Albumin-bilirubin grade and INR for the prediction of esophagogastric variceal rebleeding after endoscopic treatment in cirrhosis

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Abstract. Rebleeding following endoscopic treatment in patients with cirrhosis is a serious life-threatening complication. In the present study, a novel, reliable and non-invasive score for prediction of rebleeding following endoscopic therapy for esophagogastric variceal bleeding (EGVB) was developed. The present retrospective study recruited cirrhotic patients with EGVB (n=596) who underwent endoscopic therapy. Patients hospitalized from January 2015 to January 2020 were grouped into a training (n=437) cohort to develop the new score and those hospitalized from February 2020 to February 2022 were grouped into a validation (n=159) cohort to validate the score. The international normalized ratio (INR) and albumin-bilirubin (ALBI) grade were used to develop the INR-ALBI (IALBI) score to predict risk of rebleeding. In the training cohort, the prognostic performance of the IALBI score and other ALBI-associated scores (modified ALBI, platelet-ALBI and ALBI-fibrosis-4) at 1, 3 and 12 months was assessed using receiver operating characteristic (ROC) curve and Kaplan-Meier analysis. At each time point, most areas under the ROC curve of IALBI were higher than those of other ALBI-associated scores, particularly for prediction of early rebleeding. At 1 month, the rebleeding rates of patients with IALBI grade 2 and 3 were ~10.0- and 19.5-times higher than those of patients with grade 1, respectively. The negative predictive value (NPV) of IALBI for the training and validation cohort at 1 month was 100.0 and 97.8%, respectively. For viral and non-viral patients in the training cohort, IALBI showed good predictive ability and NPV for early rebleeding. The IALBI grading system successfully assessed rebleeding, particularly early rebleeding, in cirrhotic patients with EGVB following endoscopic therapy IALBI grade 1, predicted low risk of rebleeding and may not require endoscopic treatment again in the short-term.

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Introduction

Cirrhosis is a pathogenic hallmark of advanced liver injury and fibrosis, and changes resulting from tissue remodeling in cirrhotic liver are associated with increased intrahepatic resistance to portal blood flow, leading to portal hypertension (PH). PH leads to formation of collateral pathways, particularly esophagogastric varices (1). Esophagogastric variceal bleeding (EGVB) is a frequent and dangerous complication associated with PH in patients with cirrhosis (2). In 1991, a multicenter study carried out in Boston, New Haven and Barcelona, determined that the rate of first variceal haemorrhage was 22% (3). Endoscopic treatment of esophagogastric varices includes endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS), characterized by minimal trauma and ease of repeated operation, and is widely used in clinical practice (4). In 2009, a study by Cheung *et al* (5), which involved multiple research centers in North America/Europe and Asia, found that rebleeding was still possible following endoscopic treatment with a mortality of up to 25%. Thus, the Baveno VI consensus (6) recommended early transjugular intrahepatic portosystemic shunt (TIPS). Early identification of patients at high risk of rebleeding following endoscopic treatment improves monitoring and management and timely treatment with endoscopic secondary prophylaxis, such as EVL every 2-6 weeks, or early TIPS are important to improve the prognosis of patients (6). Several non-invasive assessment models such as albumin (ALB)-bilirubin (ALBI), ALBI-fibrosis-4 (FIB4), fibrosis index (FI) and platelet count-spleen diameter ratio are currently used to predict the occurrence of EGVB and rebleeding (7-9).

ALBI-associated scores have received a lot of attention and are considered potential alternatives to Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) for prognosis of patients with chronic liver disease, liver failure and liver cancer (10-12). However, studies have reported limitations of the ALBI score, which considered that ALBI has a better prognostic power in patients with minimal liver dysfunction, and novel scores, such as modified ALBI (mALBI), platelet-ALBI (PALBI) and ALBI-FIB4, have emerged and are considered better predictors of liver decompensated events, especially in stratifying risk for portal hypertension (13-16). An elevated international normalized ratio (INR) reflects decreased hepatic reserve capacity and coagulation disorder (17). To the best of our knowledge, the present study is the first to combine INR with ALBI to predict rebleeding in patients with EGVB following endoscopic therapy for liver cirrhosis. Furthermore, ALBI-associated scores and grades (including mALBI, PALBI and ALBI-FIB4) were evaluated and compared with the novel scoring system INR-ALBI (IALBI) to analyze their predictive ability for rebleeding in cirrhotic patients with EGVB following endoscopic therapy in the short-, medium- and long-term.

Materials and methods

Patients. The present retrospective study was performed at the Third Central Hospital of Tianjin (Tianjin, China). A total of 1,348 hospitalized patients with EGVB who underwent endoscopic treatment following their first bleeding were retrospectively screened. The entire patient population was divided into training and validation cohorts based on the date of hospitalization. Patients hospitalized between January 2015 and January 2020 were assigned to the training cohort and patients hospitalized between February 2020 and February 2022 were assigned to the validation cohort (Fig. 1). The inclusion criteria were as follows: i) aged ≥18 years; ii) diagnosis of cirrhosis by liver biopsy or imaging examinations, together with clinical features and biochemical indices and iii) EGVB caused by PH due to liver cirrhosis. The exclusion criteria were as follows: i) Diagnosis of hepatocellular carcinoma (HCC), other malignant tumors and hematological disease at the time of recruitment or during follow-up; ii) non-cirrhotic PH; iii) undergoing TIPS, splenectomy, partial splenic embolization or liver transplantation; iv) previous history of EGVB, endoscopic treatment of esophagogastric varices, use of propranolol or other drugs to reduce PH and v) severe heart and lung disease.

The study was approved by the Ethics Committee of Tianjin Third Central Hospital (approval no. IRB2021-028-01) and written informed consent was obtained from all study participants.

Endoscopic data and treatment. In the present study, endoscopy was performed using an GIF-Q260J or GIF-H290Z (Olympus Corporation) and all patients underwent endoscopy within 48 h of admission. Endoscopic examinations and treatments were performed by expert endoscopists and uniform standards of treatment and documentation were used. Bands were applied to each varix in a step ladder pattern up to a level of 5 cm above the gastroesophageal junction. Endoscopic injection was performed intravariceally using a therapeutic endoscope and a transparent T eflon injector. An attempt was made to obturate the gastric varices completely at one session by injecting lauromacrogol and tissue adhesive at multiple sites. The injected the gastric varices was palpated using the hub of the injector with the needle retracted to look for solidification and obliteration of the gastric varices. If the gastric varices was not completely obturated, cyanoacrylate was reinjected till the whole the gastric varices became solidified (18,19).

Based on Japanese Research Society for Portal Hypertension classification (20), the following information on esophageal varices was recorded: i) Location (locus superior, medialis or inferior varices); ii) form (F0, lesions lack a varicose appearance; F1, lesions are straight, small-caliber varices; F2, moderately enlarged lesions, beady varices and F3, markedly enlarged lesions, nodular or tumor-shaped varices) and iii) red color signs (red wale markings, cherry red or hematocytic spots). According to the Sarin classification (21), gastric varices were defined as gastroesophageal varices (GOV) and isolated gastric varices (IGV). GOV1 was defined as esophageal varices that extended to the lesser curvature of the stomach; GOV2 was defined as esophageal varices that extended to the fundus of the stomach and IGV1 was defined as localized to the fundus of the stomach. Variceal bleeding was diagnosed when active bleeding from esophagogastric varices or signs of recent bleeding, such as 'white nipples', were observed (6). Esophageal varices were treated with band ligation. Gastric varices were managed with lauromacrogol and tissue adhesive injections. The number of injection sites and the dose of lauromacrogol and tissue adhesive were determined according to the severity of the varices in an attempt to eradicate the visible varices in one session (19). Lauromacrogol and tissue adhesive injection combined with band ligation were performed for patients with gastroesophageal varices.

Clinical and laboratory data. Data from all patients were collected from medical records, including: i) Age, sex, etiology of liver cirrhosis, ascites grade and presence of hepatic encephalopathy; ii) white blood cell (WBC), neutrophil (NEUT) and platelet (PLT) counts, hemoglobin (HGB), prothrombin time (PT), INR, fibrinogen, ALB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total BIL (TBIL), creatinine (Cr), blood urea nitrogen (BUN), sodium and blood glucose; iii) imaging indicators, including abdominal ultrasound and computed tomography (CT) of spleen and portal vein diameter, presence of portal vein thrombosis (PVT) and CT portosystemic shunt.

Calculation of non-invasive markers. CTP, MELD (22) and ALBI-related scores were calculated as follows: ALBI=($\log_{10}$BIL x 0.66) + (ALB x -0.085) [according to ALBI, scores were graded as follows: Grade 1, ≤-2.60; grade 2, >-2.60 and ≤-1.39 and grade 3, >-1.39 (12). According to mALBI, scores were graded as follows: Grade 1, ≤-2.60; grade 2a, >-2.60 and ≤-2.27; grade 2b, >-2.27 and ≤-1.39 and grade 3, >-1.39 (13)]; PALBI=2.02 x $\log_{10}$BIL -0.37 x ($\log_{10}$BIL)^2 -0.04 x ALB -3.48 x $\log_{10}$PLT + 1.01 x ($\log_{10}$PLT)^2 [grade 1, ≤-2.53; grade 2, >-2.53 and ≤-2.09 and grade 3, >-2.09 (14)]; ALBI-FIB-4=(ALBI x1.331) + (FIB-4 x0.165) [high risk, >-1.822; low risk, ≤-1.822 (15)] and FIB-4=(age x AST)/(PLT x ALT$^{1/2}$) (23). Patients with ALBI and PALBI grade 1, 2 and 3 were assigned a score of 1, 2 or 3, respectively (12,14). Patients

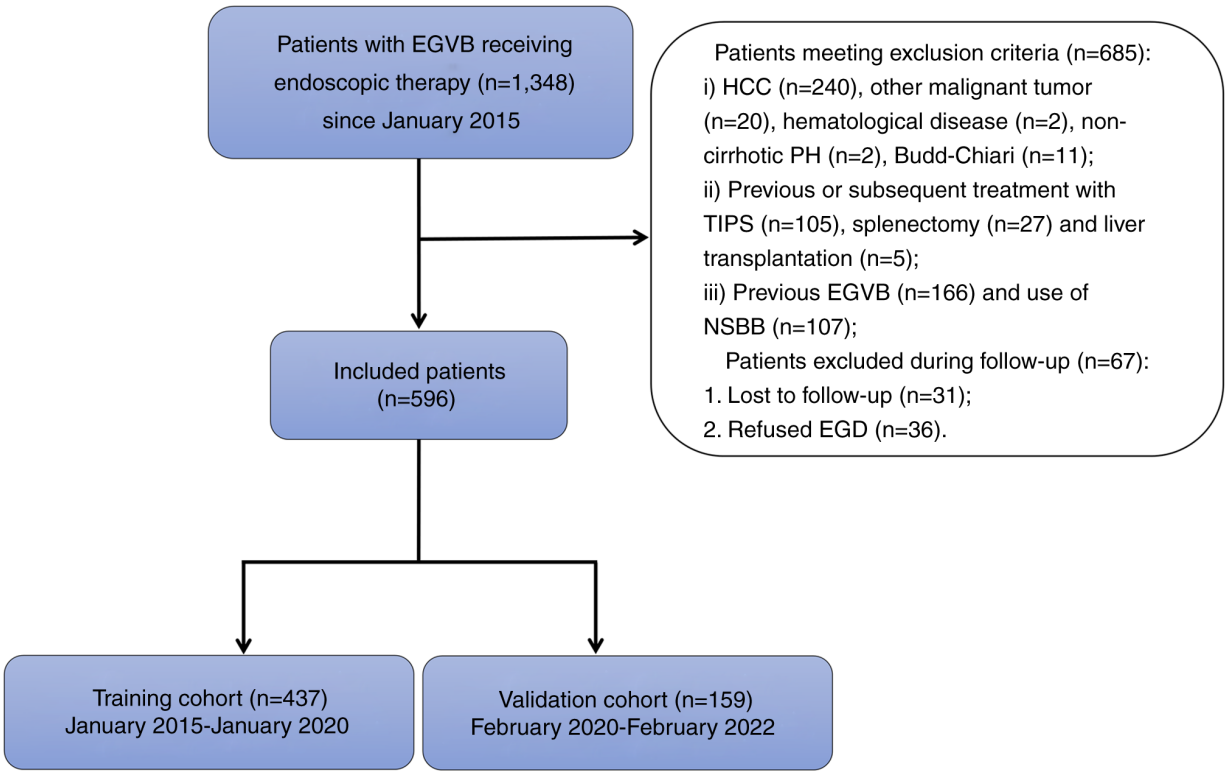

Figure 1. Retrospective selection of patients. EGVP, esophagogastric variceal bleeding; HCC, hepatocellular carcinoma; PH, portal hypertension; TIPS, transjugular intrahepatic portosystemic shunt; NSBB, non-selective β-blocker; EGD, esophagogastroduodenoscopy.

with mALBI grade 1, 2a, 2b and 3 were assigned a score of 1, 2, 3 or 4, respectively (13). Patients with ALBI-FIB4 score of low and high risk received a score of 1 or 2, respectively (15).

Definition of combined INR and ALBI grade. The optimal cut-off value of INR was determined using Receiver operating characteristic (ROC) curve analysis (SPSS 26.0; IBM Corporation), (24), based on the most prominent point on the ROC curve for 'sensitivity' and '1-specificity'. The ideal cut-off value was computed using the Youden index (sensitivity + specificity-1) (25). The ideal cut-off value of INR was 1.205; therefore, low and high INR were defined as INR values ≤1.205 and >1.205, respectively. Patients with low INR were allocated a score of 0, whereas those with high INR were allocated a score of 1. The sum of ALBI (1, 2 or 3) and INR (0 or 1) was defined as the IALBI grade and scored as follows: IALBI grade 1-2, 1; grade 3, 2 and grade 4, 3 (Table SI).

Study endpoints and follow-up. All patients were treated according to the Baveno VI criteria (3). To prevent recurrent hemorrhage, non-selective β-blockers (NSBBs) were used if not contraindicated and/or endoscopic treatment was performed every 2-6 weeks until varices were eradicated, followed by endoscopy every 3 months after variceal eradication. For patients with high-risk esophageal varices (large, medium or small varices with red signs), EVL or EIS were performed. For patients with high-risk gastroesophageal varices, lauromacrogol and tissue adhesive injection combined with EVL or EIS were used. All patients were followed up for 1 year. The endpoint event was EGVB rebleeding, which was characterized by new hematemesis and/or melena, and the bleeding lesion was confirmed by esophagogastroduodenoscopy (EGD). Patients lost to follow-up and patients who did not receive EGD were excluded during follow-up.

Statistical analysis. SPSS 26.0 (SPSS Inc.; IBM Corporation) and GraphPad Prism7 (GraphPad Software; Dotmatics) were used for data analysis. Continuous variables with normal distribution are expressed as the mean ± standard deviation (SD) and the unpaired t-test was used for comparison between two groups; non-normally distributed measures were expressed as the median and interquartile range (IQR) and Mann-Whitney U-test was used to compare two groups. Categorical data are shown as frequencies or proportions and analyzed using χ^2 test. The Cox proportional hazards model was used to identify factors associated with rebleeding. Multicollinearity was assessed using the variance inflation factor (VIF), (26); VIF>10 was considered to indicate multicollinearity. Area under ROC curve (AUC) was calculated to evaluate the discriminatory ability of each non-invasive marker. Kaplan-Meier method was used to estimate the cumulative risk of rebleeding and differences were tested using the log-rank test. The R statistical package 'pROC' (version 3.5.2) was used to calculate time-dependent ROC curves (27). A two-sided $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of the training cohort. In the training cohort, 437 patients met the inclusion criteria (Fig. 1). Patients were divided into a non-rebleeding (n=284) and rebleeding group

Table I. Baseline characteristics of patients.

Variable	All patients (n=437)	Non-rebleeding group (n=284)	Rebleeding group (n=153)	t/Z/χ^2-score	P-value
Sex				χ^2=1.701	0.192
Female	184 (42.11)	126 (44.37)	58 (37.91)		
Male	253 (57.89)	158 (55.63)	95 (62.09)		
Age, years	57.21±10.79	57.38±10.35	56.89±11.58	t=0.439	0.661
Etiology				χ^2=7.553	0.056
HBV	169 (38.67)	123 (43.31)	46 (30.06)		
HCV	30 (6.87)	17 (5.99)	13 (8.50)		
Alcohol	85 (19.45)	52 (18.31)	33 (21.57)		
Other	153 (35.01)	92 (32.39)	61 (39.87)		
Number of endoscopic treatments	2 (1,4)	2 (1,4)	2 (1,4)	Z=-0.397	0.691
Use of NSBB drugs	249 (56.98)	187 (65.85)	62 (40.52)	χ^2=26.010	<0.001
PT, sec	16.21±2.44	15.76±2.03	17.04±2.90	t=4.828	<0.001
INR	1.32±0.26	1.28±0.22	1.40±0.30	t=4.441	<0.001
Fibrinogen, g/l	2.10 (1.64,2.56)	2.09 (1.63,2.56)	2.10 (1.64,2.57)	Z=-0.033	0.973
WBC count, x10^9/l	3.88 (2.56,5.53)	3.87 (2.56,5.54)	3.89 (2.59,5.52)	Z=-0.056	0.956
NEUT count, %	69.80±10.67	69.27±10.78	70.79±10.41	t=1.418	0.157
HGB, g/l	93.99±25.90	94.33±26.34	93.36±25.13	t=0.375	0.708
PLT, x10^9/l	72.00 (51.00,96.50)	71.00 (51.00,94.00)	75.00 (54.00,100.50)	Z=-1.089	0.276
ALB, g/l	34.35±5.72	34.96±5.74	33.22±5.51	t=3.077	0.002
ALT, U/l	25.00 (16.00,34.00)	25.00 (16.00,33.00)	24.00 (16.00,35.00)	Z=-0.583	0.560
AST, U/l	30.00 (21.00,44.00)	29.00 (20.25,40.75)	32.00 (21.00,45.00)	Z=-1.471	0.141
TBIL, μmol/l	20.40 (14.45,31.00)	20.10 (14.3,29.98)	21.00 (14.75,33.90)	Z=-0.807	0.420
BUN, mmol/l	5.69 (4.24,8.08)	5.62 (4.14,8.02)	5.88 (4.51,8.11)	Z=-0.929	0.353
Cr, μmol/l	64.00 (54.00,76.00)	64.00 (54.00,75.00)	65.00 (55.00,77.50)	Z=-0.944	0.345
Na, mmol/l	139.20±3.78	139.43±3.89	138.77±3.53	t=1.741	0.082
GLU, mmol/l	7.39±3.67	7.39±3.57	7.40±3.86	t=0.033	0.974
HBV-DNA/HCV-RNA				χ^2=3.233	0.072
Negative	349 (79.86)	234 (82.39)	115 (75.16)		
Positive	88 (20.14)	50 (17.61)	38 (24.84)		
Spleen diameter, cm	15.27±2.44	15.35±2.49	15.12±2.35	t=0.967	0.334
Width of portal vein, mm	14.03±1.73	14.01±1.71	14.05±1.79	t=0.201	0.435
PVT				χ^2=3.000	0.392
None	335 (76.66)	212 (74.65)	123 (80.39)		
Only trunk	57 (13.04)	41 (14.44)	16 (10.46)		
Only branch	16 (3.66)	11 (3.87)	5 (3.27)		
Trunk and branches	29 (6.64)	20 (7.04)	9 (5.88)		
CT portosystemic shunt				χ^2=0.250	0.617
No	390 (89.24)	255 (89.79)	135 (88.24)		
Yes	47 (10.76)	29 (10.21)	18 (11.76)		
Form of esophageal varices				χ^2=4.000	0.261
F0	25	17	8		
F1	24	17	7		
F2	97	71	26		
F3	291	179	112		
Gastric varices				χ^2=3.000	0.392
GOV-1	182	110	72		
GOV-2	124	85	39		
GOV-1 and GOV-2	31	22	9		
IGV1	25	17	8		

Table I. Continued.

Variable	All patients (n=437)	Non-rebleeding group (n=284)	Rebleeding group (n=153)	t/Z/χ^2-score	P-value
CTP grade				χ^2=-1.841	0.066
A	232 (53.09)	158 (55.63)	74 (48.37)		
B	173 (39.59)	111 (39.09)	62 (40.52)		
C	32 (7.32)	15 (5.28)	17 (11.11)		
MELD score	7.11 (4.31,10.36)	6.52 (4.14,9.70)	8.09 (4.76,10.98)	Z=-3.198	0.001
ALBI grade				χ^2=-3.170	0.002
1	66 (15.10)	54 (19.01)	12 (7.84)		
2	313 (71.63)	198 (69.72)	115 (75.17)		
3	58 (13.27)	32 (11.27)	26 (16.99)		
mALBI grade				χ^2=-3.411	0.001
1	66 (15.10)	54 (19.01)	12 (7.84)		
2a	96 (21.97)	66 (23.24)	30 (19.61)		
2b	217 (49.66)	132 (46.48)	85 (55.56)		
3	58 (13.27)	32 (11.27)	26 (16.99)		
PALBI grade				χ^2=-2.062	0.039
1	129 (29.52)	96 (33.80)	33 (21.57)		
2	176 (40.27)	106 (37.33)	70 (45.75)		
3	132 (30.21)	82 (28.87)	50 (32.68)		
ALBI-FIB-4				χ^2=1.162	0.281
Low-risk	221 (50.57)	149 (52.46)	72 (47.06)		
High-risk	216 (49.43)	135 (47.54)	81 (52.94)		
FIB-4 index	4.97 (3.07,7.78)	4.95 (3.16,7.69)	5.15 (2.92,7.86)	Z=-0.019	0.984

Values are expressed as the mean ± standard deviation, median (interquartile range), n or n (%). HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; NEUT, neutrophil; HGB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; GLU, blood glucose; PVT, portal vein thrombosis; GOV, gastroesophageal varices; IGV, isolated gastric varices type 1; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; mALBI, modified albumin-bilirubin; PALBI, platelet-ALBI; FIB-4, fibrosis-4.

(n=153). The rebleeding rates at 1,3 and 12 months were 7.1 (31/437), 11.4 (50/437) and 35.0 (153/437)%, respectively. There were nine individuals who died during the follow-up period; causes of death were gastrointestinal bleeding (n=4), liver failure (n=3) and abdominal infection and pneumonia (both n=1). The mortality rate was 0.3, 0.7 and 2.1% at 1, 3 and 12 months, respectively. Furthermore, 249 out of 437 patients received NSBB after the first endoscopic treatment. For patients with and without NSBB, the 12 months rebleeding rates were 24.9% (62/249) and 48.4% (91/188), respectively. A total of 156 of 437 patients only received endoscopic treatment once during follow-up. For patients who underwent a single endoscopic treatment and those who received multiple treatments, the 12 months rebleeding rates were 35.3% (55/156) and 34.9% (98/281), respectively. PT and INR were higher in the rebleeding group than the non-rebleeding group and ALB was lower in the rebleeding group than the non-rebleeding group (Table I). MELD, ALBI, mALBI and PALBI scores were higher in the rebleeding than the non-rebleeding group (Table I).

Combined ALBI score and INR in the training cohort. AUCs for IALBI at 1, 3 and 12 months were 0.739, 0.697 and 0.620, respectively; those for INR were 0.634, 0.623 and 0.604, respectively, and those for ALBI were 0.687, 0.654 and 0.573, respectively. The AUC of IALBI predicting 1-month rebleeding was higher than that of INR and ALBI, AUC for prediction of 3-month rebleeding was higher than that of INR and the AUC for prediction of rebleeding at 12 months was higher than that of ALBI (Fig. 2; Table SII).

IALBI was compared with other liver function scores (CTP and MELD). AUCs for CTP at 1, 3 and 12 months were 0.666, 0.613 and 0.547, respectively, and those for MELD were 0.655, 0.668 and 0.593, respectively. AUCs of IALBI to predict rebleeding at 3 and 12 months were higher than those of CTP. At each time-point, AUCs of IALBI were higher than those of MELD; however, the differences were not statistically significant. Over time, the liver function scores showed progressively lower predictive power for rebleeding and only IALBI had predictive power at 12 months (Fig. 3; Table SIII).

Risk factors for rebleeding at 12 months in the training cohort. Sex, age, etiology (viral and non-viral), PT, INR, fibrinogen, WBC, NEUT, HGB, PLT, ALB, ALT, AST, TBIL, BUN, Cr, Na, CLU, spleen and portal vein diameter, PVT, CT

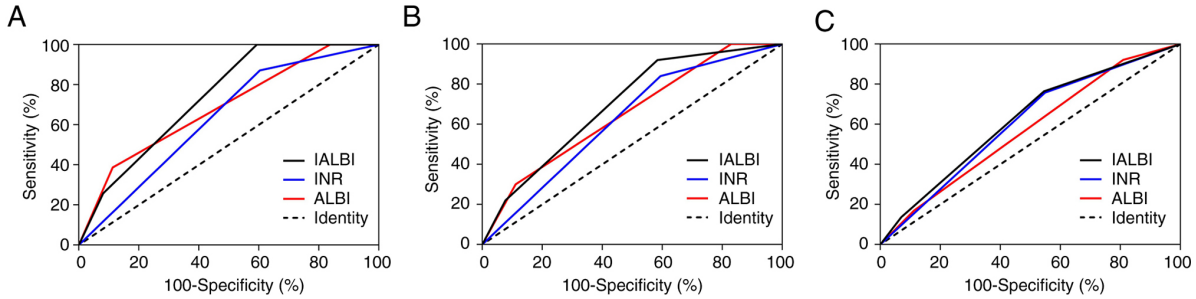

Figure 2. ROC curves of INR, ALBI and IALBI. ROC curve at (A) 1, (B) 3 and (C) at 12 months. ROC, receiver operating characteristic; INR, international normalized ratio; IALBI, INR-albumin-bilirubin.

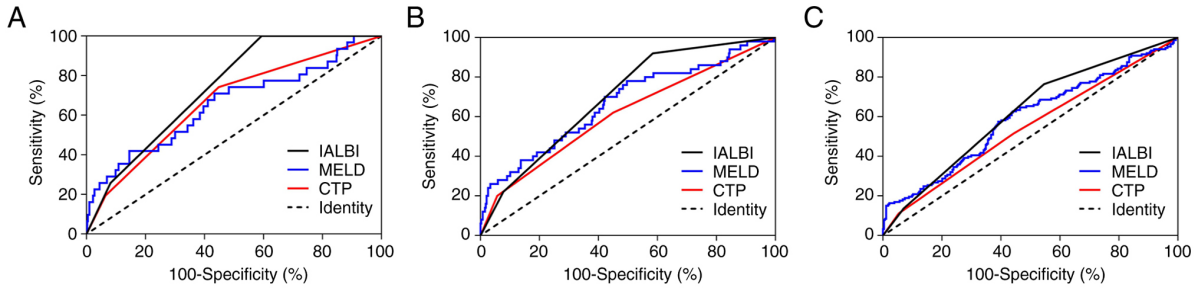

Figure 3. ROC curves of IALBI, CTP and MELD. ROC curve at (A) 1, (B) 3 and (C) 12 months. ROC, receiver operating characteristic; IALBI, international normalized ratio- albumin-bilirubin; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

portosystemic shunt, CTP, MELD, IALBI and FIB-4 were used as independent variables to establish the Cox proportional risk model. The results indicated a significant association between rebleeding and PT, INR, ALB, TBIL, CTP, MELD and IALBI. Significant variables in the univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model (excluding variables with VIF >9 to avoid collinearity). IALBI was the significant variable in the model and could be used to predict rebleeding (Table II).

Predictive value of IALBI based on etiologies and CTP grades in the training cohort. The patients in the training cohort were divided into viral and non-viral groups based on etiology. Of 199 patients in the viral group, 59 patients (29.6%) experienced rebleeding within 12 months; of 238 patients in the non-viral group, 94 (39.5%) experienced rebleeding within 12 months. In patients with viral cirrhosis, PT and INR were higher in the rebleeding than the non-rebleeding group and Na was lower in the rebleeding group than the non-rebleeding group. A total of 38 patients (64.4%) were positive for hepatitis B virus DNA or hepatitis C virus RNA in the rebleeding group, which was higher than that in the non-rebleeding group [35.7% (50/140)]. CTP, ALBI, mALBI, PALBI and IALBI were higher in the rebleeding than the non-rebleeding group (Table SIV). Among patients with non-viral cirrhosis, PT, INR and FIB were higher in the rebleeding than the non-rebleeding group and IALBI was higher in the rebleeding than the non-rebleeding group (Table SIV).

In all of the patients in the training cohort and viral group, the incidence of rebleeding increased with increasing IALBI grade at all time-points. At 1 month, no patient experienced rebleeding in the IALBI grade 1 group. In the non-viral group, the incidence of rebleeding increased with the increasing IALBI grade at 1 and 3 months. At 12 months, the incidence of rebleeding increased with increasing IALBI grade; however, the difference was not statistically significant. No patient experienced rebleeding in the IALBI grade 1 group at 1 and 3 months (Fig. 4). The predictive value of IALBI for rebleeding of patients with different etiology is presented in Table III.

The sensitivity and NPV of IALBI for rebleeding decreased with time in the different CTP stages. For CTP A, B and C, the sensitivity and NPV of the IALBI score to predict 1-month rebleeding were all 100% (Table III).

Cumulative rebleeding rate of training cohort classified by ALBI-associated scoring systems. In the training cohort, 165 patients (37.8%) with IALBI grade 1 had cumulative rebleeding rates of 0.0, 2.4 and 21.8% at 1, 3 and 12 months, respectively. Overall, 231 (52.9%) patients with IALBI grade 2 had cumulative rebleeding rates of 10.0, 15.2 and 41.7% at 1, 3 and 12 months, respectively. The cumulative rebleeding rates at 1, 3 and 12 months were 19.5, 26.8 and 51.2%, respectively, in patients with IALBI grade 3. The differences in cumulative rebleeding rates between the three IALBI grades were statistically significant, and the risk of rebleeding was significantly lower in patients with IALBI grade 1 than in those with grade 2 or 3 (Fig. 5; Table SV).

At 1 month, rebleeding rate of the IALBI grade 2 group was ~10-times higher than that of the grade 1 group and that of the grade 3 group was ~19.5-times higher than that of the grade 1 group. At 3 months, rebleeding rates of the IALBI grade 2 and 3 groups were ~6.3- and 11.2-times higher than

Table II. Competing risk factors of 12 months rebleeding in all patients.

	Univariate				Multivariate		
Variable	HR (95% CI)	Wald χ^2	P-value	VIF	HR (95% CI)	Wald χ^2	P-value
Sex	1.191 (0.859-1.651)	1.103	0.294		-	-	-
Age	0.997 (0.983-1.012)	0.129	0.720		-	-	-
Etiology							
Viral	1.000	-	-		-	-	-
Non-viral	1.317 (0.913-1.901)	2.171	0.141		-	-	-
PT	1.219 (1.151-1.292)	45.097	<0.001	9.182	-	-	-
INR	5.243 (3.094-8.886)	37.903	<0.001	10.150	-	-	-
Fibrinogen	1.065 (0.87-1.303)	0.369	0.543		-	-	-
WBC	1.005 (0.96-1.053)	0.054	0.817		-	-	-
NEUT	1.012 (0.997-1.028)	2.410	0.121		-	-	-
HGB	1.000 (0.994-1.006)	0.002	0.964		-	-	-
PLT	1.002 (0.998-1.006)	1.243	0.265		-	-	-
ALB	0.949 (0.922-0.976)	12.875	<0.001	2.111	-	-	-
ALT	1.001 (0.998-1.003)	0.160	0.689		-	-	-
AST	1.002 (0.999-1.005)	2.971	0.085		-	-	-
TBIL	1.010 (1.005-1.015)	16.016	<0.001	1.630	-	-	-
BUN	1.018 (0.976-1.061)	0.672	0.412		-	-	-
Cr	1.005 (0.998-1.012)	2.162	0.141		-	-	-
Na	0.967 (0.93-1.005)	2.924	0.087		-	-	-
CLU	1.001 (0.958-1.045)	0.001	0.975		-	-	-
Spleen diameter	0.969 (0.908-1.034)	0.887	0.346		-	-	-
Portal vein diameter	1.008 (0.921-1.103)	0.028	0.866		-	-	-
PVT	0.766 (0.514-1.142)	1.706	0.192		-	-	-
CT portosystemic shunt	1.17 (0.715-1.913)	0.391	0.532		-	-	-
CTP grade	-	-	-	1.829	-	1.125	0.570
A	1.000	-	-		1.000	-	-
B vs. A	1.193 (0.851-1.672)	1.049	0.306		0.951 (0.669-1.351)	0.08	0.778
C vs. A	2.244 (1.324-3.804)	9.009	0.003		1.300 (0.712-2.371)	0.729	0.393
MELD	1.088 (1.048-1.13)	19.103	<0.001	2.009	1.045 (1.001-1.091)	4.101	0.060
IALBI grade	-	-	-	2.697	-	10.215	0.043
1	1.000	-	-		1.000	-	-
2 vs. 1	2.314 (1.577-3.395)	18.396	<0.001		1.929 (1.257-2.960)	9.054	0.003
3 vs. 1	3.377 (1.97-5.788)	19.585	<0.001		2.416 (1.262-4.626)	7.092	0.008
FIB-4	1.019 (0.987-1.051)	1.362	0.243		-	-	-

VIF, variance inflation factor; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; NEUT, neutrophil; HGB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; GLU, blood glucose; PVT, portal vein thrombosis; CTP, Child-Turcotte-Pugh, based on hepatic encephalopathy, ascites, total bilirubin, albumin and prothrombin time; MELD, model for end-stage liver disease; IALBI, INR-albumin-bilirubin, based on INR, albumin and bilirubin; FIB-4, fibrosis-4.

the grade 1 group, respectively. At 12 months, the rebleeding rates of the IALBI grade 2 and 3 groups were ~1.9- and 2.3-times higher than those of the grade 1 group, respectively (Table SV).

The differences in cumulative rebleeding rates for different grades of mALBI and PALBI scores were significant. For the ALBI-FIB4 score, the difference in cumulative rebleeding rates between the low- and high-risk groups was not significant (Fig. 5; Table SV).

Predictive ability of ALBI-associated scoring systems for rebleeding based on ROC curves in the training cohort. In the training cohort, IALBI grade showed good discrimination in predicting rebleeding at all time points (AUC, 0.739, 0.697 and 0.620 at 1, 3 and 12 months, respectively). The sensitivity, specificity and negative predictive value (NPV) of IALBI for rebleeding decreased with time (Table III). AUCs of IALBI for predicting rebleeding at all time points were higher than those of PALBI and ALBI-FIB4. AUCs of IALBI grade were

Table III. Predictive value of IALBI for rebleeding by CTP grade and etiology.

A, 1 month

Group	Sensitivity, %	Specificity, %	PPV, %	NPV, %
All patients	100.0	40.6	11.4	100.0
CTP A	100.0	54.5	14.4	100.0
CTP B	100.0	26.9	9.5	100.0
CTP C	100.0	53.8	14.2	100.0
Viral	100.0	65.3	18.0	100.0
Non-Viral	40.0	84.5	16.5	94.9

B, 3 months

Group	Sensitivity, %	Specificity, %	PPV, %	NPV, %
All patients	100.0	27.5	15.1	100.0
CTP A	72.7	54.1	17.0	93.9
CTP B	100.0	27.5	15.1	100.0
CTP C	70.0	54.5	16.6	93.4
Viral	70.0	65.4	20.7	94.4
Non-Viral	100.0	18.8	13.7	100.0

C, 12 months

Group	Sensitivity, %	Specificity, %	PPV, %	NPV, %
All patients	91.5	32.7	42.3	87.7
CTP A	66.7	60.7	47.8	77.2
CTP B	91.5	32.7	42.3	87.7
CTP C	64.7	60.0	46.6	75.9
Viral	63.5	72.8	55.7	78.7
Non-Viral	90.3	20.8	38.1	79.9

PPV, positive predictive value; NPV, negative predictive value; CTP, Child-Turcotte-Pugh.

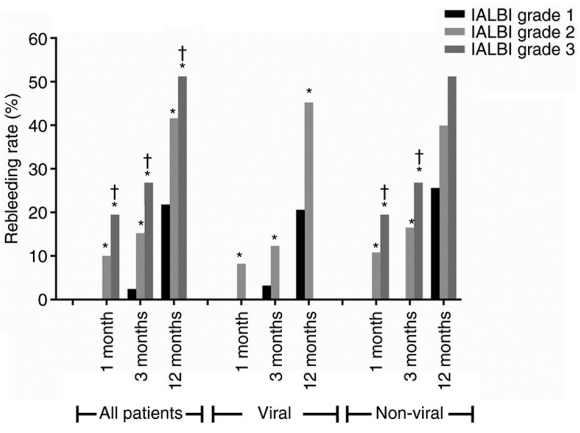

Figure 4. Prevalence of rebleeding in IALBI classification groups. IALBI, international normalized ratio- albumin-bilirubin. *P<0.05 vs. 1 month; †P<0.05 vs. 3 months.

consistently higher than those of mALBI grade at all time points; however, the difference was not significant. Specifically, mALBI grade did not predict 12 months rebleeding (Fig. 6A-C; Table IV).

In the viral group, IALBI grade showed better discrimination in predicting rebleeding at all time points (AUC, 0.826, 0.674 and 0.620 at 1, 3 and 12 months, respectively). AUCs of IALBI grade for predicting rebleeding at all time points were higher than those of ALBI-FIB4 and AUC of IALBI grade for the prediction of 1-month rebleeding was higher than that of PALBI. AUCs of IALBI grade were higher than those of mALBI grade except at 3 months; however, the difference was not statistically significant (Fig. 6D-F; Table IV).

In the non-viral group, IALBI grade predicted rebleeding at 1 and 3, but not at 12 months (AUC, 0.645, 0.642 and 0.575 at 1, 3 and 12 months, respectively). AUCs for IALBI to predict rebleeding at 1 and 3 months were higher than those of ALBI-FIB4 and PALBI. mALBI grade did not predict rebleeding at 3 or 12 months (Fig. 6G-I; Table IV).

To illustrate the variation of AUCs over time for ALBI-associated scores, time-dependent ROC curves were plotted. During follow-up, IALBI performed best compared

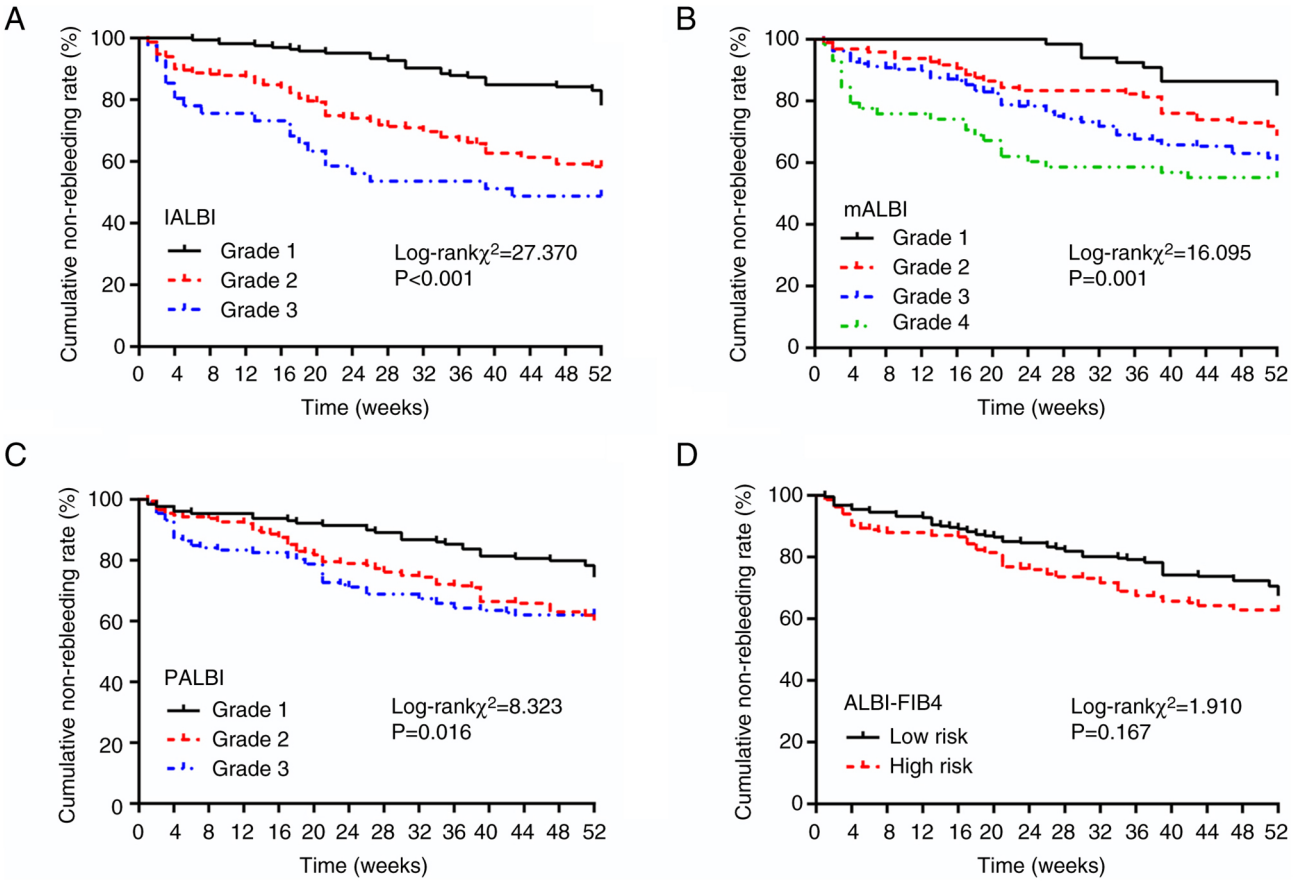

Figure 5. Performance of mALBI, PALBI, ALBI-FIB4 and IALBI grading in rebleeding in patients with EGVB. Kaplan-Meier curves of rebleeding according to (A) mALBI, (B) PALBI, (C) ALBI-FIB4 and (D) IALBI grade. mALBI, modified albumin-bilirubin; PALBI, platelet-ALBI; FIB-4, fibrosis-4; IALBI, international normalized ratio-ALBI.

with other ALBI-associated scores, while AUCs to predict rebleeding decreased over time (Fig. 6J).

Validation cohort. Characteristics of the validation cohort (n=159) are shown in Table SVI. In the validation cohort, IALBI grade showed good discrimination in predicting rebleeding (AUC, 0.742, 0.728 and 0.592 at 1, 3 and 12 months, respectively). The sensitivity, specificity and NPV of the IALBI score to predict 1-month rebleeding were 94.1, 31.0 and 97.8%, respectively (Fig. S1).

Discussion

Previous studies have revealed that the mortality rates of acute variceal bleeding in patients with liver cirrhosis are 10-20% within 6 weeks and ~40% within 1 year (28,29). Each year, ~12% of cirrhotic patients experience a first variceal bleeding event and in the absence of secondary prophylaxis, the risk of rebleeding within 1 year is up to 60% (28,29). Endoscopic treatment is an effective method for variceal bleeding, and rebleeding after endoscopic treatment seriously affects prognosis of patients with liver cirrhosis. In the present training cohort, the rebleeding rates at 1, 3 and 12 months were 7.1, 11.4 and 35.0%, respectively, and the mortality rate was 2.1% at 12 months. If patients with EGVB and a high risk of rebleeding following endoscopic therapy are identified early, the mortality can be reduced by improving monitoring and providing early clinical intervention. The gold standard tests used to assess PH and gastroesophageal varices are measuring hepatic venous pressure gradient (HVPG) via hepatic vein catheterization and EGD, respectively. However, measurement of HVPG is invasive and not routinely performed in all centers. Endoscopy carries certain risks, such as bleeding and perforation, and it may be uncomfortable (30). Thus, certain patients refuse regular EGD as recommended by the Baveno VI consensus (6). Therefore, non-invasive models have been used to predict esophagogastric variceal bleeding as an alternative to EGD (7-9).

The ALBI score is a prognostic tool proposed in 2015, involving two parameters, ALB and TBIL, originally applied for patients with HCC to assess the severity of liver dysfunction (12). ALBI is associated with HVPG and can be used to assess in-hospital mortality in patients with acute upper gastrointestinal bleeding with liver cirrhosis (31). The ALBI score has limitations, as a large number of patients are categorized as ALBI grade 2 (13). Thus, mALBI, in which grade 2 is divided into grade 2a and 2b, has been proposed (13). mALBI classification is associated with the severity of esophagogastric varices in patients with cirrhosis (32).

In 2015, Roayaie *et al* (14) developed the PALBI score by adding platelet counts to the ALBI score and adequately stratified the survival of patients with HCC. Recent studies have suggested that the PALBI score can predict rebleeding in patients with acute variceal bleeding in cirrhosis (33,34). In 2019, Guha *et al* (15) combined ALBI and FIB4 scores to assess

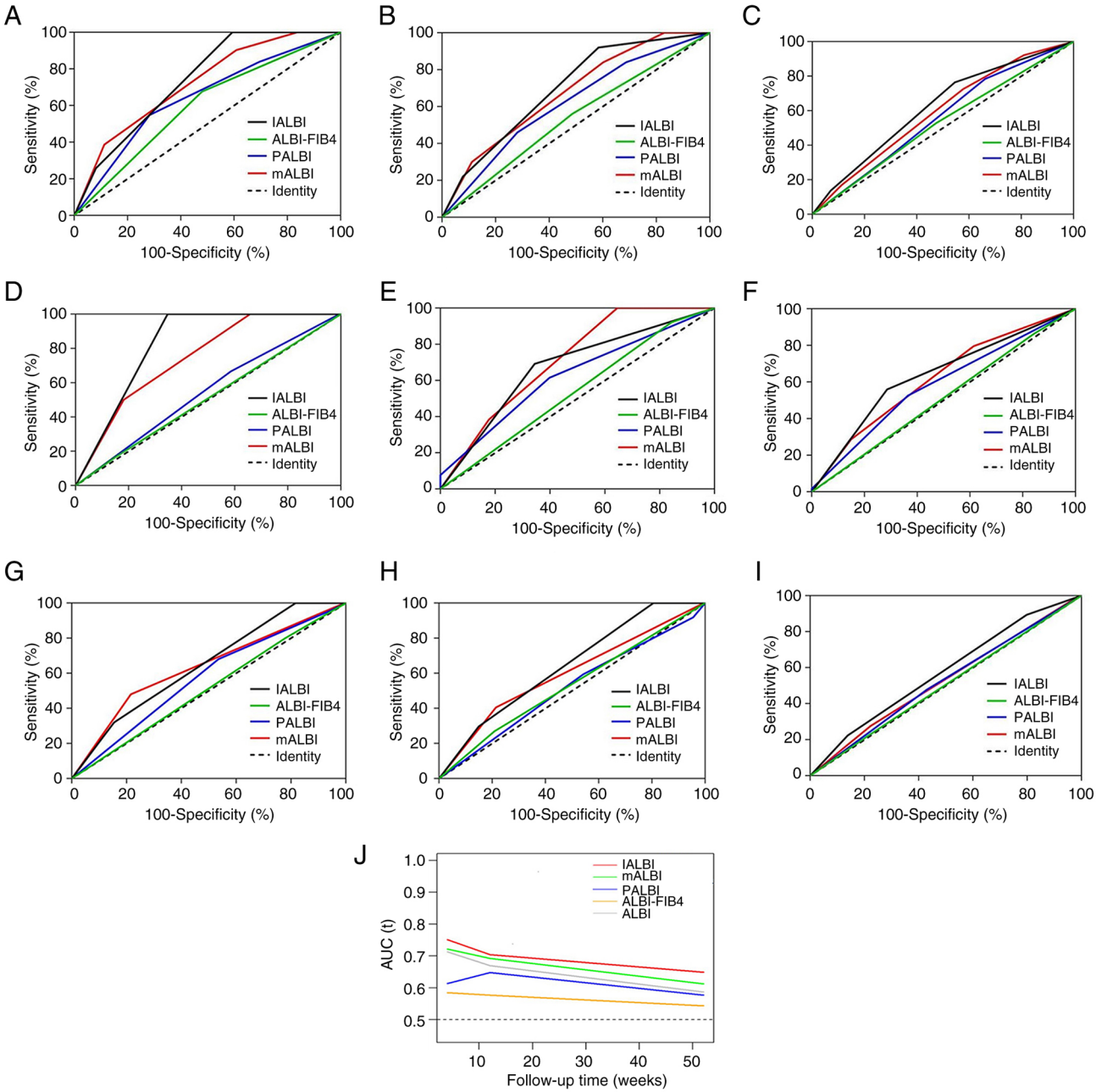

Figure 6. ROC curves for discriminative ability of mALBI, PALBI, ALBI-FIB4 and IALBI to detect rebleeding. All patients at (A) 1, (B) 3 and (C) 12 months. Patients with viral cirrhosis at (D) 1, (E) 3 and (F) 12 months. Patients with non-viral cirrhosis at (G) 1, (H) 3 and (I) 12 months. (J) Time-dependent ROC curves for ALBI-related scores. ROC, receiver operating characteristic; mALBI, modified albumin-bilirubin; PALBI, platelet-ALBI; FIB-4, fibrosis-4; IALBI, international normalized ratio-ALBI.

risk of decompensation, including gastrointestinal bleeding, ascites and hepatic encephalopathy, in patients with compensated cirrhosis. Hsu *et al* (35) concluded that ALBI-FIB4 score shows better predictive ability than the ALBI score for the risk of decompensatory events.

The liver is the site where coagulation factors, such as I, II, V, VII and X, are synthesized. When severe liver disease occurs, the ability of the liver to synthesize coagulation factors is decreased, resulting in elevated PT and INR (36). Elevated INR is associated with poor prognosis in patients with liver failure. INR is an independent predictor of liver fibrosis in chronic hepatitis C and predicts severe esophageal varices in hepatitis C-induced cirrhosis (37). In the present training cohort, INR was higher in the rebleeding group than the non-rebleeding group and INR could predict rebleeding in patients with EGVB after endoscopic treatment. This was similar to the findings of Zhang *et al* (38), who found that INR ≥1.2 is an independent predictor of first variceal bleeding in cirrhosis. Recently, Ding *et al* (39) reported that the INR-to-platelet ratio could be used to predict the extent of liver fibrosis in chronic hepatitis B. Farid *et al* (37) used α-fetoprotein, INR and platelets to develop a model that predicted development of large esophageal varices in cirrhosis of hepatitis C. To the best of our knowledge, the present study is the first to combine ALBI and INR to establish the IALBI model to predict rebleeding in patients with EGVB following

Table IV. Predictive value of scoring systems at different time points.

A, All patients

Time, months	Variable	AUC (95% CI)	P1	P2	P3	P4
1	IALBI	0.739 (0.687-0.792)	Ref.	0.566	0.029	0.001
	mALBI	0.722 (0.645-0.799)	0.566	Ref.	0.057	0.002
	PALBI	0.644 (0.546-0.741)	0.029	0.057	Ref.	0.318
	ALBI-FIB4	0.599 (0.511-0.686)	0.001	0.002	0.318	Ref.
3	IALBI	0.697 (0.638-0.755)	Ref.	0.355	0.024	<0.001
	mALBI	0.676 (0.610-0.742)	0.355	Ref.	0.07	<0.001
	PALBI	0.616 (0.540-0.692)	0.024	0.07	Ref.	0.032
	ALBI-FIB4	0.537 (0.463-0.611)	<0.001	<0.001	0.032	Ref.
12	IALBI	0.620 (0.572-0.668)	Ref.	0.167	0.009	<0.001
	mALBI	0.592 (0.541-0.642)	0.167	Ref.	0.083	0.004
	PALBI	0.556 (0.504-0.608)	0.009	0.083	Ref.	0.226
	ALBI-FIB4	0.527 (0.478-0.576)	<0.001	0.004	0.226	Ref.

B, Viral cirrhosis

Time, months	Variable	AUC (95% CI)	P1	P2	P3	P4
1	IALBI	0.826 (0.793-0.86)	Ref.	0.283	0.001	<0.001
	mALBI	0.745 (0.596-0.894)	0.283	Ref.	0.027	0.08
	PALBI	0.459 (0.250-0.667)	0.001	0.027	Ref.	0.748
	ALBI-FIB4	0.508 (0.343-0.673)	<0.001	0.08	0.748	Ref.
3	IALBI	0.674 (0.539-0.809)	Ref.	0.526	0.645	0.003
	mALBI	0.713 (0.615-0.810)	0.526	Ref.	0.314	<0.001
	PALBI	0.624 (0.473-0.775)	0.645	0.314	Ref.	0.095
	ALBI-FIB4	0.461 (0.381-0.540)	0.003	<0.001	0.095	Ref.
12	IALBI	0.637 (0.563-0.711)	Ref.	0.653	0.251	<0.001
	mALBI	0.620 (0.542-0.698)	0.653	Ref.	0.398	0.002
	PALBI	0.584 (0.507-0.660)	0.251	0.398	Ref.	0.03
	ALBI-FIB4	0.489 (0.436-0.543)	<0.001	0.002	0.03	Ref.

C, Non-viral cirrhosis

Time, months	Variable	AUC (95% CI)	P1	P2	P3	P4
1	IALBI	0.645 (0.562-0.728)	Ref.	0.758	0.142	0.006
	mALBI	0.633 (0.530-0.737)	0.758	Ref.	0.304	0.015
	PALBI	0.571 (0.470-0.673)	0.142	0.304	Ref.	0.265
	ALBI-FIB4	0.510 (0.426-0.595)	0.006	0.015	0.265	Ref.
3	IALBI	0.642 (0.573-0.711)	Ref.	0.108	0.003	<0.001
	mALBI	0.597 (0.512-0.682)	0.108	Ref.	0.089	0.003
	PALBI	0.517 (0.424-0.609)	0.003	0.089	Ref.	0.319
	ALBI-FIB4	0.469 (0.392-0.547)	<0.001	0.003	0.319	Ref.
12	IALBI	0.575 (0.513-0.636)	Ref.	0.053	0.006	0.027
	mALBI	0.530 (0.473-0.587)	0.053	Ref.	0.121	0.307
	PALBI	0.476 (0.41-0.542)	0.006	0.121	Ref.	0.591
	ALBI-FIB4	0.496 (0.442-0.55)	0.027	0.307	0.591	Ref.

P1, mALBI, PALBI and ALBI-FIB4 vs. IALBI; P2, IALBI, PALBI and ALBI-FIB4 vs. mIALBI; P3, IALBI, mALBI and ALBI-FIB4 vs. PIALBI; P4, IALBI, mALBI and PALBI vs. ALBI-FIB4; mALBI, modified albumin-bilirubin; PALBI, platelet-ALBI; FIB-4, fibrosis-4; IALBI, international normalized ratio-ALBI.

endoscopic therapy. By contrast, Majid *et al* (40) demonstrated that neither ALBI nor MELD scores were correlated with esophageal varices. In the present training cohort, the AUCs of IALBI for the prediction of rebleeding were 0.739, 0.697 and 0.620 at 1, 3 and 12 months, respectively. In multivariate analysis, IALBI was an independent risk factor associated with rebleeding in patients with EGVB following endoscopic therapy. Therefore, IALBI score could be used to predict rebleeding following endoscopic treatment in patients with EGVB. For rebleeding prediction, IALBI score was better than either the INR or ALBI scores alone. Compared with other liver function scores (CTP and MELD), IALBI showed better predictive power and the AUCs of IALBI were higher than those of MELD at all time points; however, the difference was not statistically significant.

To the best of our knowledge, the present study is the first to compare all ALBI-related scores (including mALBI, PALBI and ALBI-FIB4) with a novel scoring system (IALBI) to analyze predictive ability for early-, intermediate- and long-term rebleeding in cirrhotic patients with EGVB following endoscopic therapy. Time-dependent ROC curves showed that, among all ALBI-associated scores, AUC of the IALBI grade was consistently higher than that of ALBI, mALBI, PALBI and ALBI-FIB4 grades at all time points. This indicated that the proposed classification system had high predictive power.

The present study validated the predictive power of the IALBI grading system in different populations in the training cohort. In the viral group, IALBI score exhibited good predictive power for rebleeding at all time points. IALBI score had the best predictive power for early rebleeding. In the non-viral group, IALBI score was able to predict 1- and 3-month rebleeding and was superior to ALBI-FIB4 and PALBI scores, while mALBI score only showed predictive power for 1-month rebleeding. Similarly, in the validation cohort, IALBI predicted rebleeding, particularly early rebleeding.

IALBI may have the best predictive ability for rebleeding, especially early rebleeding, while the predictive efficacy for rebleeding after 3 months was decreased. This was similar to the findings of Xavier *et al* (41), who concluded that ALBI is more appropriate to evaluate the short-term prognosis of patients with acute upper gastrointestinal bleeding. Chen *et al* (42) found that ALBI grade is a useful score to predict not only the development of post-banding ulcer bleeding (PBUB) but also 6-week mortality after PBUB. The predictive power of IALBI for rebleeding decreased with time. This may be due to external factors, such as NSBB drugs and prophylactic endoscopic treatment. Liver stiffness measurement (LSM) predicts rebleeding events of hepatitis B-induced liver cirrhosis (43). Adding other factors (such as LSM) to IALBI may improve the long-term predictive power of the model. Future studies will further explore how to improve the stability of IALBI.

To investigate the predictive power of IALBI score, the IALBI score was divided into grades 1-3 and Kaplan-Meier curves were plotted in the training cohort. The present study revealed marked differences of cumulative rebleeding rates between patients with grade 1 and 3. The incidence of rebleeding increased with increasing IALBI grade at all time-points. At each time point, grade 1 patients had lower risk of rebleeding than grade 2 and 3 patients. For example, at 1 month, rebleeding rate of patients with IALBI grade 2 was ~10-times higher than that of patients with grade 1, and that of patients with grade 3 was ~19.5 times higher than that of patients with grade 1. Similarly, cumulative rebleeding rates of mALBI and PALBI scores differed by grade, while those of the ALBI-FIB4 score did not. Therefore, patients with IALBI grade 1 had lower risk of rebleeding than those with IALBI grade 2 and 3.

In the training cohort, the predictive value of the IALBI score was evaluated for different CTP classifications and etiologies and it was revealed that IALBI had excellent NPVs, especially for 1-month rebleeding (100% for CTP A, B and C and the viral group, and 94.9% for the non-viral group) and the NPVs gradually decreased over time. Therefore, the graded treatment of patients according to IALBI may avoid unnecessary endoscopic screening.

In the present study, ALBI-associated scores were compared with the proposed scoring system. IALBI score was found to be the best predictor of rebleeding in patients with EGVB following endoscopic treatment, particularly for prediction of early rebleeding. Additionally, by grading IALBI score, it was revealed that risk of rebleeding increased with the increasing IALBI grade and rate of rebleeding was markedly lower in patients with IALBI grade 1 than in those with grade 2 and 3. No patients with IALBI grade 1 experienced rebleeding within 1 month in both the viral and non-viral groups. IALBI showed excellent NPV.

In conclusion, IALBI score may be a simple, objective and clinically applicable non-invasive tool for identification of patients at low risk of rebleeding and who may not require endoscopic secondary prophylaxis and TIPS in the short-term. This conclusion should be validated in further research since this was a single-center study.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JLi, FL and TW designed the study. FL, TW, BQ, FT and YG performed data extraction and the data were analyzed by FL, TW, BQ, FT and JLv. FL and TW confirm the authenticity of all the raw data. The manuscript draft was prepared by JLv and revised by JLi, FL and TW. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tianjin Third Central Hospital (approval no. IRB2021-028-01)

and performed in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all study participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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