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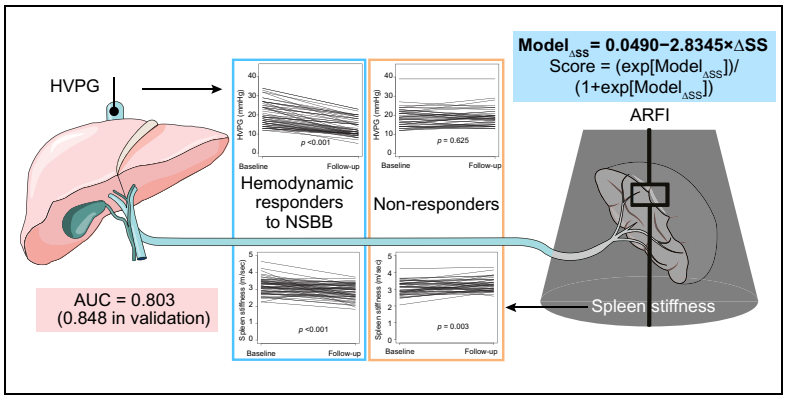
Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices

Graphical abstract



Highlights

- ARFI-measured ΔSS predicted hemodynamic response to prophylactic carvedilol.
- Prediction model = 0.0490–2.8345 × ΔSS; score = (exp [ModelΔSS])/(1 + exp[ModelΔSS]).
- Using 0.530 as the threshold value, AUC was 0.803 (in validation, AUC = 0.848).
- ΔSS may predict carvedilol response non-invasively, obviating HVPG measurement.

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Lay summary

Non-selective beta-blockers are the mainstay of primary prophylaxis to prevent variceal bleeding in patients with cirrhosis and high-risk esophageal varices. This prospective study showed that a prediction model based on changes in spleen stiffness before *vs.* after dose titration might be a non-invasive marker for response to prophylactic non-selective beta-blocker (carvedilol) therapy in patients with cirrhosis and high-risk esophageal varices.

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Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices

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Background & Aims: Non-selective beta-blockers (NSBBs) are the mainstay of primary prophylaxis of esophageal variceal bleeding in patients with liver cirrhosis. We investigated whether non-invasive markers of portal hypertension correlate with hemodynamic responses to NSBBs in cirrhotic patients with esophageal varices.

Methods: In this prospective cohort study, 106 cirrhotic patients with high-risk esophageal varices in the derivation cohort received carvedilol prophylaxis, and completed paired measurements of hepatic venous pressure gradient, liver stiffness (LS), and spleen stiffness (SS) at the beginning and end of dose titration. LS and SS were measured using acoustic radiation force impulse imaging. A prediction model for hemodynamic response was derived, and subject to an external validation in the validation cohort (63 patients).

Results: Hemodynamic response occurred in 59 patients (55.7%) in the derivation cohort, and in 33 patients (52.4%) in the validation cohort, respectively. Multivariate logistic regression analysis identified that ΔSS was the only significant predictor of hemodynamic response (odds ratio 0.039; 95% confidence interval 0.008–0.135; p <0.0001). The response prediction model ($Model_{\Delta SS}$ = 0.0490–2.8345 × ΔSS; score = (exp[$Model_{\Delta SS}$])/(1 + exp[$Model_{\Delta SS}$]) showed good predictive performance (area under the receiver-operating characteristic curve [AUC] = 0.803) using 0.530 as the threshold value. The predictive performance of the $Model_{\Delta SS}$ in the validation set improved using the same threshold value (AUC = 0.848).

Conclusion: A new model based on dynamic changes in SS exhibited good performance in predicting hemodynamic response to NSBB prophylaxis in patients with high-risk esophageal varices.

Lay summary: Non-selective beta-blockers are the mainstay of primary prophylaxis to prevent variceal bleeding in patients with cirrhosis and high-risk esophageal varices. This prospective study showed that a prediction model based on changes in spleen stiffness before *vs.* after dose titration might be a non-invasive marker for response to prophylactic non-selective beta-blocker (carvedilol) therapy in patients with cirrhosis and high-risk esophageal varices.

ClinicalTrials.gov Identifier: NCT01943318.

Introduction

Gastroesophageal varices are significant challenges that are commonly faced by patients with cirrhosis.[1] Variceal hemorrhage occurs in 10–15% of patients annually depending on the size of varices, the presence of red wale marks, and the severity of liver disease.[2] In addition, acute variceal hemorrhage carries significant risks of morbidity and mortality, with reported 6-week mortality rates of 15–25%.[3]

Primary prophylaxis for variceal hemorrhage using non-selective beta-blockers (NSBBs) has shown efficacy in patients with cirrhosis and high-risk varices.[4] Reducing the hepatic venous pressure gradient (HVPG) by NSBBs has been shown to be associated with a decreased risk of variceal hemorrhage and ascites, along with other benefits including amelioration of bacterial translocation and prevention of spontaneous bacterial peritonitis, resulting in positive effects on survival.[5–9] However, it is difficult to routinely measure HVPG in cirrhotic patients who receive prophylactic NSBBs in many institutions.

Shortcomings of HVPG measurements, such as invasiveness and expensiveness, have led to numerous studies on non-invasive measurements of portal hypertension in the last decade. Measurements of liver stiffness (LS) using transient elastography (TE) have proven its accuracy for diagnosing clinically significant portal hypertension.[10] In addition, spleen stiffness (SS) measured via TE has recently been suggested as a promising method to assess portal hypertension.[11,12] However, measuring SS using TE requires additional ultrasound examination and its measurement feasibility largely depends on the size of the spleen, which limits its wide applicability. Therefore, newer ultrasound-based elastographic methods have emerged as tools for facilitating SS measurements, including point shear wave elastography such as acoustic radiation force impulse (ARFI) imaging, and 2-dimensional real-time shear

Keywords: Portal hypertension; Beta-blocker; Hemodynamic response; Elastography.
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wave elastography. These newer elastographic methods have shown similar accuracy as TE for predicting portal hypertension.[13,14]

Although elastographic assessments of portal hypertension using the aforementioned technologies have yielded promising data, non-invasively predicting changes in HVPG during NSBB therapy represents an unmet clinical need. Hence, the aim of this study was to investigate whether non-invasive markers such as LS and SS measurements using ARFI elastography can predict hemodynamic response to NSBBs as primary prophylaxis in cirrhotic patients with high-risk esophageal varices.

Patients and methods

The present study was a prospective cohort study which was conducted at a single university-affiliated referral hospital (ClinicalTrials.gov Identifier: NCT01943318). This proof-of-concept study consisted of 2 parts. The first part aimed to derive a prediction model for hemodynamic response to NSBBs from the earlier derivation cohort (between May 2013 and February 2016). The second part was designed as an external validation including more recently recruited patients (between March 2016 and October 2017) at the same institution.[15,16]

Patients with liver cirrhosis who underwent endoscopic evaluation of gastroesophageal varices and hemodynamic evaluation of portal hypertension were eligible for this study. Inclusion criteria were the presence of high-risk esophageal varices on upper gastrointestinal endoscopic examination without a history of previous hemorrhage and a baseline HVPG >12 mmHg. High-risk varices were defined as medium-large varices, small varices with red wale marks or Child-Pugh class C disease.[17]

Exclusion criteria were as follows: age <18 years; pre- or postsinusoidal causes of portal hypertension; previous history of variceal hemorrhage or endoscopic band ligation (EBL); active alcoholism (noncompliant to abstinence >3 months before enrollment); severe decompensated liver disease (*e.g.*, refractory ascites, uncontrolled hepatic encephalopathy, serum bilirubin >5 mg/dl, international normalized ratio of prothrombin time >2.5, and history of spontaneous bacterial peritonitis); renal insufficiency (serum creatinine >1.5 mg/dl); contraindications to NSBB use (*e.g.*, asthma, chronic obstructive pulmonary disease, severe aortic stenosis, brittle diabetes mellitus, and atrioventricular block); presence of portal venous thrombosis; coexistence of malignancies including hepatocellular carcinoma (HCC); and patient refusal to participate in the study.

All study participants gave their written informed consent to participate in the study. The present study was approved by the institutional review board and was conducted according to the ethical guidelines of the World Medical Association Declaration of Helsinki.

Carvedilol treatment, measurements of HVPG, liver and spleen stiffness, and follow-up of liver-related events after NSBB prophylaxis

In the derivation cohort, carvedilol (Hoffmann La-Roche, Vienna, Austria) was started at a dose of 6.25 mg/day and titrated to a maximum dose of 25 mg/day in biweekly steps of 6.25 mg until systolic arterial blood pressure was not less than 95 mmHg and heart rate was not less than 50 beats per minute, according to the previously described protocol with minor modifications.[18] Compliance with carvedilol therapy was evaluated by monitoring adverse events, blood pressure, and heart rate at each clinical visit. However, in the validation cohort we used lower doses of carvedilol, with a maximum dose of 12.5 mg/day, because of concerns about worsening arterial hypotension which could be less tolerated by cirrhotic patients.[19,20]

HVPG was measured according to the standard methodology at baseline (prior to administration of carvedilol) and within 2 weeks of the end of dose titration by an intervention radiologist (YHS with more than 10 years of experience) who was blinded to clinical data, as previously described.[21] Hemodynamic response to carvedilol therapy was defined as either a decrease in HVPG by ≥20% of the baseline value or an absolute value of HVPG <12 mmHg after dose titration.[17] For non-responders, carvedilol was gradually tapered and permanently discontinued, and prophylactic EBL was implemented.

All patients in the derivation and validation cohorts were followed up every 2–3 months with clinical assessment including adherence to drug and monitoring of heart rate and blood pressure, development of all-cause and portal hypertension-related gastrointestinal bleeding or liver-related events (hepatic decompensation [ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy], mortality or liver transplantation), and laboratory tests.

Ultrasound examination was simultaneously performed using a Siemens Acuson S2000TM ultrasound system (Siemens AG, Erlangen, Germany) at baseline and within 2 weeks of the end of carvedilol dose titration by an expert radiologist (HW with more than 10 years of experience as a sonographer) who was blinded to clinical data, as described elsewhere.[22] LS was measured in the right lobe using the 9th to 10th rib intercostal approach, with the right arm in maximum abduction. SS was measured using the intercostal approach in the left upper quadrant, with the left arm in maximum abduction. A 10×5 mm region of interest box was placed on the liver and spleen parenchyma without large blood vessels or abnormal lesions at a depth of 3 to 5.5 cm below the liver and spleen capsule. For each patient, 10 repetitive measurements were performed for the liver and spleen while the patient held their breath for a few seconds per measurement. The median value of the 10 valid measurements was calculated and represented as an LS or SS value. LS or SS was expressed as shear wave velocity (meters per second, m/s). Acceptable LS or SS values were defined as the ratio of the interquartile range to the median value ≤30%.[23]

Statistical analysis

For baseline characteristics, continuous variables are expressed as medians and ranges, and categorical variables are expressed as frequencies with percentages. In the derivation cohort, single binary logistic regression analysis was used to identify relevant features associated with hemodynamic response to carvedilol, in which variables with p <0.1 were subsequently included in the multivariate analysis. The selected variables for the logistic regression analysis included clinical characteristics, laboratory parameters, LS, and SS. Forward and backward stepwise selection procedures were sequentially used to select the best-fitted model based on the Akaike information criterion.[24] We performed a two-step approach to find the best cut-off value of our model. First, an optimal cut-off value was determined based on the Youden's index to maximize both sensitivity and specificity for risk stratification. Second, we applied several different conditions to emphasize either sensitivity or specificity, because the determination of a single definitive cut-off value

based on the maximal Youden's index for this prediction model might be less appropriate given the proof-of-concept nature of this study.[25]. Next, the predictive performance of the final model was confirmed based on the areas under the receiver-operating characteristic curves (AUCs) and calibration plots. The model was internally validated and optimized with bootstrapping.[26] For internal validation of the predictive model, 3-fold cross-validation was performed. We examined goodness of fit of the logistic regression model by comparing the observed response with the expected response estimated from the risk score and performing a Hosmer-Lemeshow test. Finally, we externally validated the performance of the prediction model as described. Outcomes such as rates of gastrointestinal hemorrhage and hepatic decompensation, and liver transplantation-free survival were estimated using the Kaplan–Meier method and compared by log-rank test. In addition, we also compared cumulative incidence rates of liver-related outcomes considering death or liver transplantation as competing risks.

All tests were based on 2-sided probability, and p <0.05 was considered statistically significant. All statistical analyses were performed with R language ver. 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics and hemodynamic response to carvedilol therapy in the derivation cohort

In the derivation cohort, 153 consecutive patients with cirrhosis and esophageal varices were evaluated for eligibility. Among them, 47 patients were excluded for the following reasons: non-compliance to alcohol abstinence (n = 18); discontinuation of medication due to adverse events (n = 15); loss to follow-up (n = 9); development of HCC (n = 4); and liver transplantation (n = 1). Finally, 106 patients completed paired measurements of HVPG and were included in this study. Measurement of SS was unsuccessful in 3 patients: because of previous splenectomy in 1 patient and because of anatomical difficulty in measurement in the other 2 patients. However, these patients were excluded due to noncompliance with alcohol abstinence or carvedilol-related adverse events. LS measurements were successful in all study participants. Finally, a total of 106 patients completed paired LS and SS measurements. Flowcharts for patient selection are depicted (Fig. 1A).

The baseline characteristics of the derivation and validation cohorts are summarized (Table 1). The mean age of the enrolled patients was 59 years, and 75 patients were male (70.8%). The primary etiologies of cirrhosis were alcohol (42.5%) and viral (hepatitis B, 31.1%; hepatitis C, 11.3%). The mean model for end-stage liver disease (MELD) score was 9.51. At baseline, 84 patients (79.2%) had medium- or large-sized esophageal varices, and 66 patients (62.3%) had red wale marks. Six patients with small varices received prophylactic carvedilol because they were Child-Pugh class C. Baseline HVPG was 19.6 ± 5.8 mmHg. ARFI-measured LS and SS were 2.44 ± 0.69 m/s and 3.14 ± 0.45 m/s, respectively.

Following the median duration of 13.2 weeks (IQR 10.3–17.2) for dose titration of carvedilol toward the maximum tolerated dose, the follow-up HVPG was measured in each study participant. Hemodynamic response was observed in 59 patients (55.7%) at a median 25 mg of carvedilol. A high dose (25 mg or higher; n = 64) was administered to patients with Child-Pugh class A disease (n = 52, 81.3%) and those with preexisting arterial hypertension (n = 12, 19.7%). There were no significant differences in the changes in HVPG (p = 0.918) or hemodynamic response rates between the low-dose (≤12.5 mg; 23/42) and high-dose (≥25 mg; 36/64) groups (p = 0.777). Baseline demographic and clinical characteristics were not significantly different between hemodynamic responders and non-responders, including HVPG, SS, and spleen length (Table 1), although the baseline LS tended to be marginally higher in non-responders (p = 0.066). The changes in the hemodynamic parameters between baseline and follow-up after carvedilol therapy are presented (Table 2). Hemodynamic responders had significantly lower LS and SS at follow-up than non-responders. However, blood pressure, heart rate, and spleen length were not

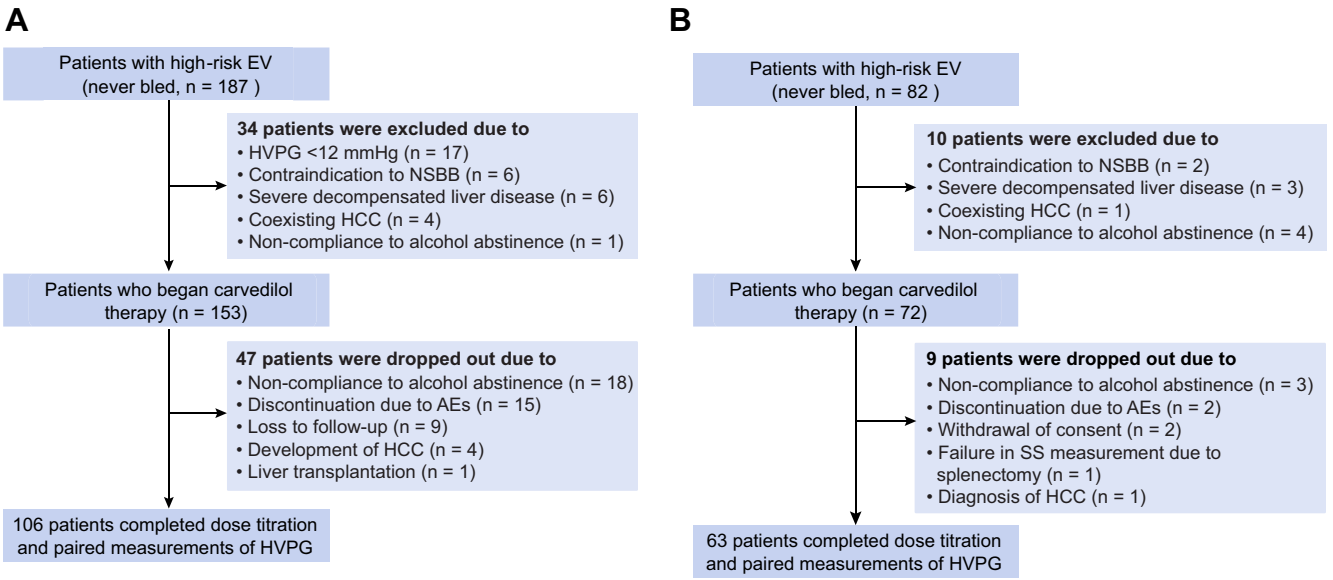

Fig 1. Flowcharts for patient selection. (A) Derivation cohort. (B) Validation cohort. AE, adverse event; EV, esophageal varices; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; NSBB, non-selective beta-blocker; SS, spleen stiffness.

Table 1. Baseline characteristics of the derivation and validation cohorts the values are expressed as the mean ± standard deviation, median (range) or frequency (percentage).

Variable	Derivation cohort				Validation cohort			
	All (n = 106)	Responders (n = 59)	Non-responders (n = 47)	*p*	All (n = 63)	Responders (n = 33)	Non-responders (n = 30)	*p*
Age (years)	58.7 ± 10.6	57.7 ± 10.8	60.0 ± 10.4	0.2717	57.5 ± 9.6	57.4 ± 10.2	57.5 ± 9.2	0.9646
Male gender	75 (70.8)	43 (72.9)	32 (68.1)	0.7456	44 (69.8)	24 (72.7)	20 (66.7)	0.8036
BMI	24.0 ± 3.4	23.7 ± 3.4	24.5 ± 3.4	0.1916	23.9 ± 3.3	24.4 ± 3.6	23.5 ± 3.0	0.2697
MAP (mmHg)	90.3 ± 11.6	90.9 ± 11.9	89.5 ± 11.4	0.5461	88.8 ± 10.4	90.0 ± 11.8	87.4 ± 8.6	0.3233
SBP	123.1 ± 15.6	123.8 ± 14.9	122.2 ± 16.5	0.5909	121.3 ± 14.7	123.1 ± 16.3	119.3 ± 12.7	0.3104
DBP	73.8 ± 11.3	74.4 ± 12.1	73.2 ± 10.2	0.5748	72.5 ± 9.8	73.5 ± 11.1	71.4 ± 8.2	0.4178
Heart rate (bpm)	73.4 ± 11.0	74.0 ± 11.4	72.7 ± 10.7	0.5492	72.6 ± 10.7	73.3 ± 9.4	71.8 ± 12.0	0.5888
Etiology								
HBV	33 (31.1)	22 (37.3)	11 (23.4)	0.1610	20 (31.8)	11 (33.3)	9 (30.0)	0.8205
HCV	12 (11.3)	5 (8.5)	7 (14.9)		8 (12.7)	5 (15.2)	3 (10.0)	
Alcohol	45 (42.5)	23 (38.9)	22 (46.8)		23 (36.5)	10 (30.3)	13 (43.3)	
Others	16 (15.1)	9 (15.3)	7 (14.9)		12 (19.0)	7 (21.2)	5 (16.7)	
Child-Pugh class								
A	52 (49.1)	30 (50.9)	22 (46.8)	0.8796	32 (50.8)	17 (51.5)	15 (50.0)	1.0000
B	42 (39.6)	23 (39.0)	19 (40.4)		28 (44.4)	14 (42.4)	14 (46.7)	
Prothrombin time (INR)	1.33 ± 0.19	1.31 ± 0.18	1.35 ± 0.21	0.7216	1.35 ± 0.19	1.33 ± 0.17	1.37 ± 0.21	0.3351
Albumin (g/dl)	3.4 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	0.3106	3.3 ± 0.5	3.3 ± 0.6	3.2 ± 0.4	0.2516
Bilirubin (mg/dl)	2.1 ± 2.4	2.3 ± 2.9	1.8 ± 1.4	0.8187	2.2 ± 2.1	2.2 ± 2.2	2.2 ± 1.9	0.9506
Creatinine (mg /dl)	0.92 ± 0.39	0.91 ± 0.38	0.93 ± 0.42	0.7698	0.78 ± 0.28	0.82 ± 0.30	0.73 ± 0.26	0.2829
Platelet count ($\times 10^3/\mu l$)	93.5 ± 57.2	91.2 ± 51.7	96.4 ± 63.9	0.7577	92.5 ± 51.3	97.4 ± 52.5	87.1 ± 50.3	0.3284
AST (IU/L)	62.0 ± 46.8	60.6 ± 50.0	63.7 ± 43.0	0.2683	74.3 ± 112.9	55.3 ± 29.2	95.3 ± 159.5	0.2205
ALT (IU/L)	30.0 ± 21.8	29.8 ± 22.4	30.3 ± 21.1	0.6721	45.4 ± 91.0	29.8 ± 17.3	62.5 ± 129.5	0.3635
APRI	2.30 ± 2.66	2.43 ± 3.17	2.14 ± 1.87	0.6516	2.64 ± 3.76	2.00 ± 1.89	3.34 ± 5.03	0.1721
FIB-4	9.55 ± 7.40	9.99 ± 8.78	8.99 ± 5.21	0.5585	8.83 ± 5.90	7.78 ± 5.31	9.98 ± 6.38	0.1949
PSR	785.2 ± 599.0	761.6 ± 551.8	815.4 ± 659.7	0.5416	756.0 ± 554.8	811.3 ± 560.8	696.9 ± 551.7	0.2898
MELD	9.51 ± 4.72	9.42 ± 5.31	9.62 ± 3.91	0.6289	9.15 ± 4.71	9.00 ± 5.14	8.57 ± 4.49	0.7210
Esophageal varices (size)								
Small	22 (20.8)	13 (22.0)	9 (19.2)	0.8776	10 (15.9)	5 (15.1)	5 (16.7)	1.0000
Medium	72 (67.9)	40 (67.8)	32 (68.1)		46 (73.0)	25 (75.8)	21 (70.0)	
Large	12 (11.3)	6 (10.2)	6 (12.7)		7 (11.1)	3 (9.1)	4 (13.3)	
Red wale marks	66 (62.3)	36 (61.0)	30 (63.8)	0.9242	47 (74.6)	24 (72.7)	23 (76.7)	0.7590
Gastric varices	7 (6.6)	6 (10.2)	1 (2.1)	0.1295	7 (11.1)	5 (15.2)	2 (6.7)	0.6819
PHG	67 (63.2)	38 (64.4)	29 (61.7)	0.9329	27 (56.3)	13 (50.0)	14 (63.6)	0.5112
Ascites	46 (43.4)	24 (40.7)	22 (46.8)	0.5781	27 (42.9)	13 (39.4)	14 (46.7)	0.8130
HVPG (mmHg)	19.6 ± 5.8	20.4 ± 6.3	18.6 ± 5.0	0.1995	19.2 ± 4.9	20.6 ± 5.6	17.6 ± 3.7	0.0308
Maximal carvedilol dose (mg)	24.0 ± 6.0	24.1 ± 6.5	23.9 ± 5.4	0.7941	12.1 ± 1.5	11.9 ± 1.8	12.3 ± 1.1	0.3616
LS (m/sec)	2.44 ± 0.69	2.33 ± 0.72	2.57 ± 0.62	0.0656	2.38 ± 0.65	2.39 ± 0.69	2.37 ± 0.62	0.9059
SS (m/sec)	3.14 ± 0.45	3.19 ± 0.47	3.07 ± 0.41	0.1763	3.12 ± 0.56	3.25 ± 0.51	2.97 ± 0.59	0.0864
Spleen length (cm)	13.1 ± 2.5	13.2 ± 2.5	12.9 ± 2.4	0.5447	13.1 ± 2.5	12.7 ± 2.5	13.5 ± 2.3	0.1263

ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LS, liver stiffness; MAP, mean arterial pressure; MELD, model for end-stage liver disease; PHG, portal hypertensive gastropathy; PSR, platelet count/spleen diameter ratio; SBP, systolic blood pressure; SS, spleen stiffness. Comparisons between groups were performed using *t*-test, Mann-Whitney U test, and chi-squared test.

Table 2. Follow-up radiologic characteristics and changes in hemodynamic parameters in the derivation cohort.

Variable	All (n = 106)	Responders (n = 59)	Non-responders (n = 47)	*p*
LS at follow-up (m/sec)	2.26 ± 0.50	2.10 ± 0.46	2.46 ± 0.48	0.0002
SS at follow-up (m/sec)	3.03 ± 0.46	2.86 ± 0.45	3.25 ± 0.38	<0.0001
Spleen length at follow-up (cm)	12.71 ± 3.32	13.10 ± 2.83	12.23 ± 3.83	0.2011
Change in HVPG	−3.90 ± 5.06	−7.28 ± 3.75	0.20 ± 2.96	<0.0001
Change in LS	−0.18 ± 0.58	−0.23 ± 0.61	−0.11 ± 0.52	0.8189
Change in SS	−0.10 ± 0.52	−0.33 ± 0.50	0.18 ± 0.39	<0.0001
Change in spleen length	−0.34 ± 2.53	−0.09 ± 2.15	−0.66 ± 2.95	0.6675
Change in MAP	−5.44 ± 12.68	−5.72 ± 10.64	−5.11 ± 14.94	0.8137
Change in SBP	−6.58 ± 18.75	−8.33 ± 15.61	−4.43 ± 22.01	0.2158
Change in DBP	−4.88 ± 11.13	−4.41 ± 9.94	−5.45 ± 12.53	0.6385
Change in heart rate	−8.37 ± 13.20	−9.29 ± 14.52	−7.23 ± 11.41	0.4293

The values are expressed as the mean ± standard deviation.
DBP, diastolic blood pressure; LS, liver stiffness; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; SBP, systolic blood pressure; SS, spleen stiffness. Comparisons between groups were performed using *t*-test or Mann-Whitney U test.

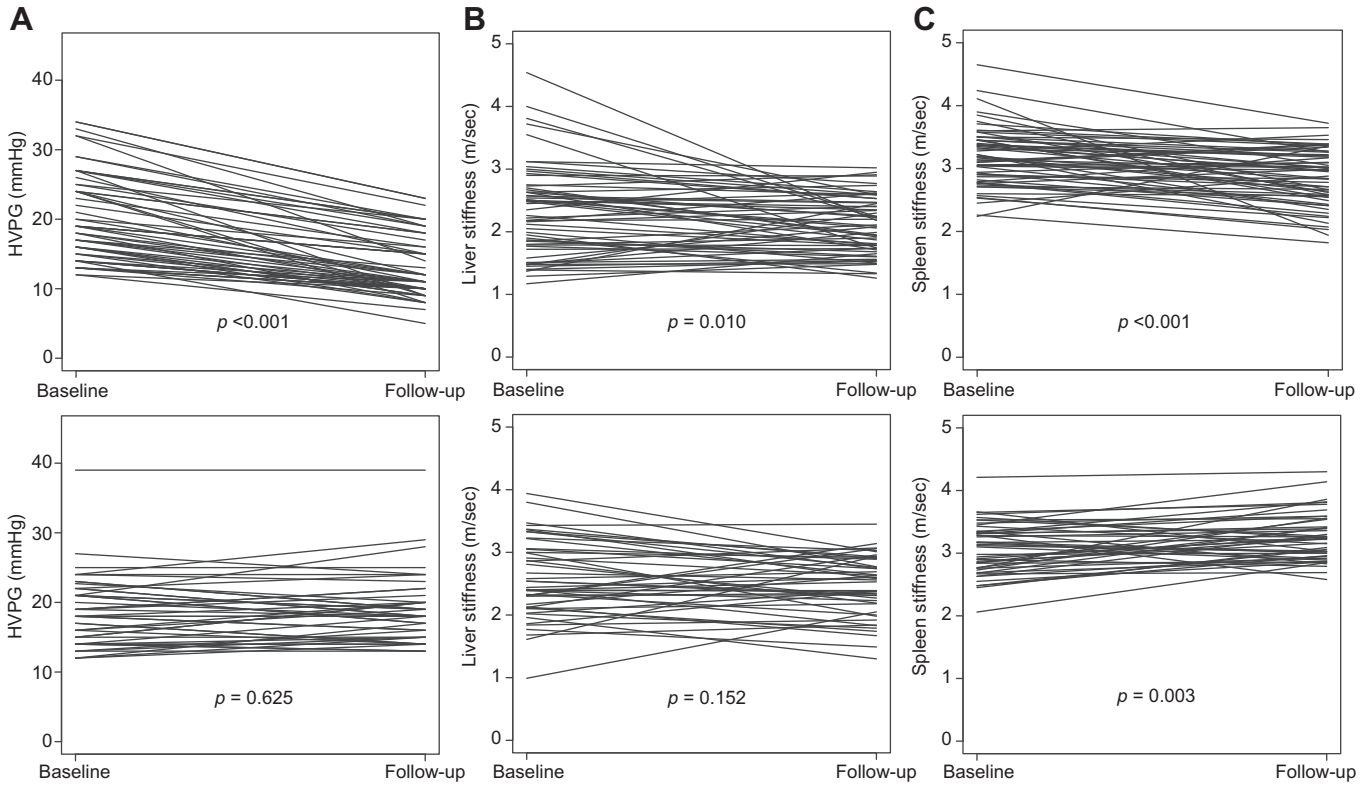

Fig 2. Comparison of individual patients' absolute changes in HVPG, liver and spleen stiffness from baseline to the end of the dose titration of carvedilol between responders and non-responders in the derivation cohort. (A) HVPG (upper panel, responders; lower panel, non-responders). (B) Liver stiffness (upper panel, responders; lower panel, non-responders). (C) Spleen stiffness (upper panel, responders; lower panel, non-responders). Comparisons of parameters were performed using paired *t* test or Wilcoxon signed-rank test. HPVG, hepatic venous pressure gradient.

significantly different between the 2 groups. The individual patient data on the absolute changes in HVPG, LS and SS stratified by the response group are shown (Fig. 2A-C). A significant reduction in LS was observed in the responders ($p = 0.010$) compared with the non-responders ($p = 0.152$). The responders showed a significant reduction in SS ($p < 0.001$); in contrast, SS increased in the non-responders ($p = 0.003$).

Non-invasive predictions of baseline HVPG and hemodynamic response to carvedilol therapy

Univariate logistic regression analysis revealed that the following variables were significantly associated with hemodynamic response: follow-up LS (*i.e.*, LS2; odds ratio [OR] 0.203; 95% confidence interval [CI] 0.079–0.479); follow-up SS (*i.e.*, SS2; OR 0.099; 95% CI 0.028–0.289); and difference between SS1 and SS2 (*i.e.*, ΔSS [=SS2 − SS1]; OR 0.059; 95% CI 0.015–0.185). Multivariate logistic regression analysis identified that ΔSS was the only significant predictor of hemodynamic response (OR 0.039; 95% CI 0.008–0.135; $p < 0.0001$) (Table 3).

A prediction model for hemodynamic response was generated using ΔSS as follows: $\text{Model}_{\Delta SS} = 0.0490 - 2.8345 \times \Delta SS$; score = $(\exp[\text{Model}_{\Delta SS}])/(1 + \exp[\text{Model}_{\Delta SS}])$. Using 0.530 as the threshold value, the AUC was 0.803 (Fig. 4A). $\text{Model}_{\Delta SS}$ maintained good discriminant function in the internal validation using 3-fold cross-validation (AUC = 0.801). The sensitivity, specificity, accuracy, positive- and negative likelihood ratios for predicting hemodynamic response were 0.814, 0.745, 0.783, 3.192, and 0.250, respectively. In addition, when we tried to explore other cut-off values under various conditions, emphasizing either sensitivity or specificity, a cut-off value of 0.731 was identified with maximized specificity (95% CI 0.542–0.902); the resultant sensitivity, specificity, and accuracy were 0.552, 0.894, and 0.705, respectively.

External validation of the ΔSS-based prediction model

In the validation cohort, 72 consecutive patients were evaluated for eligibility. Of these, 9 patients were excluded for the following reasons: noncompliance to alcohol abstinence (n = 3); discontinuation of medication due to adverse events (n = 2); withdrawal of consent (n = 2); failure in SS measurement due to splenectomy (n = 1); and diagnosis of HCC (n = 1). Finally, a total of 63 patients completed dose titration of carvedilol and paired HVPG, LS and SS measurements, and were included in the analysis (Fig. 1B).

The baseline characteristics of the validation cohort are shown (Table 1). The mean age of the enrolled patients was 57 years, and 44 patients were male (69.8%). Etiologies of cirrhosis were mainly alcohol (36.5%) and viral (hepatitis B, 31.8%; hepatitis C, 12.7%). The mean MELD score was 9.15. At baseline, 56 patients (88.9%) had medium- or large-sized esophageal varices, and 66 patients (62.3%) had red wale marks. Baseline HVPG was 19.2 ± 4.9 mmHg. ARFI-measured LS and SS were 2.38 ± 0.65 m/s and 3.12 ± 0.56 m/s, respectively. In comparison with the derivation cohort, there were no significant differences in baseline characteristics, except for maximal carvedilol dose. Hemodynamic response was observed in 33 patients (52.4%) at a median 12.5 mg of carvedilol. Baseline demographic and clinical characteristics were not significantly different between hemodynamic responders and non-responders, with the exception of higher HVPG in responders

Table 3. Factors affecting hemodynamic responses to carvedilol therapy in the logistic regression analysis.

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Baseline						
Age	0.979	0.943–1.016	0.2697			
Sex (female)	0.794	0.341–1.848	0.5900			
BMI	0.926	0.822–1.037	0.1921			
Etiology (nonviral)	0.788	0.358–1.716	0.5495			
MAP	1.010	0.978–1.043	0.5450			
LS	0.597	0.326–1.055	0.0823			
SS	1.844	0.772–4.639	0.1773			
Spleen length	1.006	0.868–1.165	0.9399			
Log INR	0.270	0.015–4.536	0.3643			
Albumin	1.385	0.654–2.976	0.3963			
Total bilirubin	1.104	0.931–1.363	0.2914			
Log AST	0.747	0.380–1.450	0.3897			
Log ALT	0.883	0.485–1.570	0.6716			
Platelet count	0.998	0.991–1.005	0.6383			
APRI	1.045	0.902–1.241	0.5716			
FIB-4	1.019	0.967–1.079	0.4867			
PSR	1.000	0.994–1.006	0.9890			
Esophageal varices						
Medium	0.865	0.320–2.264	0.7699			
Large	0.692	0.164–2.882	0.6106			
Red wale marks	0.887	0.398–1.956	0.7667			
Gastric varices	5.208	0.847–100.273	0.1330			
PHG	1.123	0.506–2.489	0.7743			
Ascites	0.563	0.169–1.826	0.3370			
Changes						
Changes in LS	0.689	0.334–1.355	0.2905			
Changes in SS	0.059	0.015–0.185	<0.0001	0.039	0.008–0.135	<0.0001
Changes in MAP	0.993	0.965–1.021	0.5986			
Follow-up						
MAP	1.002	0.972–1.034	0.8905			
LS	0.203	0.079–0.479	0.0005			
SS	0.099	0.028–0.289	0.0001			
Spleen length	1.085	0.965–1.232	0.1847			
Log INR	0.316	0.011–8.491	0.4918			
Albumin	1.464	0.646–3.395	0.3632			
Total bilirubin	1.057	0.773–1.498	0.7296			
Log AST	0.556	0.199–1.490	0.2483			
Log ALT	1.034	0.516–2.067	0.9234			
Platelet count	1.000	0.992–1.008	0.9464			
APRI	0.974	0.668–1.427	0.8915			
FIB-4	0.993	0.927–1.064	0.8324			
PSR	0.730	0.403–1.087	0.2085			
Ascites	0.476	0.109–1.883	0.2952			

ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; INR, international normalized ratio; LS, liver stiffness; MAP, mean arterial pressure; OR, odds ratio; PHG, portal hypertensive gastropathy; PSR, platelet count/spleen diameter ratio; SS, spleen stiffness. Uni- and multivariate logistic regression analyses were performed.

($p = 0.0308$). The changes in hemodynamic parameters between baseline and follow-up after carvedilol therapy are presented (Table 4). Hemodynamic responders had significantly lower SS at follow-up than non-responders. However, blood pressure, heart rate, and spleen length were not significantly different between the 2 groups. The individual patient data on the absolute changes in HVPG, LS and SS stratified by the response group are shown (Fig. 3A-C). Significantly reduced SS was observed in responders ($p < 0.001$). The predictive performance of the Model$_{\Delta SS}$ in the validation set improved using the same threshold value (AUC = 0.848) (Fig. 4B); the sensitivity, specificity, and accuracy for predicting hemodynamic response with this ΔSS cut-off were 0.848, 0.733 and 0.794, respectively. In addition, using the other cut-off value 0.731 that maximized specificity in the prediction of hemodynamic response in the derivation set, the sensitivity, specificity, and accuracy in the validation set were 0.545, 0.833, and 0.683, respectively.

Comparison of clinical outcomes between hemodynamic responders and non-responders after carvedilol therapy

During follow-up, 10 patients developed alcohol recidivism and 7 patients discontinued NSBBs because of drug-related side effects (*e.g.*, dizziness, impotence, *etc.*) in the responder group of the derivation cohort; 5 patients developed alcohol recidivism in the non-responder group. By excluding these 22 patients, portal hypertension-related bleeding was reported in 7 patients out of the responders (16.7%) and 8 out of the non-responders (19.0%). ($p = 0.353$) In the validation cohort, however, the occurrence of portal hypertension-related bleeding was significantly more frequent in the non-responder group

Table 4. Follow-up radiologic characteristics and changes in hemodynamic parameters in the validation cohort.

	Validation cohort			
Variable	**All (n = 63)**	**Responders (n = 33)**	**Non-responders (n = 30)**	***p***
LS at follow-up (m/sec)	2.27 ± 0.53	2.26 ± 0.51	2.29 ± 0.57	0.8120
SS at follow-up (m/sec)	2.93 ± 0.54	2.70 ± 0.52	3.21 ± 0.43	0.0002
Spleen length at follow-up (cm)	13.12 ± 2.85	12.88 ± 2.45	13.40 ± 3.27	0.2300
Change in HVPG	−3.46 ± 5.89	−7.50 ± 4.71	0.85 ± 3.46	<0.0001
Change in LS	0.08 ± 0.83	0.02 ± 0.88	0.14 ± 0.78	0.3148
Change in SS	−0.09 ± 0.89	−0.51 ± 0.55	0.38 ± 0.96	<0.0001
Change in spleen length	0.22 ± 1.14	0.07 ± 1.11	0.40 ± 1.19	0.2630
Change in MAP	−6.50 ± 16.88	−8.44 ± 18.93	−4.36 ± 14.31	0.4657
Change in SBP	−6.58 ± 20.13	−9.31 ± 20.17	−3.67 ± 20.01	0.2733
Change in DBP	−4.77 ± 12.37	−4.84 ± 12.89	−4.70 ± 12.01	0.9640
Change in heart rate	−9.15 ± 10.96	−10.00 ± 10.98	−8.23 ± 11.05	0.5302

DBP, diastolic blood pressure; LS, liver stiffness; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; SBP, systolic blood pressure; SS, spleen stiffness. Comparisons between groups were performed using *t*-test or Mann-Whitney U test.

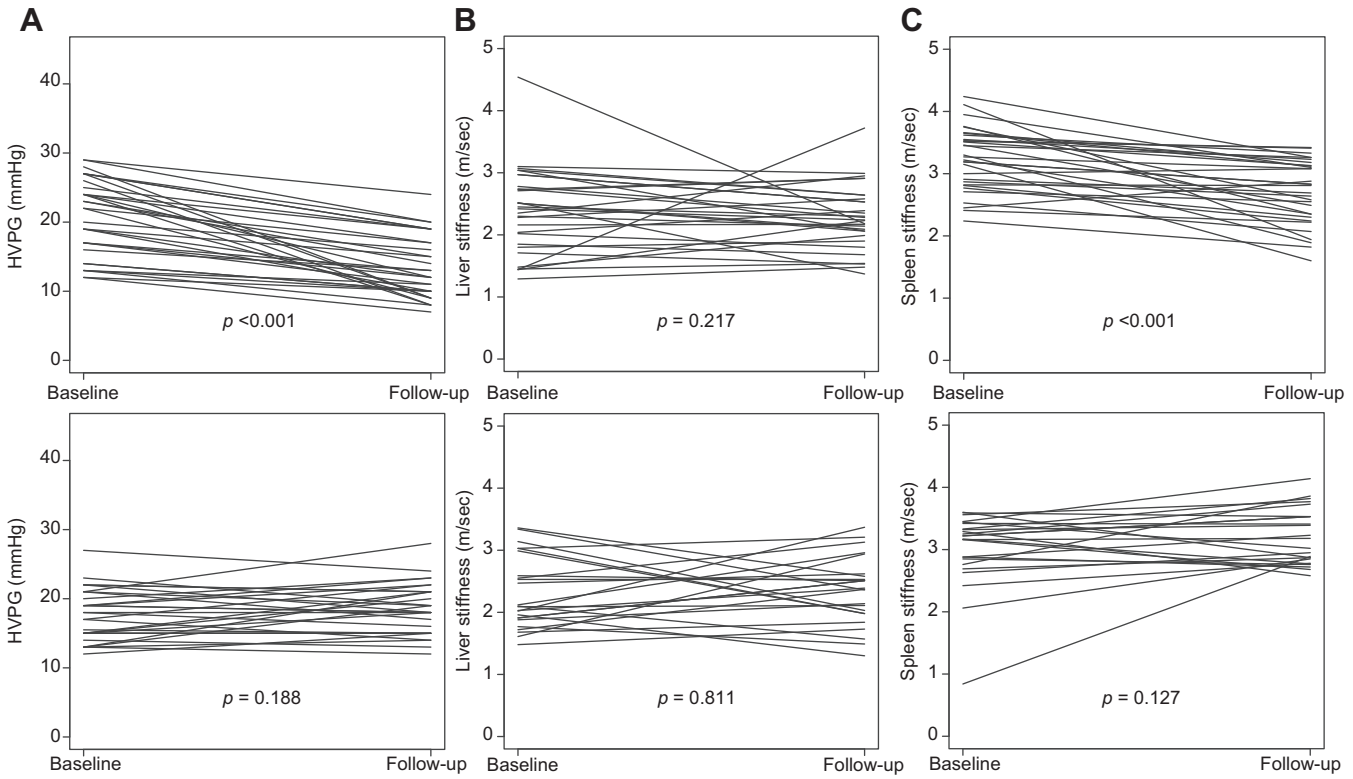

Fig 3. Comparison of individual patients' absolute changes in HVPG, liver and spleen stiffness from baseline to the end of the dose titration of carvedilol between responders and non-responders in the validation cohort. (A) HVPG (upper panel, responders; lower panel, non-responders). (B) Liver stiffness (upper panel, responders; lower panel, non-responders). (C) Spleen stiffness (upper panel, responders; lower panel, non-responders). Comparisons of parameters were performed using paired *t*-test or Wilcoxon signed-rank test. HVPG, hepatic venous pressure gradient.

(7/25; 28.0%) than in the responder group (1/26; 3.8%), respectively ($p = 0.021$), after excluding 9 patients with alcohol recidivism (4 responders and 5 non-responders) and 3 patients with noncompliance in the responder group. In addition, the competing risk analysis, which considered death or liver transplantation as competing risks, demonstrated that portal hypertension-related gastrointestinal bleeding developed more frequently in the non-responders than in the responders ($p = 0.035$), unlike ascites ($p = 0.451$), spontaneous bacterial peritonitis ($p = 0.980$) or hepatic encephalopathy ($p = 0.077$) (Figs. S1, S2). Among the hemodynamic responders (n = 68) of the entire mixed cohort (*i.e.*, derivation + validation), 36 patients achieved follow-up HVPG of less than 12 mmHg (52.9%), and 32 achieved ≥20% reduction of HVPG from baseline (an absolute value ≥12 mmHg), respectively. Portal hypertension-related hemorrhage developed in 3 out of 36 patients with follow-up HVPG <12 mmHg ($p = 0.044$), whereas 5 out of 32 patients with ≥20% HVPG reduction developed hemorrhage ($p = 0.149$).

Discussion

In this prospective cohort study, we investigated ARFI-based, non-invasive prediction of hemodynamic response to beta-blocker therapy as primary prophylaxis in patients with cirrhosis and high-risk esophageal varices. A prediction model for

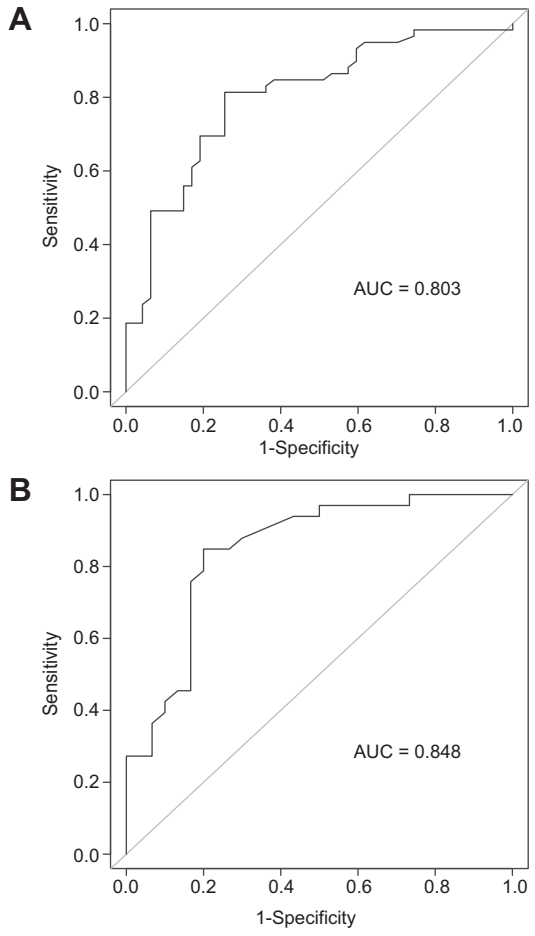

Fig 4. AUCs of the prediction model for hemodynamic response. (A) Derivation cohort. $Model_{\Delta SS}$ (= 0.0490–2.8345 × ΔSS): Using 0.530 as the threshold value, the AUC was 0.803. $Model_{\Delta SS}$ maintained good discriminant function in the internal validation using 3-fold cross-validation (AUC = 0.801). The threshold value was determined based on the Youden's index. (B) Validation cohort. The predictive performance of the $Model_{\Delta SS}$ in the validation set slightly improved using the same threshold value (AUC = 0.848). AUC, area under the receiver-operating characteristic curve; SS, spleen stiffness.

hemodynamic response to carvedilol therapy was developed based on changes in SS, showing good predictive performance (AUC >0.8). Changes in the ARFI-measured SS values from before the initiation of carvedilol therapy to after dose titration may enable the prediction of hemodynamic response to prophylactic beta-blocker therapy, obviating the need for paired measurements of HVPG.

Cirrhotic patients with high-risk esophageal varices may benefit from NSBBs used to prevent the first variceal hemorrhage. Therefore, recent practice guidelines recommend either NSBBs or EBL as primary prophylaxis for such patients.[27,28] Carvedilol, an NSBB with intrinsic anti–α1-adrenergic activity, was recently adopted in guidelines for primary prophylaxis.[29,30] Carvedilol was used in the present study due to superior efficacy in reducing portal venous pressure compared with other NSBBs.[18,31] However, the significant reduction in mean arterial pressure is the major concern regarding the use of carvedilol, which may be harmful in cirrhotic patients.[31] Given that the maximal recommended dose of carvedilol was not clearly defined in the global practice guidelines at the time of the study design, the dose used in the derivation cohort was titrated according to systolic arterial blood pressure and heart rate, as previously described, to a maximum of 25 mg/day (or higher in cases of preexisting arterial hypertension) instead of the recently recommended dose (12.5 mg/day).[18] The proportion of hemodynamic responders (n = 59, 55.7%) was similar to the result of a recent Korean report,[32] in which the maximal carvedilol dose was 12.5 mg daily; the response rate of the present study was comparable to the results of Reiberger *et al.*'s study (56% [38/67]), in which carvedilol was used as rescue therapy for non-responders to propranolol.[18] In the derivation cohort of the present study, both changes in HVPG and hemodynamic response rates were not significantly different between the high-dose group and the low-dose group, supporting the prioritized use of a lower dose.[33,34]

To date, there are scarce data on the prediction of hemodynamic response to NSBB prophylaxis in the literature.[35] Although HVPG measurement *per se* provides prognostic information and enables assessment of hemodynamic response to NSBBs based on treatment-related changes in its values, it is invasive, relatively expensive, not always available in all institutions, and even requires expertise. Likewise, TE-measured SS has been suggested as a novel non-invasive predictor of portal hypertension with promising results.[11,12] However, measurement of SS using TE calls for separate ultrasound examination and tends to be dependent on the size of the spleen. Alternatively, newer ultrasound-based elastographic methods have recently been developed to facilitate SS measurement for evaluating portal hypertension. Recent prospective studies on ARFI-measured SS have shown promising results regarding its ability to predict the degree of portal hypertension and the severity of varices: one study identified cirrhotic patients with high-risk esophageal varices at the SS cut-off value of 3.30 m/s, and the other study (n = 60) including 29 patients (48.3%) with severe portal hypertension (HVPG ≥12 mmHg) reported a better correlation between HVPG and SS (correlation coefficient, $r = 0.876$) than LS ($r = 0.609$, $p < 0.0001$).[36,37] In the latter study (n = 60), the SS cut-off for high-risk varices was 3.51 m/s,[37] which was higher than the mean SS value of 3.14 m/s at baseline shown in the present study. The difference in the major etiology of cirrhosis between the studies might explain the discrepancy in the SS values for predicting high-risk varices: hepatitis C (58.3%)[37] *vs.* alcohol (only patients under abstinence were enrolled in the present study; 42.5%). Indeed, the cut-off SS value for high-risk varices was 3.40 m/s according to our previous study (n = 125), in which hepatitis B was the main etiology (50.4%) of cirrhosis.[38] In the present study, only baseline LS in the derivation cohort tended to be slightly higher in non-responders than in responders, without statistical significance. Significant predictors of baseline HVPG included baseline LS, prothrombin time, and ascites but not SS, suggesting that there is no additional role in discriminating the severity of portal hypertension of SS in these patients who are uniformly accompanied by high-risk varices. More prominent treatment-related reductions in SS and HVPG were observed in the responders compared to the non-responders.

To our knowledge, prospective studies on the prediction of hemodynamic response using dynamic changes in LS or SS under NSBB treatment have not yet been published. Although a recent study demonstrated better diagnostic performance of SS for the identification of clinically significant (≥10 mmHg) and severe (≥12 mmHg) portal hypertension and the presence of (high-risk) esophageal varices than that of LS,[37] evidence

regarding the use of SS in predicting hemodynamic response to NSBBs has been limited. Our results showed that ΔSS was the only significant predictor of hemodynamic response according to multivariate logistic regression analysis. In addition, the changes in HVPG paralleled the changes in SS. Based on these findings, the prediction model ($Model_{\Delta SS}$) was generated using ΔSS as a single parameter and showed good performance for predicting hemodynamic response. $Model_{\Delta SS}$ maintained good discriminant performance in the internal validation using 3-fold cross-validation. Moreover, its predictive performance improved in the validation cohort where patients were treated with current standard dose of carvedilol (AUC = 0.848). The results suggest that ΔSS may help to non-invasively identify hemodynamic responders to NSBB therapy, as primary prophylaxis against hemorrhage, in cirrhotic patients with high-risk esophageal varices. In addition, several recent studies reported a positive correlation between changes in SS and those in portal pressure before and after placement of a transjugular intrahepatic portosystemic shunt, which was not pertinent to LS.[39–43] Taken together, the role of SS in the prediction of dynamic changes in HVPG seems promising if the results can be reproduced and properly validated.

When we compared liver-related outcomes between responders and non-responders during follow-up, the occurrence rate of portal hypertension-related hemorrhage was significantly lower in the responders than in the non-responders of the validation group. The competing risk analysis also showed the same results in the reduction of bleeding risk. Absence of difference in the bleeding rates between the responders and non-responders in the derivation cohort might occur for several reasons: i) slightly higher proportion of alcoholic patients in the derivation cohort (42.5%) than in the validation cohort (36.5%), ii) underpowered study design to identify significant difference in bleeding rates, particularly the relatively small number of study participants, and iii) positive influence of lower-dose carvedilol on the outcome of responders in the validation cohort compared with that of the responders in the derivation cohort. A previous study reported that carvedilol treatment was associated with lower bleeding rates than EBL,[18] whereas these 2 modalities showed comparable bleeding rates and bleeding-related mortality in another larger scale study.[30] In our *post hoc* analysis, dividing the hemodynamic responders into 2 groups (follow-up HVPG <12 mmHg *vs.* HVPG reduction ≥20% [yet above 12 mmHg]), those with follow-up HVPG <12 mmHg showed significant risk reduction in bleeding, as was shown in earlier studies.[44,45] Recent studies with larger sample sizes than the present study generally reported favorable outcomes in terms of risk reduction in mortality in patients with decompensated cirrhosis, including a systematic review and a network meta-analysis.[46–50] Given those liver-related outcomes were not the primary objectives of the present study, our results at least seem helpful in identifying responders who were able to avoid invasive procedures for the prevention of bleeding.

Caution is needed in the interpretation of the present study for the following reasons. First, the prediction model was developed based on data that were obtained under primary prophylaxis with carvedilol in a Korean population with predominantly alcohol-related cirrhosis followed by hepatitis B-related cirrhosis. Whether this model would retain its predictive performance under different clinical circumstances (use of other NSBBs, secondary prophylaxis, and different patient characteristics) remains unclear. Second, we designed this study using the latest available evidence and guidelines at the time of study design. The use of high-dose carvedilol in the derivation cohort may have caused more profound reductions in portal venous pressure and SS, although the reproducibility of these results in case of lower doses was partially proven in our results. Third, given that false positivity for HVPG response in non-responders could make them lose an opportunity to discontinue useless NSBB therapy and switch to band ligation, the modified cut-off value for maximizing specificity (0.731) might be better than the original cut-off value. However, the most optimal cut-off value of ΔSS-based prediction model remains to be determined in further studies.

In conclusion, paired SS measurements using ARFI elastography may be a promising non-invasive tool for predicting hemodynamic response to carvedilol therapy as primary prophylaxis in patients with cirrhosis and high-risk esophageal varices. Replacement of HVPG measurement with ARFI-measured SS for the prediction of NSBB responses requires further investigation in different clinical settings, including different etiologies, treatment settings, types, and doses of NSBBs.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study conception and design by HYK and WK; data collection by HYK, YHS, D-WA, YJJ, HW and WK; data analysis and interpretation by HYK, WK, DK, MYK and SKB; manuscript writing by HYK, YHS and WK; critical review, revision and approval of the manuscript by HYK, YHS, WK, D-WA, YJJ, HW, DK, MYK and SKB.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.018.

References

Author names in bold designate shared co-first authorship

[1] Kovalak M, Lake J, Mattek N, Eisen G, Lieberman D, Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. Gastrointest Endosc 2007;65:82–88.
[2] Brocchi E, Caletti G, Brambilla G, La Mantia L, Lupinacci G, Pisano G, et al. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983–989.
[3] Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology 2014;146, 412–419 e413.

[4] D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis 1999;19:475–505.
[5] D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611–1624.
[6] **Abraldes JG**, **Tarantino I**, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902–908.
[7] Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506–512.
[8] Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol 2013;58:911–921.
[9] Senzolo M, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, et al. beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int 2009;29:1189–1193.
[10] Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int 2013;33:62–71.
[11] Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646–654.
[12] Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol 2014;60:1158–1164.
[13] Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015;275:589–598.
[14] **Procopet B**, **Berzigotti A**, Abraldes JG, Turon F, Hernandez-Gea V, Garcia-Pagan JC, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015;62:1068–1075.
[15] **Moons KG**, **Kengne AP**, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;98:691–698.
[16] Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453–473.
[17] de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762–768.
[18] Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62:1634–1641.
[19] **Sinagra E**, **Perricone G**, D'Amico M, Tine F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther 2014;39:557–568.
[20] Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. Dig Liver Dis 2017;49:3–10.
[21] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280–282.
[22] Woo H, Lee JY, Yoon JH, Kim W, Cho B, Choi BI. Comparison of the reliability of acoustic radiation force impulse imaging and supersonic shear imaging in measurement of liver stiffness. Radiology 2015;277:881–886.
[23] Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, Update 2017 (Long Version). Ultraschall Med 2017;38:e16–e47.
[24] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.
[25] Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb) 2016;26:297–307.
[26] Steyerberg EW, Harrell Jr FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–781.
[27] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310–335.
[28] de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–752.
[29] Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009;50:825–833.
[30] Shah HA, Azam Z, Rauf J, Abid S, Hamid S, Jafri W, et al. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol 2014;60:757–764.
[31] Banares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, de Diego A, et al. Carvedilol, a new nonselective beta-blocker with intrinsic anti-Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology 1999;30:79–83.
[32] **Kim SG**, **Kim TY**, Sohn JH, Um SH, Seo YS, Baik SK, et al. Open-label study to evaluate the efficacy of carvedilol vs. propranolol to reduce portal pressure in patients with liver cirrhosis. Am J Gastroenterol 2016;111:1582–1590.
[33] Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC. Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. Aliment Pharmacol Ther 2002;16:373–380.
[34] Stanley AJ, Therapondos G, Helmy A, Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. J Hepatol 1999;30:479–484.
[35] **Mandorfer M**, **Kozbial K**, Schwabl P, Freissmuth C, Schwarzer R, Stern R, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;65:692–699.
[36] Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Toshikuni N, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology 2013;144, 412–419 e413.
[37] Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. Radiology 2016;279:609–619.
[38] **Kim HY**, **Jin EH**, Kim W, Lee JY, Woo H, Oh S, et al. The role of spleen stiffness in determining the severity and bleeding risk of esophageal varices in cirrhotic patients. Medicine (Baltimore) 2015;94 e1031.
[39] Gao J, Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG. The stiffness of the liver and spleen on ARFI Imaging pre and post TIPS placement: a preliminary observation. Clin Imaging 2012;36:135–141.
[40] Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG, Chen J, et al. Spleen stiffness and splenoportal venous flow: assessment before and after transjugular intrahepatic portosystemic shunt placement. J Ultrasound Med 2013;32:221–228.
[41] Guo J, Buning C, Schott E, Kroncke T, Braun J, Sack I, et al. In vivo abdominal magnetic resonance elastography for the assessment of portal hypertension before and after transjugular intrahepatic portosystemic shunt implantation. Invest Radiol 2015;50:347–351.
[42] Hernandez-Gea V, Procopet B, Giraldez A, Amitrano L, Villanueva C, Thabut D, et al. Preemptive-TIPS improves outcome in high-risk variceal bleeding: an observational study. Hepatology 2018.
[43] Piecha F, Paech D, Sollors J, Seitz HK, Rossle M, Rausch V, et al. Rapid change of liver stiffness after variceal ligation and TIPS implantation. Am J Physiol Gastrointest Liver Physiol 2018;314:G179–G187.
[44] Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology 1990;99:1401–1407.
[45] Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056–1059.
[46] Bang UC, Benfield T, Hyldstrup L, Jensen JE, Bendtsen F. Effect of propranolol on survival in patients with decompensated cirrhosis: a nationwide study based Danish patient registers. Liver Int 2016;36:1304–1312.

[47] Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146, 1680–1690 e1681.
[48] Bossen L, Krag A, Vilstrup H, Watson H, Jepsen P. Nonselective beta-blockers do not affect mortality in cirrhosis patients with ascites: post Hoc analysis of three randomized controlled trials with 1198 patients. Hepatology 2016;63:1968–1976.
[49] Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut 2015;64:1111–1119.
[50] Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, et al. Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology 2018.