Fibrosis index predicts variceal bleeding and reduces need for nonselective beta-blocker in compensated cirrhosis with initial small esophageal varices without red-color sign

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Background: Various non-invasive markers predicting hepatic fibrosis are poor predictors of esophageal variceal bleeding (EVB). Elastography performs well but resource-limited. Controversy for small EV prevention also exists. We aim to investigate if a non-invasive marker could predict subsequent EVB within 1 and 2 years in patients with compensated liver cirrhosis (CLC), initial small EV without red-color sign (RCS), without use of non-selective beta-blockers (NSBB) and endoscopic variceal ligation (EVL). This marker would also be tested if it could help reduce use of NSBB, thereby avoiding potential side effects and saving medical costs.

Methods: In this retrospective cohort study, 6,803 CLC patients fulfilling the inclusion-exclusion criteria were enrolled between 2001 and 2018, and were followed-up for 1 year, 2 years. The primary outcomes were subsequent EVB within 1 and 2 years of enrollment. Another 281 CLC patients with NSBB use were compared for additional outcome analysis.

Results: In total, 539 patients and 710 patients experienced EVB within 1 year and 2 years, respectively. The fibrosis index (FI) with cut-off value of 3.95 showed a negative predictive value (NPV) of 94.3% and an area under receiver operating characteristic (AUROC) of 62.95% for predicting subsequent EVB within 1 year. The EVB and mortality of patients with FI <3.95 and not taking NSBB were significantly lower than those of the other 3 groups. Similar results were demonstrated within 2 years.

Conclusions: In CLC patients with initial small EV and no RCS, low FI scores showed a high NPV and moderate AUROC in predicting subsequent EVB and mortalities, signifying clinically non-significant portal hypertension. Patients with low FI scores and not taking NSBB had significantly lowest EVB and mortality. The medical cost savings for cutting NSBB in these patients would be estimated at least $3 million per year in the U.S. Further randomized control trial study needed to validate this screening tool.

Keywords: Fibrosis index (FI); non-selective beta-blockers (NSBB); small esophageal varices; esophageal variceal bleeding (EVB); compensated liver cirrhosis (CLC); endoscopic variceal ligation (EVL); medical cost savings

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Introduction

Esophageal variceal bleeding (EVB) is a common but life-threatening complication in patients with liver cirrhosis regardless of cirrhosis etiology, resulting in high morbidity and mortality despite the improvement in the efficacy of endoscopic, pharmacologic, surgical, and radiologic techniques (1). In addition, the reported 1-year mortality for variceal bleeding ranges from 14.1% to 57% (2-4). Therefore, selecting high-risk patients to undergo preventative measures is crucial. On the other hand, distinguishing those low-risk patients for less aggressive care may also help reduce medical expenditure and avoid side effects.

The main factors leading to the development of varices are continued hepatic injury, degree of portosystemic shunting, endoscopic appearances and portal pressure (5). Among these, the presence of large varices has demonstrated a major risk factor for the emergence of variceal hemorrhage (6,7). In patients with approximate portal hypertension, the likelihood of acute variceal bleeding is significantly increased in patients with large varices (6).

Furthermore, certain endoscopic variceal stigma collectively referred to as "red-color sign" (red-whale markings, cherry-red spots, nipple symptoms, hematocystic spots), were correlated with a significantly higher risk of acute variceal bleeding (7,8). In addition, patients with advanced liver disease [Child-Turcotte-Pugh C (CTP-C), presence of ascites or hepatic encephalopathy] are also more likely to experience EV bleeding (6,9). Hence, it is strongly recommended that either non-selective beta-blocker (NSBB) usage or esophageal variceal ligation (EVL) be performed to prevent primary variceal bleeding among medium or large varices (10).

However, previous studies show debatable results for primary prevention of small esophageal varices by NSBB, especially for those with no endoscopic red-color sign (RCS) or with compensated liver cirrhosis (CLC) (11-13). UK guidelines recommend NSBBs as primary prophylaxis in grade I varices only when red-signs are present, and also recommended annual EGD monitoring (5). Baveno V/VI and AASLD guidelines recommend that NSBBs should be used for primary prophylaxis in patients with small varices who are judged to be at increased risk of bleeding, i.e. those that show red color/wale sign upon initial endoscopy or who are graded as CTP-C (9,10). Consequently, for these compensated cirrhotic patients with small varices and lack of red color/wale sign, further studies were suggested in Baveno VI and AASLD guideline to confirm the benefit of NSBB (9,10).

Moreover, a group of cirrhotic patient with small varices indicate clinically significant portal hypertension (CSPH) but may have uneven risk of bleeding with different hepatic venous pressure gradient (HVPG) (14). Nevertheless, HVPG is an invasive procedure and one study showed that HVPG monitoring did not change outcome in cirrhotic patients with small EV (13). Moreover, the cost-effectiveness of HVPG measurement has been challenged in the primary prevention of EV bleeding (15,16). Therefore it is less frequently practiced in Taiwan.

Recently, various non-invasive markers such as model for end-stage liver disease (MELD), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AST/ALT), AST to platelet ratio index (APRI), platelet count to spleen diameter (PC/SD), fibrosis-4-index (FIB-4), fibrosis index (FI) and King's score, have been demonstrated as simple, non-invasive, and easier practical alternatives to predict the presence of EV in cirrhotic patients (17). Additionally, the combination of albumin-bilirubin grade and platelets (PALBI) to predict EVB in compensated patients with hepatocellular carcinoma has also been described (18). However, the predictive abilities of these non-invasive markers for predicting EVB are poor with area under receiver operating characteristic (AUROC) between 0.45 and 0.55 (17).

Therefore, we aim to identify an acceptable non-invasive screening tool for distinguishing between high or low-risk EVB group in CLC population with initial small EV, no RCS, and no history of beta-blocker prophylaxis and prophylactic EVL unless EVB or EV progression in a one and two-year follow-up. Since primary prevention may be needed for the high-risk group and spared for the low-risk group, this marker would also be tested if it could help reduce the use of NSBB in low-risk group.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2444).

Methods

Study design and data source

This was a retrospective cohort study conducted at the Chang Gung Memorial Hospital (CGMH) system, which is the largest hospital system composing two medical centers,

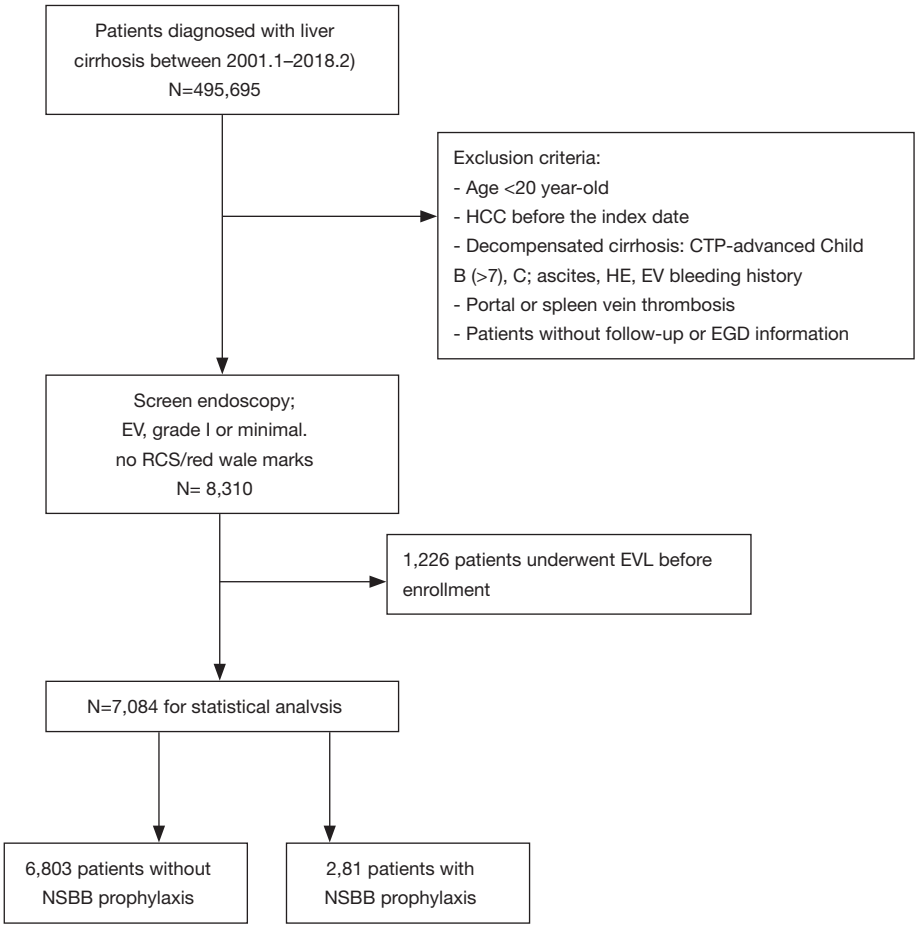

Figure 1 Enrollment flowchart. After inclusion and exclusion, 8,310 compensated liver cirrhotic patients with low-risk EV enrolled in our study from January 2001 to February 2018. After excluding patients who had undergone prophylactic therapy with EVL, the remaining 6,803 patients without NSBB prophylaxis were the main group for primary endpoint analysis. The minor group was 281 matched patients (3.97%) with NSBB prophylaxis for secondary endpoint analysis. EV, esophageal variceal; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blockers.

two regional hospitals, and three district hospitals located from the northeast to southern regions of Taiwan (19). Data were obtained from the Chang Gung Research Database (CGRD), an electronic medical records based research database maintained by the CGMH system. The CGRD includes not only outpatient, emergency, and inpatient claim records, but also contains laboratory, endoscopic, microbiological, and image, etc. reports. The more detail information about CGRD had reported in the previous article (20). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Institutional Review Board (IRB)/ethical committees of Chang Gung Memorial Hospital (IRB number: 201802006B0). Individual consent for this retrospective analysis was waived.

Patient selection

As depicted in the enrollment flowchart (*Figure 1*), the inclusion criteria were all consecutive patients diagnosed with liver cirrhosis between January 2001 and February 2018. It also requires these patients to receive screen endoscopy and diagnosed as EV, grade 1 or minimal, and no RCS or no red wale marks. The exclusion criteria were as follows: age <20 years old, HCC before enrollment, advanced CTP-B (>7) & CTP-C (21), cirrhosis-related complications (ascites, HE, EV bleeding history), thrombosis of portal or spleen vein, and patients without

follow-up information. Patients with previous endoscopic variceal ligation (EVL) (n=1,226) were also excluded in the study.

All endoscopies were performed at our institutions by experienced gastroenterologists using Olympus GIF-240/260 gastrointestinal videoscopes. The grading of varices was evaluated using the system proposed by the Japanese Research Society for Portal Hypertension (22). Text mining using the SAS regular expression technique was performed for searching keywords "minimal EV/esophageal varices, Form 1 EV, grade 1 EV", "red-color sign/RCS/red wale marks/cherry red spot/hematocystic spot" (23), "esophageal variceal ligation/EVL", and their synonyms in the endoscopic reports. Two independent gastroenterologists had further confirmed their validity.

As a result, cirrhotic patients ≥20 years old with low-risk EV (small or grade 1 or form 1 EV, and no RCS, n=7,084) documented in CGRD were enrolled for statistic analysis. The main group was 6,803 patients without NSBB prophylaxis and without EVL for primary endpoint analysis. The minor group was 281 matched patients with NSBB prophylaxis for secondary endpoint analysis.

Diagnosis criteria

The diagnosis of liver cirrhosis was confirmed by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code: (571, 571.2, 571.5, 571.6, 572.3) or 10th Revision (ICD-10-CM) code: K70.3, K71.7, K74.3, K74.5, K74.6, K76.6 and abdominal echography report. The diagnosis of ascites was based on diagnosis code: 789.5 (ICD-9) or R18, K70.31, K71.51 (ICD-10). The diagnosis of hepatic encephalopathy was based on diagnosis code: 348.3, 572.2 (ICD-9); G93.4 (ICD-10). The diagnosis of EV bleeding was based on diagnosis code: 456.20, 530.82, 456.0 (ICD-9); I85.11, I85.01 (ICD-10).

The diagnosis of low-risk EV (small EV or grade 1/form 1 EV, no RCS) was confirmed by screening upper endoscopic reports for the earliest findings of the above keywords. Text mining using the SAS regular expression technique was performed for searching keywords in the endoscopic reports, and we further confirmed validity by two independent gastroenterologists.

Non-invasive markers for comparison of predicting EVB

The following non-invasive markers were calculated for each patient: CTP score, MELD score, MELD-Na score, Platelet-albumin-bilirubin (PALBI) score, gamma-glutamyl transpeptidase-to-platelet ratio (GPR), gamma-glutamyl transpeptidase-to-albumin ratio (GAR), AST/ALT, APRI, PC/SD, spleen diameter, portal vein size, fibrosis-4-index (FIB-4), FI, King's score, Log score, Lok index, and Forns index. In addition, spleen diameter and portal vein size were considered based on abdominal echography reports.

The formulas for these non-invasive markers were listed in *Table S1*.

The primary, secondary endpoint and follow-up time

The primary endpoint is defined as EV bleeding during 1 and 2 years' follow-up period respectively. The secondary endpoint is defined as overall mortality during 1 and 2 years' follow-up period, respectively.

Follow-up time was defined as an interval starting from a patient was enrolled until their primary or secondary endpoint event happened or until the last medical record during the study period.

Statistical analysis

For descriptive statistics, continuous variables are expressed as mean (standard deviation) or median (IQR), and categorical variables are expressed as frequencies and percentages. The independent *t*-test was used to compare continuous variables between patients with EV bleeding and non-EV bleeding, while the χ^2 test was used to compare categorical variables. Fisher's exact test was performed when more than 20% of data points presented an expected frequency of <5. Univariable and/or multivariable Cox regression analyses were used to assess the hazard ratio of various clinical factors and scores for predicting EV bleeding within 1 and 2 years, respectively.

After significant variables emerged, AUROC curve analysis was used to assess their balance cut-off value and accuracy in predicting EV bleeding within one and two years. Hanley and McNeil test (24) was used to conduct an inter-measure comparison. Post-hoc tests for pairwise comparison included the Bonferroni correction to adjust the significance level. Youden's index was calculated to determine an optimal cut-off value. The sensitivity and negative predictive values (NPV) measure the proportion of actual positives and true negative results that describe the performance of an EV bleeding predictor.

A P value of <0.05 was considered statistically significant.

All statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

There were 8,310 compensated liver cirrhotic patients with low-risk EV (small or grade 1 or form 1 EV, and no RCS) enrolled in our study from January 2001 to February 2018 in the beginning. After excluding patients who had undergone prophylactic therapy with EVL (n=1,226, 14.7%), the remaining 6,803 patients without NSBB prophylaxis were the main group for primary endpoint analysis. The minor group was 281 matched patients (3.97%) with NSBB prophylaxis for secondary endpoint analysis (*Figure 1*).

Baseline demographics

First, we studied the main group (no NSBB). Their demographic characteristics, biochemical data, and non-invasive fibrotic scores are shown in *Table 1*. Male patients are more common (71%). HBV infection accounts for 45.29% of all known etiologies of liver cirrhosis. During follow up, 539 patients (7.92%) and 710 patients (10.44%) experienced EVB within 1 year and 2 years, respectively. The result also showed that there were 266 patients (3.91%) and 433 patients (6.36%) who experienced variceal size progression from grade 1 to either grade 2 or grade 3 by endoscopy within 1 year and 2 years, respectively (*Table 1*). Overall mortality was also similar: 230 patients (3.38%) and 313 (4.6%) patients died within 1 year and 2 years, respectively (*Table 1*). Anti-viral agent use among those with HBV or HCV-related cirrhosis were at rates of 40.5% and 20.6%, respectively.

Several factors were statistically different between EV bleeding and non-EV bleeding groups within 1 year and 2 years, as is demonstrated in *Table 2* and *Table S2* respectively. The EV bleeding group was younger, contained more male, more alcoholics, more severe various fibrosis scores, and larger portal vein size (*Table 2* and *Table S2*).

Prediction of EVB within 1 year and 2 years by Cox regression analyses

Furthermore, univariable and multivariable Cox regression analyses were performed to find significant non-invasive markers that predict EVB within 1 year (*Table 3*) and 2 years (*Table S3*). After the stepwise Cox regression analysis, non-significant factors like age, gender or etiology were excluded based on stepwise model selection. Therefore, there were only GPR and FI retained in our final multivariate model. The results showed that FI (1 year: HR: 1.484, 95% CI: 1.21–1.83, P<0.001; 2 years: HR: 1.373, 95% CI: 1.156–1.63, P<0.001) and GPR (1 year: HR: 1.05, 95% CI: 1.03–1.07, P<0.001; 2 years: HR: 1.039, 95% CI: 1.018–1.060, P<0.001) could independently predict EVB within 1 year and 2 years significantly.

FI had higher accuracy than GPR in predicting EVB by ROC analysis

In addition, ROC analysis was conducted to assess the accuracy of these two non-invasive markers in predicting EVB within 1 and 2 years, followed by the Hanley and McNeil test (24) to conduct an inter-measure comparison. Results showed no significant difference, but the FI had higher accuracy in predicting EVB within 1 year (*Figure 2A*) and 2 years (*Figure 2B*). Youden's index was calculated to determine an optimal cut-off value for FI since its higher predictive value. It was revealed that a cut-off value of 3.95 of FI for predicting 1-year EVB possesses a sensitivity of 51.2%, NPV of 94.3% and an AUROC of 62.95%. A cut-off value of 3.31 possesses a sensitivity of 71.5%, NPV of 93.3% and an AUROC of 62.25% for predicting 2-year EVB. A more detailed sensitivity, specificity, and positive and NPV for FI in predicting EVB are shown in *Table S4*.

FI has high NPV in predicting over mortalities in addition to predicting EVB

It is worth noting that FI also has high NPV in predicting over mortalities in these patients: the 1-year mortality rate for those with FI <3.95 was 2.98% (NPV =97.02%) while those with FI ≥3.95 was 5.37%. The 2-year mortality rate for those with FI <3.31 was 3.98% (NPV =96.02%) while those with FI ≥3.31 was 6.13%. A more detailed sensitivity, specificity, and positive and NPV for FI in predicting mortalities are shown in *Table S5*. Moreover, the 1-year and 2-year mortality rate for those with FI score less than the cut-off value and without EV bleeding was even less (2.75% and 3.65%

Table 1 Demographic characteristics of 6,803 patients with compensated cirrhosis and EV, F1 without NSBB or prophylactic EVL as the main group. The minor group (taking NSBB) for secondary endpoint comparison analysis is also shown

Parameter	No NSBB (main group) n=6,803	NSBB (minor group) n=281
Male	4,830 (71.00)	215 (76.51)
Age (years, mean ± SD)	58.99±12.56	55.05±13.42
Etiology, n (%)		
HBV	3,081 (45.29)	123 (43.77)
HCV	1,333 (19.59)	54 (19.22)
Alcohol	650 (9.55)	65 (23.13)
Others[$]	1,739 (25.56)	39 (13.88)
Follow-up duration (months, mean ± SD)		
To mortality	11.68±1.71	10.51±3.31
Outcome, n (%)		
Esophageal variceal bleeding in 1 year	539 (7.92)	42 (14.95)
Esophageal variceal bleeding in 2 years	710 (10.44)	243 (86.48)
Variceal size progression in 1 year	266 (3.91)	84 (29.89)
Variceal size progression in 2 years	433 (6.36)	89 (31.67)
Mortality in 1 year	230 (3.38)	54 (19.22)
Mortality in 2 years	313 (4.60)	58 (20.64)
Baseline laboratory value [median, IQR]		
AST (U/L)	57 [37–98]	71 [47–112]
ALT (U/L)	40 [26–69]	36 [24–59]
Cr (mg/dL)	0.92 [0.74–1.20]	0.90 [0.73–1.30]
Na (mEq/L)	138 [135–141]	137.0 [135.0–140.0]
K (mEq/L)	4.00 [3.60–4.30]	4.00 [3.50–4.40]
Bilirubin-total (mg/dL)	1.30 [0.90–2.30]	3.00 [2.50–3.50]
Albumin (g/dL)	3.40 [2.80–4.00]	3.00 [2.50–3.50]
PT-INR	1.20 [1.10–1.39]	1.30 [1.17–1.50]
Hb (g/dL)	11.50 [9.50–13.50]	9.70 [8.00–11.70]
WBC (×1,000/μL)	5.60 [4.10–7.80]	6.60 [4.60–9.60]
Platelet (×1,000/μL)	104 [70–153]	106.0 [67.00–154.0]
r-GT	73 [34–164]	146.0 [47.00–363.0]
Cholesterol	159 [133–186]	150.0 [122.0–181.0]
Prognostic systems [median, IQR] or n (%)		
CTP score	6 [5–7]	7 [6–8]
MELD score	11.34 [8.59–15.84]	13.43 [10.19–18.59]
MELD-Na score	12.00 [9.00–18.00]	14 [11–20]

Table 1 (*continued*)

Table 1 (*continued*)

Parameter	No NSBB (main group) n=6,803	NSBB (minor group) n=281
PALBI score	–2.74 [–3.11, –2.29]	–2.49 [–2.93, –2.05]
PALBI grade 1	N=3,552/5,611 (63.30%)	125/260 (48.08%)
PALBI grade 2	N=1,031 (18.37%)	65 (25.00%)
PALBI grade 3	N=1,028 (18.32%)	70 (26.92%)
Spleen diameter	5.63 [4.80–6.50]	5.98 [5.20–6.94]
GUCI	2.27 [1.16–4.60]	2.67 [1.43–5.23]
Gamma-glutamyl transpeptidase-to-platelet ratio (GPR)	1.24 [0.55–2.72]	2.11 [0.72–4.61]
Gamma-glutamyl transpeptidase-to-albumin ratio (GAR)	2.18 [1.00–5.67]	4.82 [1.68–12.05]
AST/ALT ratio	1.37 [0.98–1.94]	1.87 [1.3–2.64]
AST to platelet ratio index (APRI)	1.75 [0.95–3.38]	1.98 [1.17–3.88]
Platelet count to spleen diameter (PC/SD)	18.80 [11.68–29.26]	17.71 [10.69–26.50]
Fibrosis-4-index (FIB-4)	5.46 [3.13–9.31]	6.12 [3.54–10.15]
Fibrosis index (FI)	3.5 [2.71–4.25]	3.84 [3.09–4.58]
King's score	45.25 [23.29–90.88]	52.37 [25.2–97.13]
Log score	1.79 [0.64–3.44]	2.98 [1.65–4.79]
Lok index	0.86 [0.65–0.97]	0.95 [0.84–0.99]
Portal vein size	1.10 [1.00–1.25]	
Forn's index	10.80 [9.5–12.04]	

[$], non-A, non-B, non-C; EV, esophageal varices; F1, form 1 EV; NSBB, non-selective beta-blocker; EVL, esophageal band ligation; HBV, hepatitis B virus; HCV, hepatitis C virus; Hb, hemoglobulin.

respectively), implying those with low FI and no EVB had the best survival outcomes.

Comparing between the matched non-NSBB group and the NSBB group for EV bleeding analysis

Hence, we selected 183 patients with matched sex, age and FI score from the major and the minor group respectively for EV bleeding analysis. As shown in *Table 4*, the sex, age, CTP, MELD, FI scores, total bilirubin, albumin, platelet count, creatinine, INR, PALBI, APRI, Log score, King's score and Fib-4 index were matched between the non-NSBB (n=183) and the NSBB group (n=183). But the limitation is that the Hb, WBC, r-GT, GPR, GAR, and AST/ALT ratio did not match. The HR in EVB for patients not taking NSBB was significantly lower than that in patients taking NSBB (HR =0.054, P<0.001, *Table 5*).

Comparing among four groups divided by NSBB and FI for EV bleeding and mortality analysis

To strengthen our assumption, we further divided our entire major group who did not take NSBB and the entire minor groups who took NSBB during follow-ups before primary endpoint into four subgroups by the FI cut-off values. As shown in *Figure 3*, the incidence of EVB and mortality were significantly the lowest in the group 4 patients (FI lower than the cut-off values and not taking NSBB). The Kaplan-Meier curve in *Figure 4A*,*B* further suggested that patients with low FI and non-NSBB use

Table 2 Statistical differences between EV bleeding and non-EV bleeding groups within 1 year

Variables	EV bleeding, n=539 (7.92%)	Non-EV bleeding, n=6,264 (92.08%)	P
Male, n (%)	404 (74.95)	4,426 (70.66)	0.0349
Age [years, mean (SD)]	56.81 (14.20)	59.18 (12.39)	<0.001
Etiology, n (%)			<0.001
HBV	194 (35.99)	2,887 (46.10)	
HCV	105 (19.48)	1,228 (19.60)	
Alcohol	76 (14.10)	574 (9.16)	
Others[$]	164 (30.43)	1,575 (25.14)	
Follow-up duration [months, mean (SD)]			
To EV bleeding	2.60 (3.07)	11.70 (1.64)	<0.001
Baseline laboratory value [mean (SD)]			
AST (U/L)	98.09 (148.4)	89.77 (174.2)	0.3371
ALT (U/L)	52.98 (64.55)	64.44 (97.00)	0.015
Cr (mg/dL)	1.45 (1.58)	1.33 (1.57)	0.1178
Na (mEq/L)	135.4 (13.29)	137.3 (8.39)	<0.001
K (mEq/L)	4.11 (2.12)	4.02 (1.08)	0.1554
Bilirubin-total (mg/dL)	3.46 (5.38)	2.57 (4.33)	<0.001
Albumin (g/dL)	2.96 (0.87)	3.38 (0.83)	<0.001
PT-INR	1.38 (0.37)	1.30 (0.52)	0.0032
Hb (g/dL)	10.11 (2.53)	11.56 (2.72)	<0.001
WBC (×1,000/μL)	7.70 (4.70)	6.49 (3.92)	<0.001
Platelet (×1,000/μL)	118.40 (107.0)	120.90 (75.10)	0.5088
r-GT	193.20 (236.1)	150.40 (241.5)	0.0079
Cholesterol	149.30 (44.48)	163 (47.38)	<0.001
Antivirals for HBV % (n/N)	33.0 (64/194)	41.0 (1,186/2,887)	
Prognostic systems [mean (SD)]			
CTP score	7.01 (1.64)	6.44 (1.52)	<0.001
MELD score	14.82 (6.25)	13.05 (6.12)	<0.001
MELD-Na score	17.04 (8.55)	14.77 (8.29)	<0.001
PALBI score	–2.44 (0.71)	–2.67 (0.69)	<0.001
Gamma-glutamyl transpeptidase-to-platelet ratio	3.93 (7.89)	2.51 (4.55)	<0.001
Gamma-glutamyl transpeptidase-to-albumin ratio	7.71 (14.31)	5.63 (40.86)	0.4374
AST/ALT	2.19 (1.72)	1.67 (1.37)	<0.001
AST to platelet ratio index (APRI)	4.26 (8.95)	3.61 (18.40)	0.4724
Platelet count to spleen diameter (PC/SD)	19.87 (14.89)	23.16 (17.11)	0.0032
Fibrosis-4-index (FIB-4)	11.67 (26.73)	9.17 (71.97)	0.4764
Fibrosis index (FI)	3.86 (1.44)	3.42 (1.18)	<0.001
King's score	121.90 (326.3)	119.40 (101.1)	0.9605
Lok score	3.45 (3.65)	2.42 (3.59)	<0.001
Lok index	0.85 (0.19)	0.78 (0.22)	<0.001
Portal vein size	1.16 (0.27)	1.11 (0.23)	0.0034
Forns index	11.11 (2.22)	10.74 (1.96)	0.0056

[$], non-A, non-B, non-C. EV, esophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; Hb, hemoglobulin.

Table 3 Univariable and multivariable Cox regression analysis for prediction of EV bleeding within 1 year

Variables	Univariate			Multivariate (stepwise)		
	Crude HR	95% CI	P value	Adjusted HR	95% CI	P value
Age	0.99	0.98–0.99	<0.01			
Sex						
Male	1.00					
Female	0.81	0.67–0.98	0.03			
Etiology						
HBV	0.66	0.52–0.84	<0.01			
HCV	0.83	0.65–1.06	0.14			
Alcohol	1.26	0.96–1.66	0.09			
Others	1.00					
Prognostic systems						
CTP score	1.24	1.16–1.31	<0.01			
MELD score	1.04	1.02–1.05	<0.01			
MELD-Na score	1.03	1.01–1.03	<0.01			
PALBI score	1.55	1.36–1.75	<0.01			
Spleen diameter	1.13	1.03–1.22	0.01			
GUCI	1.00	0.99–1.00	0.47			
Gamma-glutamyl transpeptidase-to-platelet ratio (GPR)	1.03	1.01–1.04	<0.01	1.05	1.03–1.07	<0.001
Gamma-glutamyl transpeptidase-to-albumin ratio (GAR)	1.00	0.99–1.00	0.47			
AST/ALT	1.15	1.11–1.19	<0.01			
AST to platelet ratio index (APRI)	1.00	1.00–1.01	0.06			
Platelet count to spleen diameter (PC/SD)	0.99	0.97–0.99	0.00			
Fibrosis-4-index (FIB-4)	1.00	1.00–1.01	0.01			
Fibrosis index (FI)	1.38	1.26–1.50	<0.01	1.48	1.21–1.83	<0.001
King's score	1.00	1.00–1.00	0.59			
Lok score	1.04	1.02–1.05	<0.01			
Lok index	6.92	3.89–12.28	<0.01			
Portal vein size	2.42	1.35–4.33	<0.01			
Forns index	1.10	1.03–1.16	<0.01			

The C-index for prediction of 1-year EV bleeding in this multivariable logistic regression model was 0.63 with 95% CI (0.59–0.67). The FI with a cut-off value of 3.95 showed a negative predictive value (NPV) of 94.3% for predicting subsequent EV bleeding and NPV of 97.02% for predicting mortalities within 1 year. CCI, Charlson Comorbidity Index.

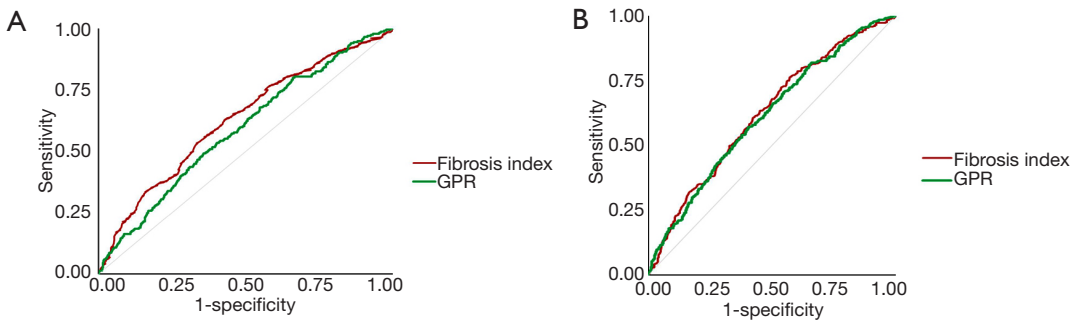

Figure 2 The fibrosis index had higher accuracy in predicting EV bleeding. (A) The fibrosis index had higher accuracy in predicting EV bleeding within 1 year than GPR had; (B) the fibrosis index had mild higher accuracy in predicting EV bleeding within 2 year than GPR had. EV, esophageal variceal; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

Table 4 Selected patients with matched sex, age and FI score from the major and the minor group respectively for EV bleeding analysis

Parameter	No NSBB (matched, n=183)	NSBB (matched, n=183)	P value
Male (n, %)	148 (80.87)	148 (80.87)	1.00
Age (years, mean ± SD)	54.68±11.71	54.68±11.71	1.00
Etiology, n (%)			<0.01
HBV	80 (43.71)	76 (41.53)	
HCV	51 (27.87)	29 (15.85)	
Alcohol	26 (14.21)	48 (26.23)	
Others	26 (14.21)	30 (16.39)	
Follow-up duration (months, mean ± SD)			
To EV bleeding	10.46±3.78	3.97±3.57	<0.01
Outcome			
Esophageal variceal bleeding in 1 year (n, %)	22 (12.02)	160 (87.43)	<0.01
Baseline laboratory value (mean ± SD)			
AST (U/L)	89.14±88.74	95.19±94.44	0.53
ALT (U/L)	58.24±60.64	51.29±49.73	0.23
Cr (mg/dL)	1.39±1.64	1.48±1.75	0.62
Na (mEq/L)	136.50±9.61	136.80±5.73	0.72
K (mEq/L)	3.93±0.56	4.09±1.44	0.18
Bilirubin-total (mg/dL)	3.46±5.55	2.85±3.34	0.20
Albumin (g/dL)	3.21±0.71	3.10±0.64	0.12
PT-INR	1.36±0.34	1.35±0.28	0.89
Hb (g/dL)	10.91±2.54	10.08±2.57	<0.01
WBC (×1,000/μL)	6.31±3.77	7.23±4.37	0.03
Platelet (×1,000/μL)	107.20±57.99	118.00±70.84	0.11

Table 4 (*continued*)

Table 4 (*continued*)

Parameter	No NSBB (matched, n=183)	NSBB (matched, n=183)	P value
r-GT	172.50±269.30	279.30±380.30	0.01
Cholesterol	151.40±48.76	161.00±49.88	0.17
Prognostic systems (mean ± SD)			
CTP score	6.80±1.67	6.89±1.37	0.61
MELD score	14.65±6.63	14.43±5.19	0.74
MELD-Na score	16.49±8.80	15.54±6.41	0.27
PALBI score	–2.54±0.73	–2.51±0.69	0.74
PALBI grade 1 (n, %)	100 (54.64)	92 (50.27)	0.41
PALBI grade 2 (n, %)	39 (21.31)	50 (27.32)	
PALBI grade 3 (n, %)	44 (24.04)	41 (22.40)	
Spleen diameter	5.97±1.15	6.11±1.19	0.39
GUCI	4.90±7.98	4.54±5.94	0.64
Gamma-glutamyl transpeptidase-to-platelet ratio (GPR)	2.68±3.62	3.88±5.26	0.04
Gamma-glutamyl transpeptidase-to-albumin ratio (GAR)	5.41±8.17	9.00±11.47	<0.01
AST/ALT ratio	1.87±1.43	2.36±2.23	0.01
AST to platelet ratio index (APRI)	3.27±3.81	3.26±4.03	0.98
Platelet count to spleen diameter (PC/SD)	18.78±10.70	20.29±13.39	0.37
Fibrosis-4-index (FIB-4)	7.75±6.52	8.53±8.91	0.34
Fibrosis index (FI)	3.72±0.95	3.72±0.95	0.99
King's score	89.47±172.65	80.07±99.28	0.54
Log score	3.09±2.86	3.53±3.48	0.20
Lok index	0.84±0.18	0.88±0.17	0.07
Portal vein size	1.14±0.25	1.15±0.26	0.93
Forns index	10.77±1.82	10.81±1.72	0.88

NSBB, non-selective beta-blockers; EV, esophageal variceal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 5 Hazard ratio for EVB between the patients in *Table 4* in the no NSBB and the NSBB group respectively

Variable	Hazard ratio	95% confidence interval	P value
No NSBB	0.054	0.034–0.087	<0.001
NSBB	1.000		

NSBB, non-selective beta-blockers.

Group 1: Fibrosis score ≥3.95 (1 year) or ≥3.31 (2 years) and took NSBB
Group 2: Fibrosis score ≥3.95 (1 year) or ≥3.31 (2 years) and did not taking NSBB
Group 3: Fibrosis score <3.95 (1 year) or <3.31 (2 years) and took NSBB
Group 4: Fibrosis score <3.95 (1 year) or <3.31 (2 years) and did not taking NSBB

A. EVB within 1 year

	Group # n (%)				P value	Group 1 *vs.* 2	P$^{\$}$<0.001
EVB	1	2	3	4	P<0.001	1 *vs.* 3	0.2452
						1 *vs.* 4	<0.001
0$^{\#}$	23 (18.85)	1758 (89.01)	19 (13.57)	3451 (94.34)		2 *vs.*3	<0.001
						2 *vs.* 4	<0.001
1	99 (81.15)	217 (10.99)	121 (86.43)	207 (5.66)		3 *vs.* 4	<0.001

EVB 0$^{\#}$, no EV bleeding; EVB 1, EV bleeding. P$^{\$}$, P value.

B. EVB within 2 years

	Group # n (%)				P value	Group 1 *vs.* 2	P$^{\$}$<0.001
EVB	1	2	3	4	<0.001	1 *vs.* 3	0.5414
						1 *vs.* 4	<0.001
0$^{\#}$	28 (15.38)	2785 (87.11)	10 (12.50)	2272 (93.27)		2 *vs.*3	<0.001
						2 *vs.* 4	<0.001
1	154 (84.62)	412 (12.89)	70 (87.50)	164 (6.73)		3 *vs.* 4	<0.001

EVB 0$^{\#}$, no EV bleeding; EVB 1, EV bleeding. P$^{\$}$, P value.

C. Mortality within 1 year

	Group # n (%)				P value	Group 1 *vs.* 2	P$^{\$}$<0.001
Death	1	2	3	4	<0.001	1 *vs.* 3	0.049
						1 *vs.* 4	<0.001
0$^{\#}$	91 (74.59)	1,869 (94.63)	118 (84.29)	3,549 (97.02)		2 *vs.*3	<0.001
						2 *vs.* 4	<0.001
1	31 (25.41)	106 (5.37)	22 (15.71)	109 (2.98)		3 *vs.* 4	<0.001

Death 0$^{\#}$, no death. Death 1, death (mortality). P$^{\$}$, P value.

D. Mortality within 2 year

	Group # n (%)				P value	Group 1 vs. 2	P$^{\$}$<0.001
Death	1	2	3	4	<0.001	1 vs. 3	0.895
						1 vs. 4	<0.001
0$^{\#}$	142 (78.02)	3,001 (93.87)	63 (78.75)	2,339 (96.02)		2 vs.3	<0.001
						2 vs. 4	<0.001
1	40 (21.98)	196 (6.13)	17 (21.25)	97 (3.98)		3 vs. 4	<0.001

Death 0$^{\#}$, no death. Death 1, death (mortality). P$^{\$}$, P value.

Figure 3 The differences in EVB and mortality rates among four groups of patients within 1 and 2 years, respectively.

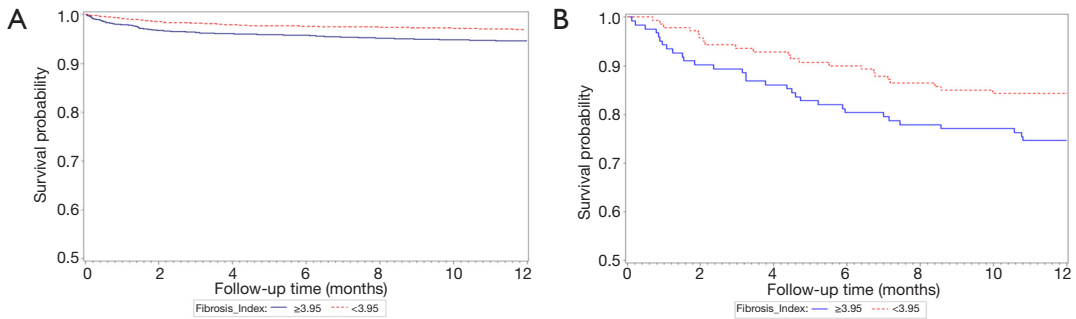

Figure 4 The Kaplan-Meier curve of four subgroups divided by the FI cut-off values (A) the entire major group who did not take NSBB and (B) the entire minor groups who took NSBB during follow-ups before the primary endpoint. FI, fibrosis index; NSBB, non-selective beta-blockers.

had the best survival outcome.

Discussion

In this study, we firstly demonstrated that the FI is an acceptable non-invasive marker for distinguishing higher or lower-risk EV bleeding group within 1 year or 2 years in patients with compensated cirrhosis and initial small varices without RCS and not taking beta-blockers and band ligation prophylaxis by its high NPV and moderate AUROC in predicting subsequent EVB. Based on our study, minimal bleeding risk is indicated when FI score is <3.95 or <3.31 for 1 year or 2 years given its high NPV, signifying clinically non-significant portal hypertension. In addition, the 1-year and 2-year mortality rates for patients with FI score less than these cut-off values were also found to be low (high NPV) and even lower in patients without EV bleeding. Therefore, we selected 183 patients with matched sex, age and FI score from the major and the minor group respectively for EV bleeding analysis. It revealed that patients not taking NSBB had lower EV bleeding risks. To strengthen our assumption, we further divided our entire major group who did not take NSBB and the entire minor groups who took NSBB during follow-ups before primary endpoint into four subgroups by the FI cut-off values. The result showed that the incidence of EVB and mortality were significantly the lowest in patients with FI lower than the cut-off values and not taking NSBB. The Kaplan-Meier curve also supported that the best survival outcome for CCC patients with initial small EV and without RCS were patients with low FI values and non-NSBB use. In other words, NSBB use was not related to death and could be avoided in this low-risk group without CSPH. Further RCT study needed to verify the benefits of cutting NSBB in those with low FI and taking NSBB in those with high FI scores.

The management for small/low-risk EV, especially in compensated cirrhotic patients, had conflicting results (25,26). Because NSBB showed adverse effects such as bradycardia, increased airway resistance, and low arterial blood pressure due to systemic vasodilation, many patients, especially those with cirrhosis, could not tolerate these drugs (27). In addition, a prior study also showed that NSBB may cause worse survival for cirrhotic patients if mean arterial blood pressure decreases to <65 mmHg (28). Another study found NSBB use was associated with increased risk of hepatic encephalopathy, which carries high mortality risk (29). Despite of a recent study that demonstrated the benefit of NSBB in preventing decompensation (mainly reduce ascites incidence) and improving decompensation-free survival in compensated cirrhotic patients with CSPH and initial none or small EV, the incidence of high-risk EV formation and death from all causes were not different between NSBB and placebo groups (30). These findings suggest that NSBB may be not beneficial for all compensated cirrhotic patients with initial small EV in terms of preventing EV bleeding. That is to say, we may benefit low-risk groups by cutting back on unnecessary medication, thereby preventing complications. On the other hand, the accuracy of FI is not strong enough to predict EV bleeding within 1 or 2 years with its low PPV, hence we cannot conclude whether these FI high-risk patients would benefit from the intervention.

There is explicit indication for prevention for cirrhotic patients with high-risk EV, including large size EV, red color sign, and Child type C patients, yet there is dispute in prophylaxis for patients with small EV due to lack of

evidence (5,6,9). While a randomized controlled trial (RCT) by Merkel *et al.* (12) demonstrated that conventional NSBB (nadolol) therapy is effective in preventing the progression from small to large varices in patients without prior bleeding, another RCT using propranolol by Sarin and colleagues (13) stated that NSBB prophylaxis was unable to prevent the growth of varices, EVB or mortality for small EV. The reason for the conflicting data shown in these studies could be that only some patients with small EV had reduced their HVPG sufficiently when using NSBB to demonstrate promising results. In this study, we not only found FI is the only valuable tool in predicting subsequent EVB in compensated cirrhotic patients with initial small EV and no RCS, but may also serve as a screening tool for low-risk patients of EVB and mortality who might not benefit from taking NSBB, as high NPV could correctly identifying a good prognosis patient (31). That is to say, these patients might not need prophylactic NSBB when FI is under a certain cut-off value. Moreover, these patients could continue to be monitored by regular monitoring modalities other than by endoscope within 2-year interval (9).

Esophagogastroduodenoscopy (EGD) is a common and safe procedure nowadays and can directly observe the severity of esophageal varices. However it is also expensive, mildly invasive, carries a certain degree of risk, and may be accompanied by discomfort, hence some patients are unwilling to stick to the regular monitoring schedule by endoscopy recommended by Baveno VI (10). Accordingly, many non-invasive markers were investigated for EV prediction power as an alternative to EGD. Deng *et al.* conducted a systemic review that showed APRI, AAR, FIB-4, Lok, and Forns scores had low to moderate accuracy in predicting EV formation, whereas the FI was not evaluated due to a lack of reports mentioning it. This is in spite of the fact that all elements in the formula play an important role in determining liver cirrhosis severity (32). The FI is a simple and reliable tool constructed using platelet count and serum albumin for predicting fibrosis in hepatitis C (33) and B patients (34). Platelet count is a noninvasive parameter with high accuracy for predicting EVs, according to one study (35). Albumin may be useful as a first-line tool for identification of adults and pediatric patients at risk of variceal onset, and hence may reduce the number of unnecessary EGDs (36,37). In this study, FI is proposed to display acceptable performance in predicting EV bleeding within 1 year and 2 years in patients with compensated cirrhosis, initial small varices and no RCS who are not on beta-blocker and not underwent band ligation prophylaxis.

The severity of portal hypertension correlates well with HVPG (38,39). According to guidelines, portal hypertension is defined as increased HVPG above 5 mmHg, and CSPH as above 10 mmHg, whereas HVPG above 12 mmHg carries increased bleeding risk (40). Furthermore, CSPH usually develops prior to the occurrence of small EV. In turn, almost every patient with EV has already developed CSPH (41). Theoretically, we should treat EV with repeated measurement of HVPGs therapy response (42). In practice, however, HVPG is not routinely checked due to invasiveness, cost, expertise requirement, and lack of wide availability (43). Therefore, noninvasive and reproducible techniques capable of substituting HVPG would be very useful in clinical practice. HVPG is directly proportional to the severity of hepatic fibrosis (44) and many studies have demonstrated the effectiveness of non-invasive methods for predicting liver fibrosis (33,45,46). Ohta *et al.* found that the FI could reflect histological liver fibrosis in hepatitis C (33). Koda *et al.* reported that Fibroindex could predict significant fibrosis in hepatitis C patients (47). Simona Bota *et al.* revealed that the PLF score, which includes the King's score, Forns score, and APRI, were more effective than transient elastography (TE) in predicting fibrosis in chronic hepatitis C (48). Vallet-Pichard *et al.* noted that FIB-4 could predict fibrosis in HCV infection (49). A systemic review and meta-analysis reported that APRI, AAR, FIB-4, Lok, and Forns scores had low to moderate diagnostic accuracy in predicting the presence of varices in liver cirrhosis (32). Moreover, Kraja *et al.* found that FIB-4 is the only strong predictor for EV formation (17) and Bhattarai *et al.* demonstrated that size of spleen diameter and portal vein could correlate with severity of EV (50).

In recent years, elastography-based liver stiffness measurement (LSM) has been a popular tool to evaluate hepatic fibrosis, which is also used to predict EV formation and varices requiring treatment. But recent studies have shown that using LSM alone could produce highly variable results, thus its combination use with another non-invasive marker is suggested (51). Although in the 2015 Baveno VI consensus, it recommended that screening endoscopy for esophageal varices can be omitted in compensated liver cirrhotic patients with LSM values <20 kPa and platelet count (PLT) >150 G/L, LSM is resource-limited and may not be available in some hospitals or clinics. Therefore, we try to use these verified non-invasive markers to predict high and low-risk of EV bleeding in compensated cirrhotic patients with small EV and no RCS. The assumption is that these patients may benefit from more aggressive monitoring

and treatment. In the last, we demonstrate that for patients with low-risk of EV bleeding signifying clinically non-significant portal hypertension, NSBB might not be indicated.

Take a step further, if patients in group 3 and 4 listed in *Figure 3* could spare the use of NSBB, the medical costs in the CGMH system would be reduced by $14,678 per year [(3,798 patients divided by 17 years) × (propranolol 10 mg average price is 0.06 US dollars/pill in Taiwan) × (average 3 times/day) ×365 days]. Assuming that the medical costs in the CGMH system is about one-tenth of Taiwan's total national health insurance, the spared medical costs in Taiwan would be estimated $146,780 per year. Assuming this scenario occurs in the U.S., the medical costs savings would be estimated at least $3,495,183 per year {[633,323 adults with cirrhosis/year (52)] × (at least 1.4% compensated cirrhosis with initial small EV and no RCS/total cirrhosis) × (propranolol 10 mg average price is $0.36/pill in U.S.) × (3 times/day) ×365 days}. Not to mention these low-risk patients could possibly benefit from reduced EVB and mortality.

There are limitations in this study. First, it is a retrospective cohort study. Although we enrolled a large number of patients to decrease bias, further randomized control studies are still needed to verify the benefits of FI in predicting EVB and mortality for compensated cirrhotic patients with small EV and no RCS. Second, the non-invasive markers we considered have been shown to predict liver fibrosis or EV size, but we may still overlook some other important markers. For example, TE, its data could not be retrieved in our database. Third, some other factors not mentioned in the study may also be associated with EVB, such as collateral vessel, shunting, and medications (statin, nitrate, etc.). However, the large sample size may minimize this bias statistically. Fourth, when comparing the non-NSBB group and the NSBB group for EV bleeding analysis, sex, age, CTP, MELD, FI scores, total bilirubin, albumin, platelet count, creatinine, INR, PALBI, APRI, Log score, King's score and Fib-4 index were matched. But the limitation is that the Hb, WBC, r-GT, GPR, GAR, and AST/ALT ratio did not match. There is a need for further prospective studies that match all these scores in order to compare between the two groups. Fifth, the NSBB chosen in the study were limited to propranolol (inderal) or carvedilol. Because this is a retrospective study analyzing data from CGRD, confirming the aim of NSBB prescription is used for prophylaxis of esophageal varix rupture, not for hypertension, tachycardia, heart failure is difficult. However, the 2014 statement from the "American Society of Hypertension and the International Society of Hypertension" recommend that beta-blockers not be used as first-line therapy for hypertension, particularly in patients over age 60 years. The reduction in cardiac output in patients with cirrhosis receiving propranolol might pose a detrimental effect to the heart especially during stress such as infection (53). Additionally, cirrhotic patients usually had peripheral vasodilatation resulted in hypotension (54). Therefore, we speculate that the NSBB used in cirrhosis were mostly used for primary prevention or secondary prevention of variceal hemorrhage.

In conclusion, we demonstrate that in compensated cirrhotic patients with initial small esophageal varices, no RCS, and not taking NSBB and not receiving band ligation prophylaxis therapy, FI shows a high NPV and moderate AUROC in predicting subsequent EV bleeding within 1 and 2 years. In addition, the 1-year and 2-year mortality rates for patients with FI score less than these cut-off values were also found to be low (high NPV) and even lower in patients without EV bleeding. Further sex, age and FI score matched study for EV bleeding analysis revealed that patients not taking NSBB had lower EV bleeding risks. To strengthen our assumption, we further divided our entire major group who did not take NSBB and the entire minor groups who took NSBB during follow-ups before primary endpoint into four subgroups by the FI cut-off values. The result showed that the incidence of EVB and mortality were significantly the lowest in patients with FI lower than the cut-off values and not taking NSBB. The Kaplan-Meier curve also supported that in CCC patients with initial small EV and no RCS, low FI and non-NSBB use had the best survival outcome. However, although sex, age, CTP, MELD, FI scores, total bilirubin, albumin, platelet count, creatinine, INR, PALBI, APRI, Log score, King's score and Fib-4 index were matched between the non-NSBB group and the NSBB group, the limitation is that the Hb, WBC, r-GT, GPR, GAR, and AST/ALT ratio did not match. There is a need for further prospective studies that match all these scores in order to compare between the two groups more accurately. In summary, the FI might help patients with compensated cirrhosis, initial small EV and no RCS reducing the need of NSBB use by selecting patients with clinically non-significant portal hypertension, hence decreasing possible side effects and medical costs. However, further randomized control trial is warranted to validate this

screening tool.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Institutional Review Board (IRB)/ethical committees of Chang Gung Memorial Hospital (IRB number: 201802006B0). Individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 The formula for non-invasive markers were as follows

MELD score	9.57× loge [creatinine (mg/dL)] +3.78× loge[bilirubin (mg/dL)]+11.2× loge (INR) +6.43
rGT platelet ration (GPR)	[(rGT/its ULN: male: 71; female: 42)/platelet (10^9/L)] ×100
GAR	rGT (IU/L)/10× albumin (g/dL)
AST/ALT ratio	AST/ALT
King score	Age (years) × AST (U/L) × INR/Platelet (10^9/L)
FI score (fibrosis index)	8−0.01× platelets (10^9/L) − albumin (g/dL)
Forns score	7.811−3.131× ln [platelets (10^9/l)]+ 0.781 ln [rGT (U/L)] +3.467× ln [age (years)] −0.014 [cholesterol (mg/dL)]
PALBI score	(2.02× Log10bilirubin) + [−0.37× (Log10bilirubin)^2] +(−0.04× albumin) +[−3.48× Log10 platelets) +[1.01× (Log10 platelets)^2]
PALBI grade	PALBI grade 1 (score ≤−2.53)
	PALBI grade 2 (score >−2.53 and ≤−2.09)
	PALBI grade 3 (score >−2.09)
PLF score	0.956+0.084× TE −0.004× King score +0.124× Forns score +0.202× APRI score
ALBI score	($\log_{10}$ bilirubin ×0.66)+ (albumin ×−0.085), bilirubin is in μmol/L and albumin in g/L
ALBI grade	ALBI grade 1 (≤−2.60)
	ALBI grade 2 (>−2.60 to ≤−1.39)
	ALBI grade 3 (>−1.39)
GUCI	(AST/34) × INR ×100/platelet
Lok score	−5.56−0.0089× number of platelets (10^3/mm^3) +1.26× (AST/ALT) +5.27× INR
Lok index	e (LogOddsLok)/[1+ e (LogOddsLok)]

Table S2 Statistical differences between EV bleeding and non-EV bleeding within 2 years

Variables	EV bleeding, n=710 (10.44%)	Non-EV bleeding, n=6,093 (89.56%)	P
Male, n (%)	523 (73.66)	4,307 (70.69)	0.0984
Age (years, mean ± SD)	57.17±13.75	59.20±12.40	<0.001
Follow-up duration (months, mean ± SD) to bleeding	6.30 (7.32)	23.23 (3.76)	<0.001
Etiology, n (%)			<0.001
HBV	259 (36.48)	2,822 (46.32)	
HCV	140 (19.72)	1,193 (19.58)	
Alcohol	105 (14.79)	545 (8.94)	
Others	206 (29.01)	1,533 (25.16)	
Baseline laboratory value [mean (SD)]			
AST (U/L)	95.02 (131.6)	89.86 (176.20)	0.3371
ALT (U/L)	54.49 (62.08)	64.60 (97.92)	0.015
Cr (mg/dL)	1.39 (1.53)	1.34 (1.57)	0.1178
Na (mEq/L)	136.0 (11.64)	137.3 (8.50)	<0.001
K (mEq/L)	4.06 (1.85)	4.03 (1.10)	0.1554
Bilirubin-total (mg/dL)	3.05 (4.77)	2.58 (4.38)	<0.001
Albumin (g/dL)	3.04 (0.84)	3.39 (0.83)	<0.001
PT-INR	1.35 (0.34)	1.30 (0.52)	0.0032
Hb (g/dL)	10.27 (2.52)	11.59 (2.73)	<0.001
WBC (×1,000/μL)	7.14 (4.41)	6.52 (3.95)	<0.001
Platelet (×1,000/μL)	111.30 (95.34)	121.80 (75.64)	0.5088
r-GT	208.40 (266.4)	147.70 (238.1)	0.0079
Cholesterol	154.60 (44.91)	162.90 (47.48)	<0.001
Antivirals for HBV % (n/N)	35.9% (93/259)	40.9% (1,175/2,822)	
Prognostic systems [mean (SD)]			
CTP score	6.84 (1.56)	6.45 (1.53)	<0.001
MELD score	14.08 (5.90)	13.09 (6.17)	<0.001
MELD-Na score	16 (8.04)	14.83 (8.37)	<0.001
PALBI score	–2.52 (0.69)	–2.66 (0.69)	<0.001
Gamma-glutamyl transpeptidase-to-platelet ratio (GPR)	4.04 (7.28)	2.46 (4.51)	<0.001
Gamma-glutamyl transpeptidase-to-albumin ratio (GAR)	7.81 (13.82)	5.56 (41.39)	0.4374
AST/ALT	2.14 (1.82)	1.66 (1.34)	<0.001
AST to platelet ratio index (APRI)	4.17 (8.20)	3.60 (18.64)	0.4724
Platelet count to spleen diameter (PC/SD)	18.87 (13.59)	23.38 (17.26)	0.0032
Fibrosis-4-index (FIB-4)	11.44 (24.11)	9.12 (72.96)	0.4764
Fibrosis index (FI)	3.85 (1.32)	3.41 (1.18)	<0.001
King's score	115.20 (288.6)	120.1 (102.6)	0.9605
Lok score	3.28 (3.53)	2.41 (3.60)	<0.001
Lok index	0.85 (0.19)	0.78 (0.22)	<0.001
Portal vein size	1.15 (0.25)	1.11 (0.24)	0.0034
Forns index	11.27 (2.07)	10.72 (1.97)	0.0056

EV, esophageal variceal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table S3 Univariable and multivariable Cox regression analysis for prediction of EV bleeding within 2 years

Variables	Univariable		Multivariable (stepwise)	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age	0.998 (0.982–0.994)	<0.001		
Sex				
Male	1			
Female	0.86 (0.73–1.02)	0.082		
Etiology				
HBV	0.71 (0.58–0.87)	0.001		
HCV	0.88 (0.71–1.09)	0.225		
Alcohol	1.4 (1.106–1.77)	0.005		
Others[$]	1			
Prognostic systems				
CTP score	1.170 (1.112–1.231)	<0.001		
MELD score	1.027 (1.014–1.040)	<0.001		
MELD-Na score	1.017 (1.008–1.027)	0.0002		
PALBI score	1.341 (1.199–1.500)	<0.001		
Spleen diameter	1.146 (1.067–1.232)	0.0002		
GUCI	1.001 (0.999–1.002)	0.5491		
Gamma-glutamyl transpeptidase-to-platelet ratio (GPR)	1.031 (1.020–1.042)	<0.001	1.039 (1.018–1.060)	0.0002
Gamma-glutamyl transpeptidase-to-albumin ratio (GAR)	1.001 (0.999–1.002)	0.3613		
AST/ALT	1.145 (1.110–1.181)	<0.001		
AST to platelet ratio index (APRI)	1.004 (1.000–1.008)	0.0413		
Platelet count to spleen diameter (PC/SD)	0.980 (0.972–0.988)	<0.001		
Fibrosis-4-index (FIB-4)	1.001 (1.000–1.002)	0.0019		
Fibrosis index (FI)	1.378 (1.282–1.482)	<0.001	1.373 (1.156–1.630)	0.0003
King's score	1.000 (1.000–1.000)	0.6824		
Lok score	1.037 (1.024–1.051)	<0.001		
Lok index	6.196 (3.818–10.5)	<0.001		
Portal vein size	1.955 (1.177–3.246)	0.0096		
Forns index	1.142 (1.084–1.204)	<0.001		

The C-index for prediction of 2-year EV bleeding in this multivariable logistic regression model was 0.63 with 95% CI (0.59–0.65). The FI with a cut-off value of 3.31 showed a negative predictive value (NPV) of 93.3% for predicting subsequent EV bleeding and NPV of 96.02% for predicting mortalities within 1 year.

Table S4 The sensitivity, specificity, and positive and negative predictive values for fibrosis index (FI) best cut-off values in predicting EVB within 1 and 2 years respectively

FI cut-off values for predicting EVB	Sensitivity	Specificity	PPV	NPV
3.95 (within 1 year)	51.2%	66.3%	11.0%	94.3%
3.31 (within 2 years)	71.5%	44.9%	12.9%	93.3%

Table S5 The sensitivity, specificity, and positive and negative predictive values for fibrosis index (FI) best cut-off values in predicting mortalities within 1 and 2 years respectively

FI cut-off values for predicting mortality	Sensitivity	Specificity	PPV	NPV
3.95 (within 1 year)	49.30%	65.50%	5.37%	97.02%
3.31 (within 2 years)	66.89%	43.80%	6.13%	96.02%