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ORIGINAL ARTICLE

Liver stiffness assessment as an alternative to hepatic venous pressure gradient for predicting rebleed after acute variceal bleed: A proof-of-concept study

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Key words
cirrhosis, liver, portal hypertension, varices.

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Abstract

Background and Aim: Hepatic venous pressure gradient (HVPG), although an important determinant in predicting rebleeding after an episode of acute variceal bleed (AVB), is seldom utilized in clinical practice. We aimed to study the role of liver stiffness measurement (LSM) after variceal bleeding as a potential noninvasive predictor of rebleed.

Methods: This was a post hoc analysis of clinical trial of patients undergoing HVPG (postbleed HVPG) and LSM (postbleed LSM) assessment within 3–5 days of index AVB. HVPG response was assessed after 4 weeks of pharmacotherapy. Comparative assessment of long-term rebleeding rates stratified using postbleed LSM, postbleed HVPG, and HVPG response was performed. Decision curve analysis (DCA) was conducted to identify the most appropriate tool for routine use.

Results: Long-term clinical and HVPG response data were available for 48 patients post-AVB, of whom 45 patients had valid postbleed LSM. Rebleeding occurred in 13 (28%) patients over a median follow-up of 4 years with no early rebleeds. Postbleed LSM >30 kPa and baseline HVPG >15 mm Hg were optimal cutoffs for identifying patients at high risk of rebleeding. Time-dependent receiver operating characteristic curves and competing risk analysis accounting for death showed similar discriminative values for all three stratification tools. At usual risk thresholds, HVPG response had maximum benefit on DCA followed by postbleed LSM. On DCA, 50–60 additional HVPGs were required to detect one additional patient at high risk of rebleed.

Conclusion: Liver stiffness measurement during AVB can potentially be used as an alternative to portal pressure indices in decompensated cirrhosis to identify those at high risk of late-onset rebleed.

Introduction

The assessment of portal pressure indices such as hepatic venous pressure gradient (HVPG) and its effective reduction with pharmacotherapy is an effective tool to predict short-term, as well as long-term, outcomes in patients with acute variceal bleed (AVB) and decompensated cirrhosis.[1–5] HVPG measurement, however, is an invasive procedure, requires expertise, and is usually performed in only a few research centers, limiting its widespread use in clinical practice.[6] Attempts to replace HVPG assessment with noninvasive methods are still in the preliminary stage with limited clinical applications.[7,8] Thus, there remains a need to identify noninvasive surrogates for portal pressure indices for them to be used regularly to identify those at high risk of rebleed.

Measurement of liver stiffness (LS) is an important adjunct in the management of compensated chronic liver disease (CLD) and predicts long-term complications in these patients.[9–11] Liver stiffness has been correlated with the risk of variceal bleeding, particularly in combination with splenic stiffness.[12] There exists a good correlation between liver stiffness measurement (LSM) and HVPG up to 12 mm Hg, but not beyond, possibly in view of the additional contribution of hyperdynamic circulation to portal hypertension at that stage.[13–15] Therefore, theoretically, LSM is not a good marker of portal pressure once clinically significant portal hypertension (CSPH) sets in. However, AVB is a unique situation where elastography values may be affected by both fibrosis and hepatic congestion secondary to an acute increase in portal pressure. LS measurement during an episode of AVB may therefore reflect both components of portal hypertension and may be a valid surrogate to portal pressure indices.

The present study assessed LSM during an episode of variceal bleed and evaluated its potential ability to stratify patients according to risk of rebleed. Risk stratification via postbleed LSM was then compared with established prognostic indicators of outcomes postvariceal bleed, that is, postbleed

HVPG, and HVPG response with pharmacotherapy. In addition, we studied the correlation of postbleed LSM with HVPG to assess its role as a noninvasive marker of portal pressures.

Methods

The present study is a post hoc analysis of a randomized controlled trial comparing the efficacy of 4 weeks of treatment with carvedilol and propranolol (CTRI/2013/10/004119) in reducing HVPG in patients with cirrhosis after an episode of AVB,[16] conducted at a tertiary care center. Previously undiagnosed patients of CLD presenting with the first episode of AVB from June to December 2013 were treated with a combination of endoscopic therapy, vasoactive drugs, and prophylactic antibiotics. After controlling the bleeding, included patients underwent measurement of HVPG on days 3–5 of the AVB episode (postbleed HVPG). This measurement of HVPG was taken 24 h after discontinuation of vasoactive agents. Valid measurement of LS was carried out within 24 h of HVPG assessment (postbleed LSM). Those with (i) presentation beyond 5 days of AVB, (ii) invalid measurement of HVPG/LS, (iii) acute-on-chronic liver failure[17] at presentation, (iv) previously diagnosed hepatocellular carcinoma, (v) renal dysfunction (serum creatinine more than 1.5 mg/dL), and (vi) Budd–Chiari syndrome (assessed by doppler of hepatic veins) and extrahepatic portal venous obstruction as a cause of portal hypertension (assessed by clinical history and ultrasonological findings of portal cavernoma) were excluded from this study. Patients with postbleed HVPG of more than 12 mm Hg were randomized to receive either carvedilol or propranolol. The dose was titrated to achieve a target heart rate of 55–60 beats per minute. A repeat HVPG measurement was taken after 4 weeks of pharmacotherapy. Depending on hemodynamic response, patients were stratified as HVPG responders and nonresponders. The objective of the original study was to compare the efficacy of propranolol *versus* carvedilol in the reduction of HVPG at 1 month after index AVB. Postassessment of HVPG response, patients in both groups were followed up prospectively from December 2013 till October 2019 or earlier if they had died or undergone liver transplantation. Over this duration, they were assessed for additional liver-related events such as new-onset decompensation, rebleeding, development of hepatocellular carcinoma (HCC), and development of acute on chronic liver failure (ACLF).

For the present post hoc analysis, the outcomes of those with a valid postbleed LSM assessed at baseline during an AVB episode and an available follow-up of more than 1 year were retrospectively reviewed and analyzed. Informed written consent was obtained from all patients at the time of inclusion, and all procedures performed in the studies were in accordance with the ethical standards of the institutional ethics committee and the 1975 Helsinki declaration and its later amendments or comparable ethical standards. In view of the retrospective nature of the study, consent was waived.

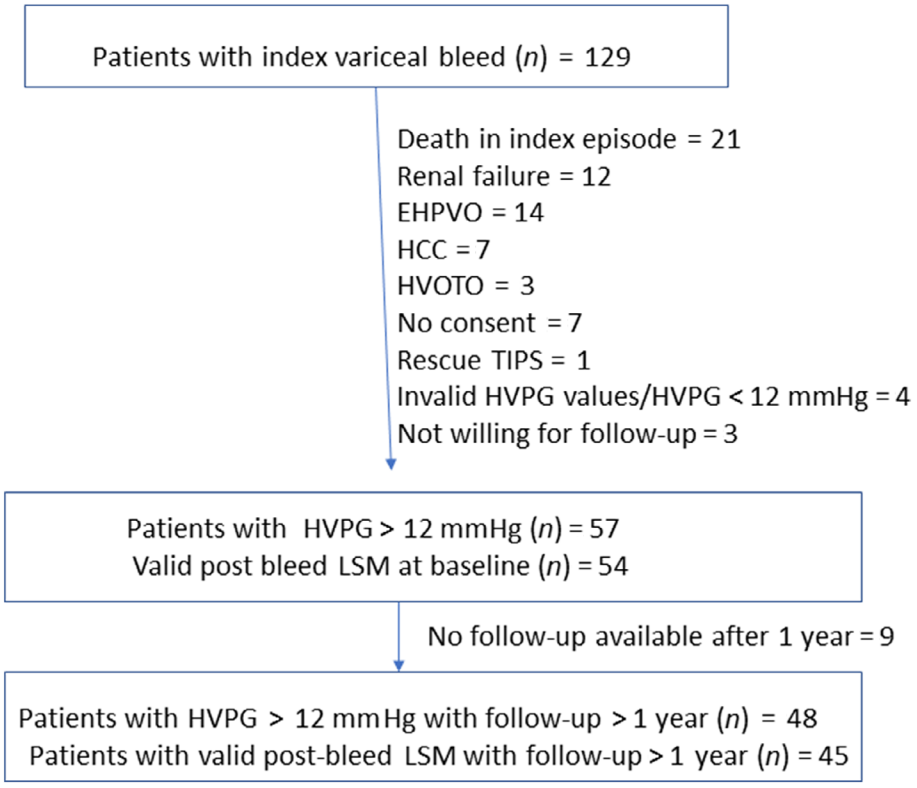

Figure 1 Flow diagram showing recruitment of patients with valid postbleed LSM values for the present study. EHPVO, extrahepatic portal venous obstruction; HCC, hepatocellular carcinoma; HVOTO, hepatic venous outflow tract obstruction; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; TIPS, transjugular intrahepatic portosystemic shunts.

Definitions. CLD was diagnosed on the basis of a composite of clinical symptoms, laboratory values, imaging/endoscopic/hemodynamic evidence of portal hypertension, and/or on liver biopsy.[18] AVB was defined as an episode of hematemesis/melena, with esophago-gastroduodenoscopy (EGD) showing active bleeding from a column of varix or the presence of high-risk varices in the absence of other source of bleeding.[19] Rebleeding from failure of secondary prophylaxis was defined as a single episode of clinically significant rebleeding from portal hypertensive sources after day 5 following an episode of AVB.[19] Early rebleeding was defined as rebleed after an episode of AVB but within the 6 weeks of the episode of AVB.[19] Rebleed occurring after 6 weeks was classified as late rebleeding. Postbleed HVPG was defined as HVPG measured on days 3–5 of AVB after attainment of hemostasis. HVPG response was defined as more than 20% reduction in HVPG or an absolute reduction to less than 12 mm Hg after 4 weeks of treatment with pharmacotherapy when compared with baseline.[1] Postbleed LSM was arbitrarily defined as LS measured within 4–6 days of onset of AVB, performed 48 h after discontinuation of vasoactive drugs and within 24 h of HVPG assessment.

Stratification of cohort. For this study, optimal cutoffs for predicting rebleeding risks were calculated for postbleed LSM and postbleed HVPG from a receiver operating characteristic (ROC) curve (detailed in statistical analysis). Depending on these cutoffs, patients were classified as low risk and high risk for rebleeding according to respective stratification tools. Stratification for rebleeding risks via HVPG response was performed as per standard definition. Comparative assessment of rebleeding risk and its association with postbleed LSM, postbleed HVPG, and HVPG response was carried out.

Table 1 Comparison of demographic and baseline parameters and outcome assessment in patients with or without HVPG response

	Overall	HVPG responders (n = 29)	HVPG nonresponders (n = 19)	P value
Demographic details				
Age	44.0 ± 11.7	42.2 ± 12.2	46.7 ± 10.6	0.192
Females	5 (10.4%)	2 (6.9%)	3 (15.8%)	0.324
Etiology				0.661
HBV	3 (6.3%)	3 (10.3%)	0 (0%)	
HCV	11 (22.9%)	7 (24.1%)	4 (21.1%)	
Alcohol	28 (58.3%)	16 (55.2%)	12 (63.2%)	
NAFLD	2 (4.2%)	1 (3.4%)	1 (5.3%)	
Cryptogenic	4 (8.3%)	2 (6.9%)	2 (10.5%)	
Baseline parameters				
CTP score	7 (6–8)	7 (6–7)	7 (6–8)	0.406
Child A	12 (25%)	9 (31%)	3 (15.8%)	0.479
Child B	31 (64.6%)	17 (58.6%)	14 (73.6%)	
Child C	5 (10.4%)	3 (10.3%)	2 (10.5%)	
MELD	11.7 ± 3.5	11.4 ± 3.9	12.1 ± 3.0	0.545
Hemoglobin	9.6 ± 2.0	9.4 ± 2.0	9.8 ± 2.1	0.469
Platelet count (mm^3)	770 000 (55000–127 000)	85 000 (55000–132 000)	75 000 (55000–123 000)	0.41
Ascites at baseline	30 (62.5%)	18 (62.1%)	12 (63.2%)	0.939
Grade of ascites				
Grade 1	20 (66.7%)	10 (55.6%)	10 (83.3%)	
Grade 2	8 (26.7%)	6 (33.3%)	2 (16.7%)	
Grade 3	2 (6.6%)	2 (11.1%)	0 (0%)	
Bilirubin (mg/dL)	1.8 (0.9–3)	2 (0.9–3)	1.7 (0.9–2.8)	0.519
AST (IU/L)	56 (40–98)	58 (45–98)	56 (36–97)	0.435
ALT (IU/L)	49 (35–76)	52 (35–80)	48 (36–66)	0.448
ALP (IU/L)	282.0 ± 118.2	288.0 ± 137.4	272.8 ± 83.6	0.67
Creatinine (mg/dL)	0.85 ± 0.17	0.84 ± 0.15	0.85 ± 0.19	0.959
Albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.5	3.4 ± 0.6	0.742
INR	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.153
Postbleed LSM (kPa)	28 (20–58)	28 (18–66)	34 (25–56)	0.914
Postbleed baseline HVPG (mm Hg)	17.3 ± 2.9	17.1 ± 3.0	17.6 ± 2.8	0.51
Treatment parameters				
Carvedilol group	25 (52.1%)	18 (62.1%)	7 (36.8%)	0.087
HVPG at 4 weeks (mm Hg)	13.1 ± 3.4	11.5 ± 3.1	15.4 ± 2.5	<0.001
Heart rate achieved (beats/min)	63 ± 3	62 ± 3	63 ± 4	0.462

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child Turcotte Pugh score; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease.

Management strategy and follow-up

Management during an episode of AVB. Medical management as part of the original trial is described in Supplementary Text And is briefly outlined here.

Management during follow-up. Management during follow-up is described in Supplementary Text.

Procedures conducted in study

HVPG measurement

Measurement of HVPG is described in detail in the original study and in Supplementary Information. For all included patients, repeat HVPG measurement was performed after 4 weeks of pharmacotherapy, and hemodynamic response was assessed.

Liver stiffness measurement

The LSM protocol has been previously published in detail[20] by our institute and is outlined in Supplementary Information.

Endoscopic band ligation

The procedure for EBL is described in detail in Supplementary Information. Sessions for EBL were repeated at 3-week intervals till varices were eradicated. Following variceal eradication, surveillance EGD was carried out at 6-month intervals, and management was optimized.

Outcomes. The primary outcome was the cumulative rate of rebleed following index variceal bleed in different risk groups as defined previously by risk stratification tools (postbleed LSM, postbleed HVPG, and HVPG response) at predefined intervals of 1 year, 3 years, and 5 years, respectively. Additional outcomes studied included diagnostic performance of different risk stratification tools in identifying patients at high risk of rebleed.

Statistical analysis. Baseline data of patients with follow-up data from the original study were reported using number (%) or mean ± standard deviation/median (interquartile range [IQR]) as appropriate, based on normality of distribution. Parameters recorded at the time of index bleed, including LSM, were compared based on whether or not HVPG response was attained using chi-square test/Fischer Exact test for categorical variables and Student's *t*-test for continuous variables with normal distribution. Continuous variables with nonnormal distribution were compared using the independent-samples Kruskal-Wallis test. For all statistical tests, a P value <0.05 was considered statistically significant.

Correlation between postbleed LSM, postbleed HVPG at baseline, and quantitative HVPG response (percentage fall in HVPG at 4 weeks of pharmacotherapy compared to baseline) was studied using an estimation of Spearman's rank correlation coefficient (ρ). Significant correlations were represented using scatter plots with a regression line.

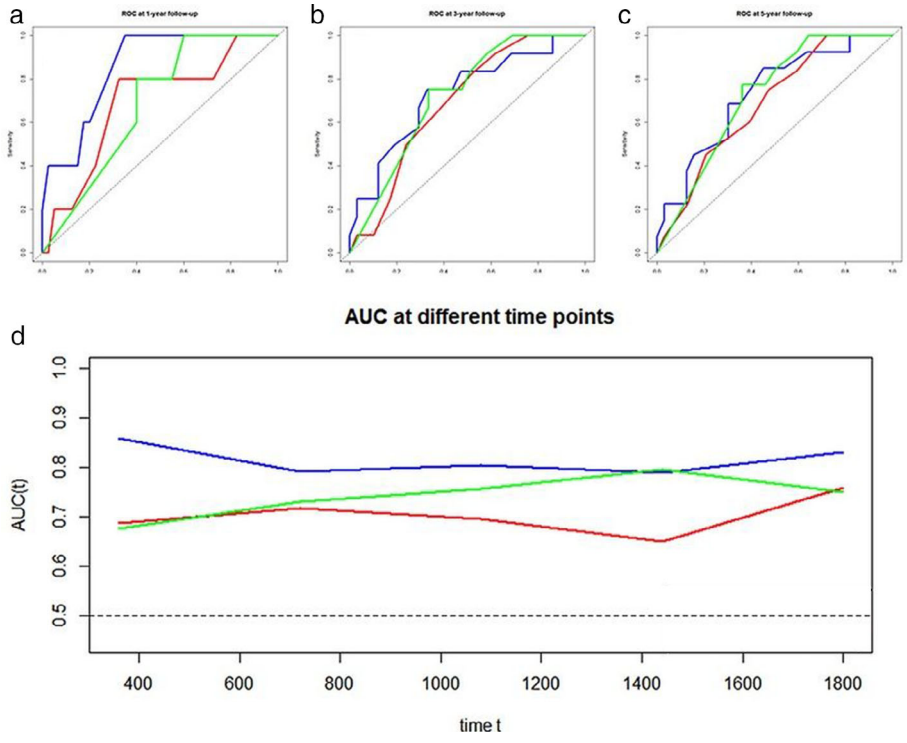

Figure 2 Time-dependent receiver operating characteristic (ROC) curves showing rebleed predictive accuracy at 1-year (a), 3-year (b), and 5-year (c) follow-up from index bleed for postbleed liver stiffness measurement (LSM) (blue), postbleed hepatic venous pressure gradient (HVPG) (red), and HVPG response (green). Panel d shows area under curve (AUC) for three predictors of rebleed up to 5 years of follow-up. Time on *x*-axis is in days from index bleed.

Performance characteristics of postbleed LSM, postbleed HVPG, and quantitative HVPG response for prediction of variceal rebleed were assessed using a time-dependent ROC[21] curve and area under ROC curve (AUROC), accounting for censored data and competing risks (death), and appropriate cutoffs were identified. See Supplementary Information for details.

Comparison of rebleeding events between groups stratified using identified cutoffs was carried out using Fine and Gray's competing-risks analysis while accounting for the deaths occurring during the course of follow-up, with rebleed and death (prior to rebleed) as competing events.

For better assessment of the clinical utility of different tests in a real-life setting to predict patients at high risk of rebleed, a decision curve analysis (DCA) was conducted.[22] Further details of the DCA are described in Supplementary Information.

All data were entered using Microsoft Excel 2011 and were analyzed using Rstudio version 1.2.5033. The DCA was implemented in R using code derived from Zhang et al.[23] In addition to the base packages in R, tidyverse, survival, survminer, boot, reshape2, time ROC, and readxl packages were used.

Results

The original study included 59 patients presenting with a first episode of AVB over the period of June to December 2013. Fifty-seven of these patients underwent a second hemodynamic study after 4 weeks of dose-titration of non-selective beta blockers (NSBB) and were included in the original randomised controlled trial (RCT). In the present study, long-term (more than 1 year) follow-up data were available for 48 of these patients. Valid postbleed LS measurements were available in 45 of these followed-up patients (Figure 1).

Baseline characteristics. The baseline characteristics of patients with complete follow-up data, stratified by HVPG response, are outlined here (Table 1). The mean age was 44 ± 11 years, with the majority being men (89.6%). Alcohol-related CLD was the most common etiology (58.3%), followed by hepatitis C virus (HCV) (22.9%) and cryptogenic liver disease (8.3%). Median child turcot pugh (CTP) score was 7, with the majority of patients being of the class Child B (64.6%). Ascites was common (62.5%), and the majority (66.7%) of these patients had mild ascites. Median postbleed LSM was 28 (IQR: 20–58) kPa, slightly higher in HVPG nonresponders [34 kPa (nonresponders) *vs* 25 kPa (responders); $P = 0.914$]. The remaining baseline parameters were similar irrespective of HVPG response.

Patients were followed up for a median duration of 1488 days (4.1 years), with 23 (51.1%) patients alive at last follow-up. Median time to rebleed was lower in those who did not attain HVPG response (1265 days [3.46 years]) in comparison to HVPG responders (1580 days [4.3 years]), although this difference was not statistically significant (log-rank $P = 0.84$). Overall, 25 patients received carvedilol, and 23 patients received propranolol, with the proportion of HVPG responders being higher in those receiving carvedilol (62% in HVPG responders *vs* 36.8% in HVPG nonresponders, $P = 0.087$). The frequency of EBL sessions required for variceal eradication was comparable in both groups (HVPG responders- 4 (IQR: 2–6) *vs* HVPG nonresponders- 4 (IQR: 2–5); $P = 0.34$). Of the 45 patients with valid LSM measurements, 13 patients (28.8%) had rebleed—nine (47.3%) among HVPG nonresponders and four among HVPG responders (15.4%)—over the follow-up duration. Variceal eradication prior to rebleeding was seen in 23 (82%) patients in the HVPG responders group and in 14 (73.6%) patients in the HVPG nonresponders group. None of the included patient had an early rebleed. All rebleeds were managed endoscopically, and no patients were subjected to transjugular intrahepatic portosystemic shunt (TIPS) or liver transplant during this period.

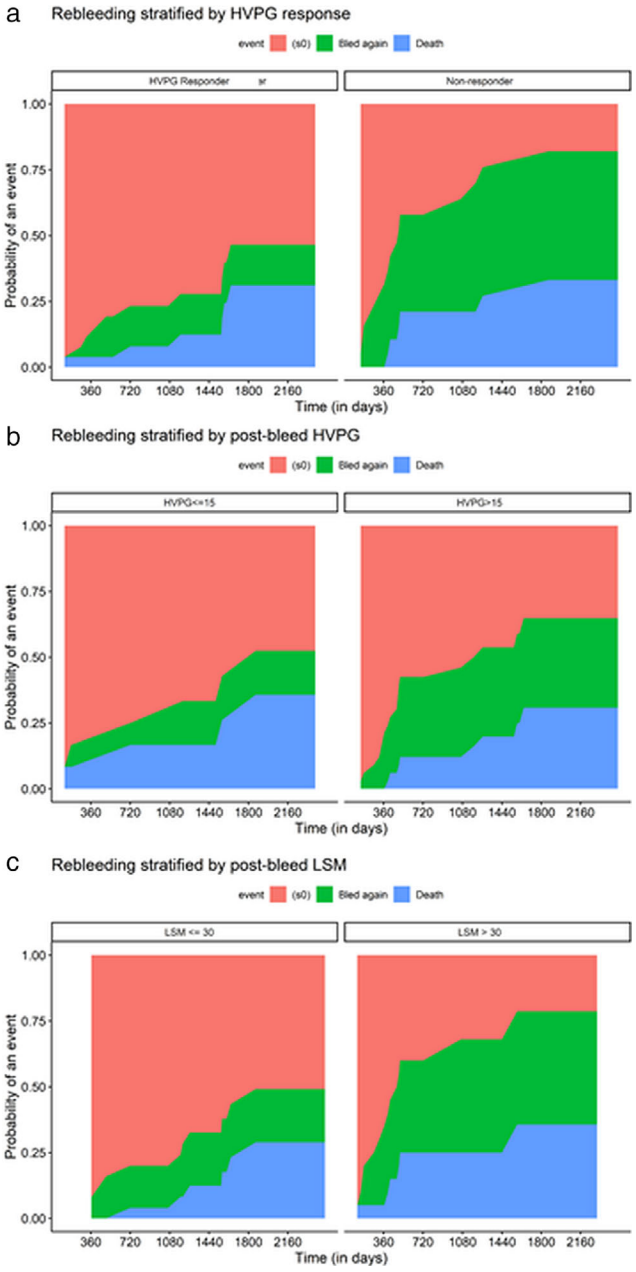

Figure 3 Competing risks plots showing cumulative rates of variceal rebleed (green) with death as a competing event (blue), stratified by hepatic venous pressure gradient (HVPG) response (a), postbleed HVPG (b), and post-bleed liver stiffness measurement (LSM) (c). Time on *x*-axis is in days from index bleed. Event: (——), s0; (——), rebleeding; (——), death.

Performance of risk stratification tools. Optimal cutoffs for postbleed LSM and postbleed HVPG for identifying patients at high rebleeding risk were >30 kPa and >15 mm Hg, respectively, while HVPG response was stratified as per standard criteria. Using these cutoffs, 20 (44.4%) and 33 (73.3%) patients were labeled as being at high risk for rebleed based on postbleed LSM and postbleed HVPG, respectively. In comparison, 19 (42.2%) patients were classified as HVPG nonresponders based on hemodynamic response assessment criteria.

Time-dependent ROC curves showed near-similar discriminative values of postbleed LSM, postbleed HVPG, and HVPG response for predicting rebleed, with death as a competing event (Figure 2). AUROC trends of all three predictors were essentially stable over time (Table S1 and Figure 2d), with no statistically significant differences at any time point. On comparison of performance characteristics of postbleed LSM for predicting rebleeding risk with postbleed HVPG and HVPG response (Table S1), postbleed LSM > 30 kPa had a higher specificity (80–85%) with a lower sensitivity (60–67%) and postbleed HVPG >15 mm Hg had good sensitivity (82–91%) but poorer specificity (36–50%) for predicting rebleed. HVPG nonresponse had intermediate sensitivity (63–71%) and specificity (66–78%) for predicting rebleed. Competing risks analysis showed that the 1-year, 3-year, and 5-year rebleeding rates were 7.7, 15.4, and 15.4% and 15.8, 42.9, and 48.9% for HVPG responders and nonresponders, respectively, this difference being statistically significant (Gray's test; $P = 0.019$). Similar rebleeding rates were obtained when stratified by postbleed LSM and postbleed HVPG as well (Figure 3 and Table 2), although the results were not statistically significant (Gray's test $P = 0.053$ for postbleed LSM and $P = 0.253$ for postbleed HVPG).

A DCA was conducted to assess the overall net benefit achieved by using different risk stratification criteria at different thresholds for rebleed (outlined above) (Fig. 4 and Table3).

Table 2 Cumulative rebleeding risk rates and survival rates calculated in high- and low-risk groups identified by different stratification tools using competing risk analysis

	Low-risk group			High-risk group			
	HVPG responder (n = 26)			HVPG nonresponder (n = 19)			*P* value
	1-year	3-year	5-year	1-year	3-year	5-year	
Rebleed	7.7%	15.4%	15.4%	15.8%	42.9%	48.9%	0.019
Death	3.9%	7.9%	31.1%	0.0%	21.1%	27.1%	0.655
	Postbleed HVPG ≤ 15 mm Hg (n = 12)			Postbleed HVPG > 15 mm Hg (n = 33)			
	1-year	3-year	5-year	1-year	3-year	5-year	
Rebleed	8.3%	8.3%	16.7%	12.1%	33.9%	33.9%	0.254
Death	8.3%	16.7%	26.2%	0.0%	12.1%	30.9%	0.837
	Postbleed LSM ≤ 30 kPa (n = 25)			Postbleed LSM > 30 kPa (n = 20)			
	1-year	3-year	5-year	1-year	3-year	5-year	
Rebleed	0.0%	16.0%	20.2%	25.0%	43.0%	43.0%	0.053
Death	0.0%	4.0%	23.3%	5.0%	25.0%	35.7%	0.285

Levels of significance were estimated for comparison of rates of rebleeding and mortality between respective high- and low-risk groups by Gray's test (see text).
HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement.

Table 3 Decision curve analysis showing net benefit of different risk stratification tools for prediction of rebleed at relevant threshold probabilities

Prediction of variceal rebleed							
	Non-HVPG-based criteria	HVPG-based criteria					
	Postbleed LSM > 30 kPa	Postbleed HVPG >15 mm Hg			HVPG response		
Threshold probability	Net benefit	Net benefit	Test tradeoff in comparison to LSM alone	Number of additional HVPG for detecting 1 additional bleed	Net benefit	Test tradeoff in comparison to LSM alone	Number of additional HVPG for detecting 1 additional bleed
10%	0.1481	0.1901	0.042 (−0.056 to 0.14)	24	0.1753	0.027 (−0.057 to 0.111)	74
20%	0.1111	0.1222	0.011 (−0.099 to 0.121)	91	0.1444	0.033 (−0.061 to 0.128)	62
30%	0.0635	0.0349	−0.029 (−0.154 to 0.097)		0.1047	0.041 (−0.067 to 0.15)	50
40%	0	−0.0815	−0.082 (−0.228 to 0.065)		0.0518	0.052 (−0.074 to 0.178)	40

Test tradeoff along with corresponding number needed to diagnose one additional patient of high risk of rebleed by HVPG response in comparison to postbleed LSM at a particular risk threshold.
HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement.

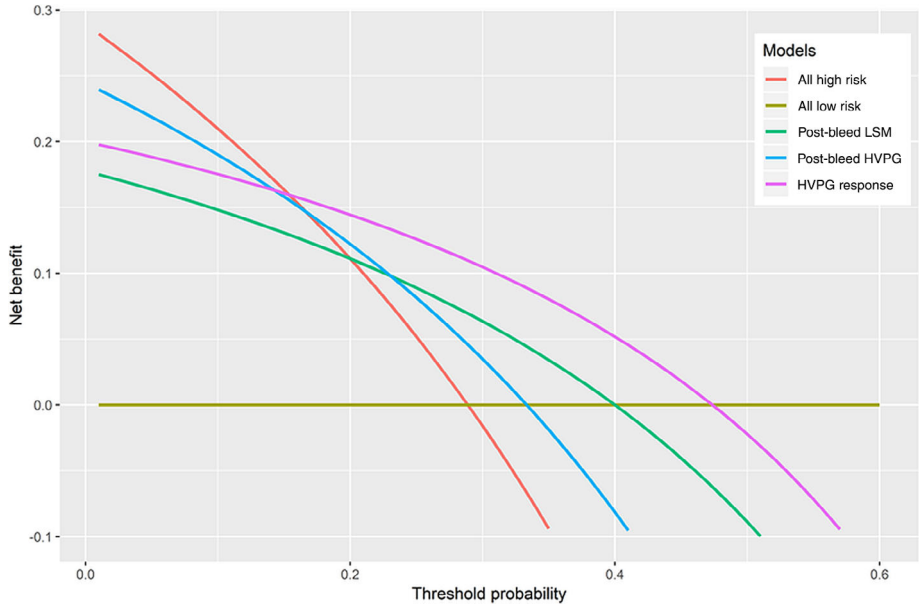

Figure 4 Decision curve analysis plot for postbleed liver stiffness measurement (LSM) (green), postbleed hepatic venous pressure gradient (HVPG) (blue), and HVPG response (violet) in comparison to default strategies of treating all patients as high risk (red) or low risk (brown).

Correlation of postbleed HVPG and postbleed LSM. An overall positive correlation was noted between postbleed HVPG and postbleed LSM (Figure S1), although the strength of the correlation was moderate (Spearman's $\rho = 0.534$; $P < 0.001$).

Discussion

Variceal rebleed can occur in about 60 % of untreated patients with index variceal bleed in cirrhosis and is associated with increased mortality.[24] The identification of those with a higher risk of rebleeding using noninvasive methods can be a useful adjunct in settings where HVPG assessment and risk stratification are not routinely available. In the present study, we followed up patients with index AVB managed with pharmacotherapy and EBL and showed that both HVPG response and postbleed LSM identify a relatively homogenous high-risk group with a 5-year rebleeding risk of 40–50%. In addition, although HVPG response was the best among risk stratification tools, measuring postbleed LSM emerged as an effective alternative for predicting risk of late rebleeding. At risk thresholds where the documentation of HVPG response is warranted, the use of postbleed LSM can be a good alternative in routine clinical practice.

LSM has been extensively used in patients with compensated cirrhosis to predict the risk of future decompensations and overall survival,[9–11] but its use in decompensated cirrhosis remains unexplored. Accurate measurement of LSM in patients with decompensated CLD is complicated by the presence of ascites and significant hepatic congestion, factors that have prevented its rigorous assessment in the past. Our data, however, show that, in patients with cirrhosis and index AVB, valid LSM measurements can be obtained in more than 90% of patients after therapeutic ascitic tap if required. This LSM measurement is not an adequate representation of portal pressure, as indicated by its modest correlation with HVPG. It is, however, unique as it is possibly affected by both hepatic congestion and fibrosis[25] and may have definite prognostic value. The fact that postbleed LSM stratifies patients at risk of rebleed, as well as HVPG response, and that its predictive accuracy remains stable over time indicates that it represents a valid measure of future rebleeding risk and is not just an artifact due to acute hepatic congestion during AVB. We believe that this assessment of LSM in decompensated cirrhosis may be relevant, particularly in those patients who present with AVB as the first manifestation of CLD.

While HVPG response has the best performance characteristics, the decision to perform/not perform two HVPG measurements for pharmacotherapy response in any population must be weighed against the discomfort and cost of performing the procedure and the possibility of providing effective treatment in a high-risk group, if identified. Threshold probability, defined as the probability of disease (rebleed) at which the benefit gained by undergoing a diagnostic test (HVPG) equals the risk of foregoing it, may vary for different patients. The DCA in our cohort showed that, for a scenario where the physician/patient regards rebleed rates of even 10% as high risk, no benefit is gained by performing HVPG, and treating all patients as high risk may be appropriate. On the other hand, if even patients with rebleed rates of 50% or more are not managed differently, there is again no benefit of performing HVPG, and a more conservative strategy is more suitable. The maximum benefit of assessing HVPG response is attained in between these threshold probabilities, with the benefit of postbleed LSM being somewhat lesser but close. Importantly, the test tradeoff for HVPG was not high when compared with LSM, translating to a need to perform 50–60 more HVPGs to detect one additional patient at high risk of rebleed when compared with postbleed LSM.

Ours is the first proof-of concept study to demonstrate the benefit of LSM-based prognostication in comparison to HVPG

response in patients with decompensated cirrhosis during AVB. In addition, we report the long-term outcomes of patients stratified using these prognostic indicators while accounting for competing risk of death. However, our study has certain important limitations. First, this is a retrospective analysis of outcomes in patients with index variceal bleed, wherein a few patients were lost to follow-up, and the possibility of few missed outcomes cannot be negated. In addition, we had a relatively small sample size available for analysis. The confidence intervals for estimates of test tradeoffs for net benefit values at all thresholds were wide, indicating the need for further studies to further establish the value of LSM-based prognostication in routine clinical practice. Third, HVPG measurement was not repeated in patients beyond 4 weeks of index bleed. It is possible that a few patients might have lost previously attained HVPG response or vice versa, However, the predictive accuracy of HVPG response remained stable over time, indicating that this was likely an insignificant event. Fourth, postbleed LSM needs validation in independent cohorts with a larger sample size before its use can be incorporated into clinical practice. Finally, while postbleed LSM was similar to HVPG response in predicting rebleed, it does not replace the role of HVPG in predicting early rebleed and response to pharmacotherapy. More studies are required to assess dynamic changes in postbleed LSM and its correlation with treatment and its overall impact on outcomes.

In conclusion, documentation of HVPG response on pharmacotherapy remains the best tool for identifying those at high risk of rebleed. LS measured during AVB predicts late-onset rebleed comparable to that of HVPG and its response. In centers where HVPG assessment is not routinely available, postbleed LSM can be used as an alternative tool for risk stratification to identify these patients.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Scatter plot showing correlation between postbleed HVPG and postbleed LSM measured during an episode of acute variceal bleed.

Table S1. Performance characteristics of postbleed HVPG, HVPG response, and postbleed LSM in predicting rebleed at different follow-up intervals

Appendix S1. Supporting information.