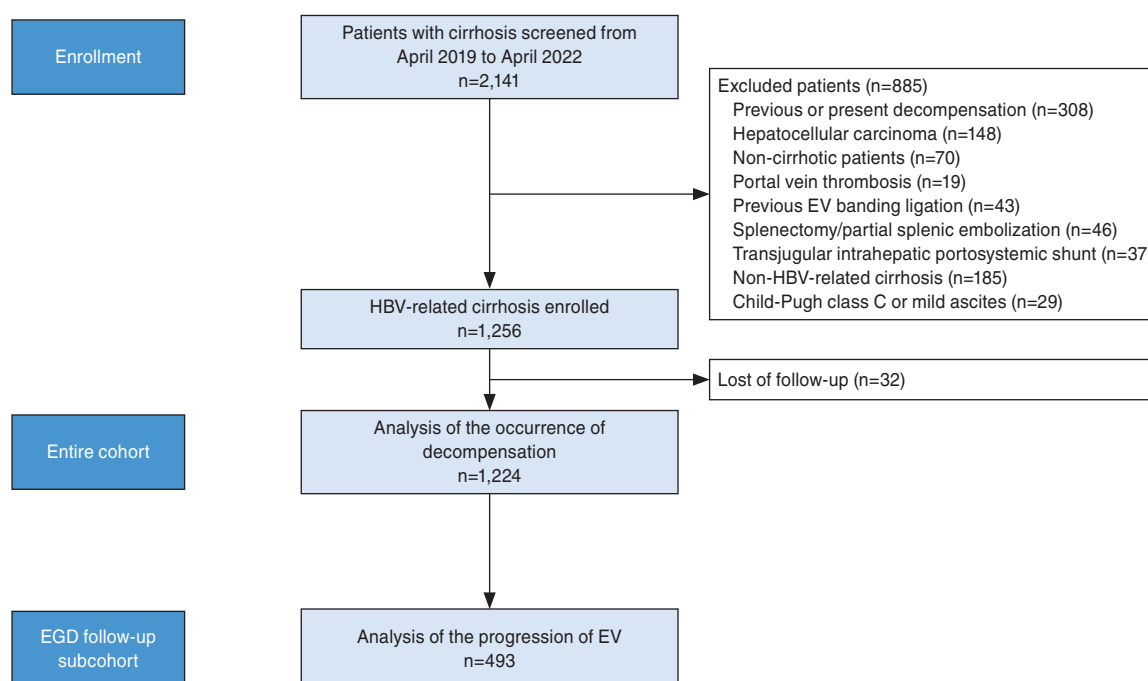


Figure 1. Flowchart for patient selection. EV, esophageal varices; HBV, hepatitis B virus; EGD, esophagogastroduodenoscopy.

that in patients with a favorable Baveno VI-SSM assessment ($P=0.0004$) (Fig. 2A). The baseline characteristics of patients classified as low and high risk by the Baveno VI-SSM model were exhibited in Supplementary Table 4. Fur-

ther analysis revealed that a greater proportion of patients at low risk for decompensation were identified by the Baveno VI-SSM model than by the Baveno VI criteria (54.2% vs. 34.6%, $P<0.0001$) (Fig. 2B).

Table 1. Baseline characteristics of the entire cohort or EGD follow-up subcohort in patients with HBV-related cirrhosis

Characteristic	Entire cohort (n=1,224)	EGD follow-up subcohort (n=493)
Age (yr)	48 (41–55)	48 (41–53)
Male sex	1,006 (82.2)	418 (84.8)
Body mass index (kg/m ²)	23.5 (21.3–25.8)	23.6 (21.1–25.7)
Antiviral therapy		
Past or ongoing antiviral treatment	1,142 (93.3)	479 (97.2)
Achieved viral suppression	932 (81.6)	396 (82.7)
Maintained viral responses duration (mo)	29 (7–65)	30 (10–68)
Child-Turcotte-Pugh score		
A	1,113 (90.9)	463 (93.9)
B	111 (9.1)	30 (6.1)
MELD score	7.4 (6.4–9.1)	7.2 (6.4–8.6)
Laboratory results		
Platelet counts (×10 ⁹ /L)	131 (89–180)	132 (94–178)
International normalized ratio	1.0 (1.0–1.1)	1.0 (0.9–1.1)
Aspartate aminotransferase (U/L)	27 (22–37)	26 (22–34)
Alanine aminotransferase (U/L)	28 (20–40)	27 (20–38)
Total bilirubin (μmol/L)	15.0 (11.2–22.3)	14.9 (11.1–20.4)
Albumin (g/L)	44.0 (40.0–46.6)	44.6 (41.7–46.8)
Creatinine (μmol/L)	76 (66–87)	76 (67–85)
Non-invasive tests		
LSM (kPa)	12.0 (7.8–20.7)	11.8 (8.0–18.2)
SSM (kPa)	43.6 (27.7–66.8)*	44.8 (28.5–66.2) [†]
Favor Baveno VI criteria	424 (34.6)	174 (35.3)
Favor Baveno VI-SSM model	664 (54.2)	270 (54.8)
EV		
No varices	414 (33.8)	168 (34.1)
Grade 1	569 (46.5) [‡]	224 (45.4) [§]
Grade 2	118 (9.6)	53 (10.8)
Grade 3	123 (10.0)	48 (9.7)
High-risk varices	247 (20.2) [‡]	102 (20.7) [§]
Follow-up time (mo)	30 (21–42)	17 (12–23)

Values are presented as median (interquartile range) or number (%).

EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; MELD, model for end-stage liver disease; LSM, liver stiffness measurement; SSM, spleen stiffness measurement; EV, esophageal varices.

*Twenty-three were invalid spleen stiffness measurements.

[†]Thirteen were invalid spleen stiffness measurements.

[‡]Six cases were grade 1 EV with red sign in the screening EGD.

[§]One cases were invalid spleen stiffness measurements.

We further explored the performance of other noninvasive models based on LSM with or without SSM, including the Baveno VII model, the Baveno VII-SSM model (dual cutoff) and the Baveno VII-SSM model (single cutoff) for CSPH differentiation, in identifying the probability of future

decompensation in our patients. The Baveno VII model (LSM <15 kPa and PLT >150×10⁹/L) at baseline identified 32.4% (396/1,224) of the overall patients as non-CSPH patients, none of whom experienced decompensation events during follow-up. The baseline Baveno VII-SSM model

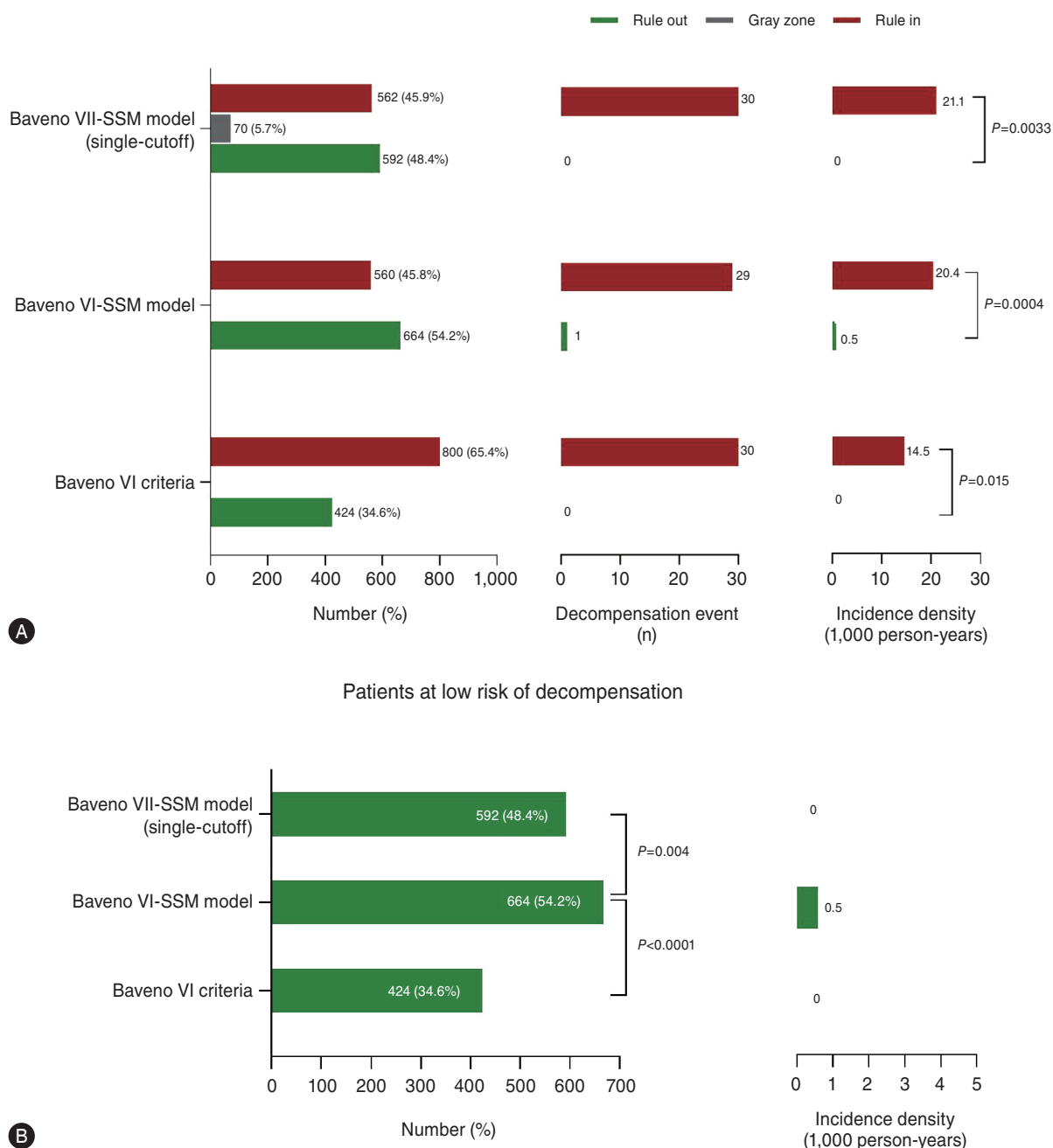
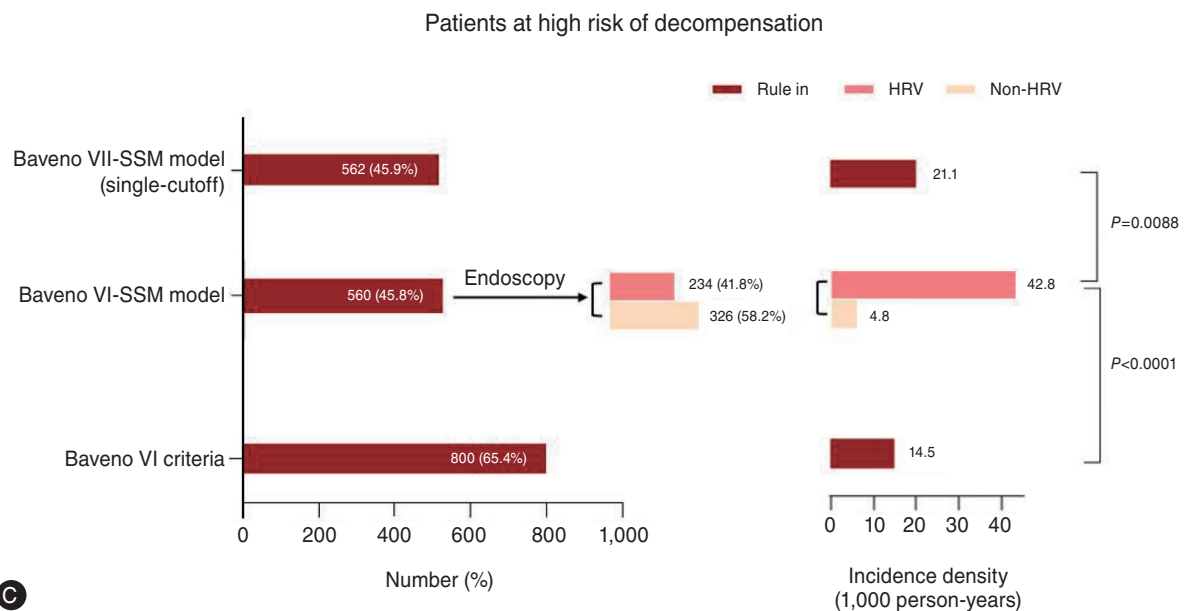


Figure 2. Occurrences of decompensation event upon baseline status of non-invasive models in HBV-related cirrhosis. (A) Occurrences of decompensation event upon baseline status of three non-invasive models in entire cohort. (B) Occurrences of decompensation event in rule-out group. (C) Occurrences of decompensation event in rule-in group. HBV, hepatitis B virus; SSM, spleen stiffness measurement; HRV, high-risk varices.



C
Figure 2. Continued.

(dual cutoff) classified 34.6% (424/1,224) of the total patients as low risk for CSPH, with no decompensation events documented during the study, whereas the Baveno VII-SSM model (single-cutoff) identified 592 patients (48.4%) as low-risk, all of whom also showed no development of decompensation (Table 2, Supplementary Fig. 1). Among these three noninvasive models for CSPH differentiation, the Baveno VII-SSM model (single-cutoff) demonstrated the greatest ability to identify patients at low risk of decompensation during the study period (Table 2, Supplementary Fig. 1). However, the Baveno VII-SSM model (single-cutoff) identified fewer patients at low risk of decompensation compared with the Baveno VI-SSM model (48.4% vs. 54.2%, $P=0.004$) (Fig. 2B). The cumulative incidence rate of decompensation among low-risk patients identified by the Baveno VI-SSM model at 1, 2, and 3 years was 0%, 0.17%, and 0.17%, respectively (Supplementary Table 5).

Moreover, we explored the potential of noninvasive models in the stratification of EV progression. In the EGD follow-up subcohort ($n=493$), 23 patients (4.7%) experienced EV progression during follow-up, with an incidence rate of 30.3 per 1,000 person-years. The baseline characteristics of patients with EV progression are shown in Supplementary Table 6.

Patients with favored Baveno VI criteria (35.3%, 174/493)

had a significantly lower rate of EV progression than those (64.7%, 319/493) with unfavored Baveno VI criteria (3.6 vs. 45.4 per 1,000 person-years, $P=0.0113$) (Supplementary Fig. 2). Similarly, patients with favored Baveno VI-SSM status (54.8%, 270/493) presented a lower EV progression rate compared to those (45.2%, 223/493) with unfavored Baveno VI-SSM status (7.1 vs. 59.7 per 1,000 person-years, $P=0.0004$) (Supplementary Fig. 2).

Baveno VI-SSM assessment sequential with EGD screening could identify patients at higher risk of decompensation

Among the 560 patients with unfavored Baveno VI-SSM status, endoscopic screening was performed according to the Baveno VII consensus. Among these patients, 326 patients (58.2%) were classified as non-HRV, had no EV or grade 1 EV without red signs, and had a decompensation incidence rate of 4.8 per 1,000 person-years (4.2 per 1,000 person-years for no EV and 5.0 per 1,000 person-years for grade 1 EV). Moreover, HRV was diagnosed in 234 patients (41.8%), who had a decompensation incidence rate of 42.8 per 1,000 person-years (16.1 per 1,000 person-years for grade 2 EV and 72.2 per 1,000 person-years for grade 3 EV) (Fig. 2C). High-risk patients identified by the Baveno VII-SSM model (single-cutoff) had a lower inci-

Table 2. Risk of the decompensation events according to the different non-invasive models based on LSM, SSM, and PLT

Model	Entire cohort (n=1,224)		
	Patient number (%)	Event number (%)	Incidence density (1,000 person-years)
Baveno VI criteria			
Rule out group			
LSM <20 kPa and platelet count >150×10 ⁹ /L	424 (34.6)	0 (0)	0
Rule in group			
LSM ≥20 kPa or platelet count ≤150×10 ⁹ /L	800 (65.4)	30 (3.8)	14.5
Baveno VI-SSM model			
Rule out group			
LSM <20 kPa and platelet count >150×10 ⁹ /L otherwise SSM <40 kPa	664 (54.2)	1 (0.2)	0.5
Rule in group			
LSM ≥20 kPa or platelet count ≤150×10 ⁹ /L sequential SSM ≥40kPa	560 (45.8)	29 (5.2)	20.4
Baveno VII model			
Rule out group			
LSM ≤15 kPa and platelet count ≥150×10 ⁹ /L	396 (32.4)	0 (0)	0
Grey zone group	615 (50.2)	15 (2.4)	9.1
Rule in group			
LSM ≥25 kPa	213 (17.4)	15 (7.0)	29.4
Baveno VII-SSM model (dual-cutoff)			
Rule out group			
Two out of: LSM ≤15 kPa Platelet count ≥150×10 ⁹ /L SSM <21 kPa	424 (34.6)	0 (0)	0
Grey zone group	323 (26.4)	2 (0.6)	2.3
Rule in group			
Two out of: LSM ≥25 kPa Platelet count <150×10 ⁹ /L SSM <50 kPa	477 (39.0)	28 (5.9)	23.2
Baveno VII-SSM model (single-cutoff)			
Rule out group			
Two out of: LSM ≤15 kPa Platelet count ≥150×10 ⁹ /L SSM ≤40 kPa	592 (48.4)	0 (0)	0
Grey zone group	70 (5.7)	0 (0)	0
Rule in group			
Two out of: LSM ≥25 kPa Platelet count <150×10 ⁹ /L SSM <40 kPa	562 (45.9)	30 (5.3)	21.1

Values are presented as number (%).

LSM, liver stiffness measurement; SSM, spleen stiffness measurement; PLT, platelet count.

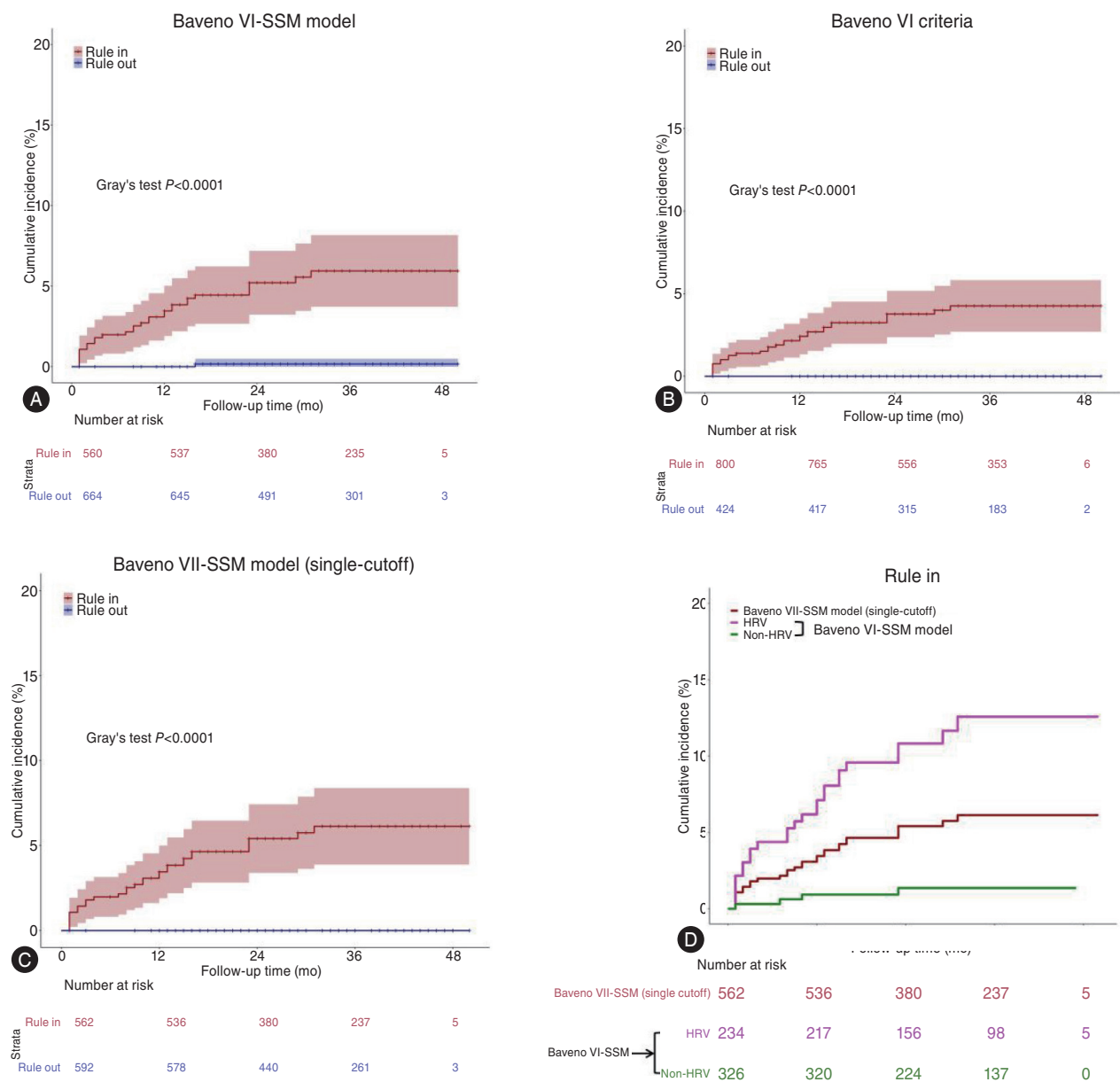


Figure 3. Performance of non-invasive models in stratification of decompensation risk in HBV-related cirrhosis. (A) Probability of decompensation stratified with the Baveno VI-SSM model. (B) Probability of decompensation stratified with the Baveno VI criteria. (C) Probability of decompensation stratified with the Baveno VII-SSM model (single-cutoff). (D) Probability of decompensation stratified in the high-risk decompensation group. HBV, hepatitis B virus; SSM, spleen stiffness measurement; HRV, high-risk varices.

dence rate of decompensation than patients diagnosed with HRV via endoscopy screening following the Baveno VI-SSM assessment (42.8 vs. 21.1 per 1,000 person-years, $P=0.0088$) (Fig. 2C).

The cumulative incidence rate of decompensation among high-risk patients identified by the Baveno VI-SSM model at 1, 2, and 3 years were 3.5%, 5.2%, and 5.9%, respectively (Supplementary Table 5, Fig. 3A). The cumulative in-

cidence of decompensation for patients with unfavored Baveno VI criteria is shown in Supplementary Table 5 and Figure 3B. The cumulative incidence of decompensation for patients with unfavored Baveno VII-SSM model (single-cutoff) is presented in Supplementary Table 5 and Figure 3C. Figure 3D shows that patients diagnosed with HRV after the Baveno VI-SSM sequential endoscopy screening had a greater cumulative incidence of decompensation

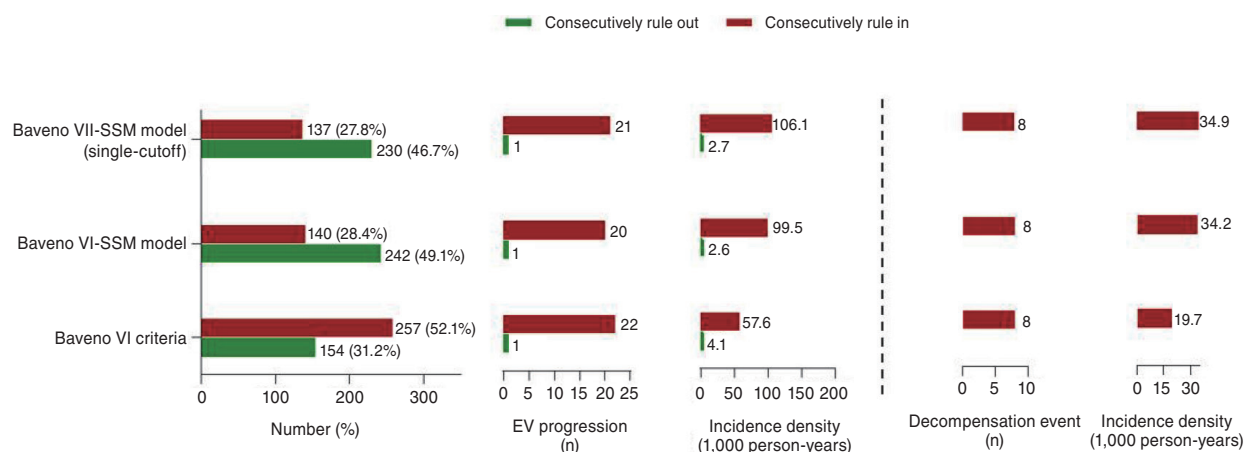


Figure 4. Stratify the risk of EV progression and future decompensation based on consecutive non-invasive models in the EGD follow-up subcohort. EV, esophageal varices; EGD, esophagogastroduodenoscopy; SSM, spleen stiffness measurement.

compared to those identified by the Baveno VII-SSM model (single-cutoff) ($P < 0.0001$).

Longitudinal assessments of the Baveno VI-SSM could stratify the risks of portal hypertension-related events

In the EGD follow-up subcohort, all 493 patients with HBV-related cirrhosis underwent a second TE assessment. Worsened Baveno VI-SSM status was found in 28 of the 270 patients who had a favored Baveno VI-SSM status at baseline (Supplementary Fig. 3), primarily due to an increase in SSM ($P < 0.0001$) (Supplementary Fig. 4), with all SSM values exceeding 40 kPa. The remaining 89.6% (242/270) of patients maintained a favored Baveno VI-SSM status at the second assessment, with only one case of EV progression, resulting in an incidence of 2.6 per 1,000 person-years, and no cases of decompensation were observed (Supplementary Fig. 3, Fig. 4).

Moreover, among the 223 patients with unfavored Baveno VI-SSM status at baseline, 140 (62.8%) remained with unfavored Baveno VI-SSM status at the second assessment (Supplementary Fig. 3), and HRV was diagnosed in 85 patients (60.7%). Among these 140 patients, 20 experienced EV progression, with an incidence rate of 99.5 per 1,000 person-years, and 8 developed decompensation events, resulting in an incidence rate of 34.2 per 1,000 person-years. Compared with patients with favored Baveno VI-SSM assessments at baseline and the second assessments, those with consecutive unfavored Baveno VI-SSM

assessments had a significantly higher rate of EV progression (99.5 vs. 2.6 per 1,000 person-years, $P = 0.0004$) and a greater incidence of decompensation (34.2 vs. 0 per 1,000 person-years, $P = 0.0265$).

DISCUSSION

Through this prospective cohort limited to patients with HBV-related compensated cirrhosis, we demonstrated that a single Baveno VI-SSM assessment was able to identify patients at very low risk of decompensation within 1 year. Additionally, longitudinal Baveno VI-SSM assessment confirmed that patients with favored Baveno VI-SSM status would have an extremely low risk of decompensation. We further demonstrated that Baveno VI-SSM sequential endoscopy assessment strategy would identify patients with a greater probability of decompensation than other noninvasive tests for CSPH.

The Baveno VII consensus recommends yearly repetition of TE and PLT monitoring for patients with no EV or grade 1 EV.⁹ This approach is increasingly being adopted, sparing many patients with cirrhosis from undergoing invasive endoscopic EV testing. This motivated us to validate the prognostic values of noninvasive models (including the models for ruling out HRV or CSPH) in patients with HBV-related cirrhosis.

All international guidelines recommend antiviral therapy for patients with HBV-related liver cirrhosis to reduce the occurrence of decompensation.¹⁵⁻¹⁷ The majority of our pa-

tients achieved viral suppression with ongoing anti-HBV therapy; however, even among these patients, EV progression and decompensation can still occur, albeit at a low incidence. Consistent with published data,¹⁸ our findings show that HBV-related compensated cirrhosis patients have a relatively low incidence of decompensation. The Baveno VI criteria, such as LSM <15 kPa and PLT >150/ μ L, are recommended for the exclusion of CSPH.⁹ Our data support this, as patients with the favored Baveno VI criteria experienced decompensation events at a rate of 0.0 per 1,000 person-years. We found that those with LSM <25 kPa had a low risk of decompensation, whereas LSM $\geq$ 25 kPa indicated a persistent risk of decompensation, which is consistent with the findings of a previous European cohort study with patients under long-term HBV suppression (>12 months).¹⁹

SSM is a promising surrogate marker of portal hypertension, and patients with SSM $\leq$ 40 kPa are supposed to be free of clinically significant portal hypertension (CSPH);¹² moreover, endoscopy screen for HRVs could be avoided. With the addition of the SSM to the Baveno VI criteria, the Baveno VI-SSM model could identify more patients at low risk of decompensation during follow-up, where SSM <40 kPa plays a major role. Patients with favored Baveno VI-SSM status were found to have a low risk of decompensation at a rate of 0.5 per 1,000 person-years, which was supposed to be discharged from portal hypertension surveillance as incidence rate lower than 1.0 per 1,000 person-years. Additionally, no decompensation events were observed in these patients within the first year, suggesting that annual repetition of LSM and SSM would be necessary during longitudinal follow-up. In our subcohort with repeated LSM and SSM assessments, we found that patients with consecutive favored Baveno VI-SSM status experienced no decompensation events during the study, further supporting the need for repeated LSM and SSM to stratify the risk of decompensation in patients with HBV-related cirrhosis.

These patients with favored Baveno VI-SSM status were able to avoid invasive portal hypertension surveillance, such as EGD surveillance or hepatic venous pressure gradient (HVPG) measurement. While the Baveno VII-SSM model (single cutoff) was able to identify patients with a low risk of decompensation during the study; it did not identify as many as Baveno VI-SSM model. Therefore, our data

endorsed that the Baveno VI-SSM model is valuable for identifying patients with HBV-related cirrhosis at low risk of decompensation who were discharged from portal hypertension screening and surveillance. However, further prospective studies with larger sample sizes are warranted for validation in patients with liver cirrhosis or ACLD, particularly with long-term follow-up.

Moreover, a model that can identify patients at high risk for decompensation is urgently needed. In our cohort, patients with unfavored Baveno VI-SSM status had a decompensation incidence of 20.4 per 1,000 person-years. The Baveno VII-SSM model (single cutoff) was also able to identify patients with a decompensation probability of 21.1 per 1,000 person-years, which was comparable to the Baveno VI-SSM model and indicated that portal hypertension surveillance including HVPG measurements was warranted. However, it is important to recognize that HVPG are not as easily accessible as endoscopy in the majority of centers.

We then tested the workup based on the Baveno VI-SSM. After low-risk patients were identified using the Baveno VI-SSM model, the remaining patients were recommended to undergo endoscopy screening or surveillance. In our study, HRV were diagnosed in patients with unfavored Baveno VI-SSM status, who had a significantly greater probability of decompensation at 42.8 per 1,000 person-years compared to the Baveno VII-SSM model (single cutoff) did. Considering that HRV is a commonly recommended indicator for carvedilol or other NSBBs,^{1,9} the Baveno VI-SSM followed by endoscopy was able to accurately identify patients who require NSBBs.

Repetition of LSM and SSM assessment during follow-up was able to identify minor portion of patients in our cohort with unfavored Baveno VI-SSM status, indicating the need for endoscopy screening or surveillance. For patients with consecutively unfavored Baveno VI-SSM status, the incidence of EV progression was high, further suggesting that endoscopy surveillance is necessary for such patients after repeated LSM and SSM assessment. Patients for whom the Baveno VI-SSM status is unfavored and who are diagnosed with HRV through endoscopy should receive treatment, whereas non-HRV patients should be closely monitored and managed.

This approach enables the development of a comprehensive management strategy for cirrhotic patients, ensuring

better patient compliance and significant savings in health-care resources, especially in hospitals that are not equipped to perform HVPG measurements. Additionally, this approach could broaden the indications for noninvasive screening in patients with chronic liver disease. Considering the cost and easy access of TE, the value of longitudinal Baveno VI-SSM assessment in patients with liver cirrhosis in terms of EV status and decompensation risk warrants further study. Currently, HRV remains the primary indication for prophylactic therapy with NSBB in cirrhosis patients. However, it is important to note that, in clinical practice, very few patients are able to adhere to NSBB therapy due to contraindications, poor compliance, or physician decision. Future research can focus on non-invasive methods to identify patients at high risk of decompensation, potentially enabling earlier initiation of NSBBs treatment.

Our study had several limitations. First, the patients in our cohort were limited to those with HBV-related cirrhosis, so it remains unclear whether the Baveno VI-SSM model would retain its performance in patients with liver cirrhosis caused by other etiologies. Second, our cohort did not have a long enough follow-up period to fully illustrate the EV outcomes. However, even with a relatively short follow-up, we observed significantly more EV progression in rule-in group patients by the Baveno VI-SSM model, especially in those who were consecutively ruled in by the Baveno VI-SSM model. Third, there are certain technical challenges associated with performing SSM, such as a small-diameter spleen and obesity, which may limit the success of achieving effective measurements. However, Asians tend to have a lower body mass index (BMI), which could potentially improve the success rate of SSM. In our cohort, the SSM failure rate was very low at 1.8%, which we consider acceptable and possibly attributable to the lower BMI of our patients. The application of the Baveno VI-SSM warrants future studies in various clinical scenarios, particularly those involving cirrhotic patients who are obese. Additionally, SSM was assessed with the liver-dedicated probe in our patients, while the spleen-dedicated probe is market available nowadays, the performance of SSM@100 Hz in differentiating EV progression or decompensation occurrences would warrant future studies in various clinical scenarios. Furthermore, the sample size for the EGD follow-up subcohort was not large enough to achieve more than 30

EV progression events. In fact, physicians were more reluctant to order endoscopy assessments for their liver cirrhosis patients since the publication of the Baveno VII consensus, especially for a second endoscopy evaluation. Nevertheless, our cohort is the largest to date regarding endoscopy surveillance in patients with HBV-related liver cirrhosis, highlighting that EV progression is not negligible in patients with unfavorable Baveno VI-SSM status. Additionally, very few patients in our cohort are able to adhere to NSBB therapy due to contraindications, poor compliance, or physician decisions. In clinical practice, it is crucial to raise awareness among healthcare providers and guide patients toward initiating treatment as early as possible.

In conclusion, our results indicate that the Baveno VI-SSM model is a valuable prognostic tool for categorizing patients on the basis of their risk of EV progression and future decompensation. The Baveno VI-SSM model can safely spare more patients from unnecessary EGD, and when combined with endoscopy screening, it can effectively stratify high-risk patients for appropriate treatment. We have provided evidence that repetition of the Baveno VI-SSM is a safe approach for identifying patients at low risk of EV progression and decompensation. Prospective, larger studies are needed to further evaluate the performance of the Baveno VI-SSM in the management of portal hypertension surveillance.

Authors' contribution

Jinjun Chen: concept and design, acquisition of funding, supervision, review and edit; Haiyu Wang: concept and design, acquisition of funding, methodology, investigation, data collection, data analysis and writing of the article, review and edit; Weihao Liang, Ling Zhou, Biao Wen, and Jiakang Song: investigation, data collection; Qiaoping Wu: data collection, operating transient elastography; Yuanjian Zhang, Xiaofeng Zhang, Haoran Ke, Yujun Tang, Fuyuan Zhou, Youfu Zhu, Weiqun Wen, Zhihua Liu, Yali Ji, Qintao Lai, Qinqun He, Wenfan Luo, Tingting Qi, Miaoxia Liu, Xiaoqin Lan, Yongpeng Chen, Ranran Xi, Junting Wan, Lin Dai, and Yuan Li: methodology, investigation.

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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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