Original Article

Performance of Non-invasive Liver Fibrosis Tests in Predicting Variceal Bleeding among Patients with Upper Gastrointestinal Bleeding

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Background: Many studies have been performed of various non-invasive liver fibrosis tests (NIFTs) which aim to predict degrees of liver fibrosis and the presence of esophageal varices in patients with cirrhosis. However, the use of NIFTs to predict variceal bleeding (VB) in the setting of upper gastrointestinal bleeding (UGIB) remains unexplored.

Objective: To evaluate the performance of NIFTs in predicting VB in patients with UGIB.

Materials and Methods: The authors prospectively enrolled consecutive patients who presented with UGIB and underwent esophagogastroduodenoscopy between June 2018 and August 2019 at Rajavithi Hospital, Bangkok. Baseline clinical/lab characteristics and NIFTs-scoring systems were evaluated including APRI, AAR, FIB-4, Fibrosis Index, Lok Index, GUCI, and King's score.

Results: A total of 215 patients with UGIB were included. Their mean age was 56.4 years, their mean Glasgow-Blatchford score was 9.8, and 39.5% of them had VB. In overall analysis, the AUCs of NIFTs for predicting VB ranged between 0.686 and 0.867. GUCI and APRI (both at the cut-off of 0.5) showed the best performance in predicting VB with sensitivity of 95.3% and 90.6% and specificity of 73.1% and 75.4% respectively.

Conclusion: GUCI and APRI scores displayed good performance in predicting VB in patients presenting with UGIB regardless of known cirrhosis status. They may therefore be helpful when selecting patients for prompt administration of vasoactive agents, antibiotics and urgent esophagogastroduodenoscopy.

Keywords: Biomarker, Cirrhosis, Endoscopy, Esophageal varices, Gastrointestinal hemorrhage, Liver fibrosis, Portal hypertension

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Upper gastrointestinal bleeding (UGIB) is one of the most common medical emergencies and has a considerable mortality rate. Despite advances in endoscopic and pharmacologic therapies, morbidity and mortality rates from UGIB have remained considerable (ranging from 2% to 10%)[1-3]; thus, the cost of UGIB treatment is high, placing a significant burden on large-scale healthcare resources. Effective early risk assessment for patients with UGIB is very important and plays a key role in delivering optimal individualized therapeutic plans, taking into account such aspects as the degree of resuscitation/monitoring and the timing for esophagogastroduodenoscopy (EGD)[4]. Several clinical predictors (e.g. age, comorbidities, and hemodynamic status) and scoring systems (e.g. Rockall and Glasgow-Blatchford scores) have been proposed to predict the outcomes of UGIB in terms of rebleeding and complications; among these, the etiology of UGIB is one of the most robust predictors of outcomes and also dictates therapeutic strategies.

The etiology of UGIB can be classified principally into 1) variceal bleeding (VB) and 2) non-variceal bleeding (NVB), which have different prognoses and require distinct management strategies. Typically, VB which develops in patients with underlying cirrhosis tends to be more severe, and, thus, it is associated with a higher mortality rate[5]. Specific vasoactive agents used to lower portal pressure e.g. somatostatin, octreotide and terlipressin, as well as prophylactic antibiotics, have been shown to reduce active bleeding and lower the rates of rebleeding and mortality in VB[6-8]. Thus, urgent endoscopy within 12 hours, which is earlier than that recommended for those patients with NVB has been recommended if VB is suspected[9]. Early and accurate prediction of VB at presentation is hence critical and may be considered a game-changer in the management of UGIB.

Various non-invasive liver fibrosis tests (NIFTs) have previously been studied as predictors of significant and advanced fibrosis in patients with chronic viral hepatitis,

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mostly with moderate positive predictive values (PPV) and high negative predictive values (NPV)[10-12]; thus, they have also been studied to predict the absence or presence of esophageal varices (EV) in stable cirrhotic patients to circumvent the need for endoscopic screening[10]. However, studies of NIFTs in predicting VB in patients with UGIB remain limited. The present study aimed to evaluate the performance of various NIFTs in predicting VB as a cause of bleeding in patients with UGIB. The authors hypothesized that NIFTs could be potentially useful in predicting VB prior to EGD.

Materials and Methods

Study design

This prospective study was conducted at Rajavithi Hospital, Bangkok which is a large referral center of the Department of Medical Services, Ministry of Public Health of Thailand.

Study population

Consecutive patients who presented with UGIB and underwent EGD were enrolled between June 2018 and August 2019, and informed consent was obtained from all patients. The study protocol was reviewed and approved by the Medical Ethics Committee of the Rajavithi Hospital (ID 61069, document number 078/2018). Exclusion criteria were patients who were: 1) pregnant; 2) diagnosed with hematologic disease or any comorbidities which could possibly interfere NIFTs; and 3) were currently taking vitamin K antagonists. Fourteen patients with UGIB were excluded from the present study: 6 were taking warfarin, 4 had hematological diseases, and another 4 had extreme abnormal laboratory values from other conditions. Notably, repeated admissions after 30 days were not excluded.

Outcomes

The primary outcome of the present study was to determine the predictive ability of certain NIFTs-scoring systems: aspartate aminotransferase-to-platelet ratio (APRI); aspartate aminotransferase-to-alanine aminotransferase ratio (AAR); Fibrosis-4 (FIB-4); Fibrosis Index (FI); Kings scores; Lok index; Goteborg University Cirrhosis Index (GUCI); and platelet count in predicting VB as the culprit lesion in patients presenting with acute UGIB. Secondary outcomes were to establish short-term treatment outcomes, including complications, length of hospital stay, and mortality rates.

Definitions

UGIB was defined as bleeding in the gastrointestinal tract proximal to the ligament of Treitz. Patients who presented with hematemesis, coffee ground emesis, or melena were presumed to have UGIB and were enrolled in the present study. The standard management for all UGIB patients in the authors' institution included initial resuscitation with intravenous fluid and administration of intravenous proton pump inhibitors. For those patients in whom VB was suspected, adjunctive use of vasoactive agents included somatostatin and its analogues, or terlipressin. Ceftriaxone prophylaxis was also administered intravenously in all cirrhotic patients presenting with UGIB[13]. VB in the present study was defined as any UGIB related to portal hypertension including EV, gastric varices (GV), and portal hypertensive gastropathy (PHG). VB was documented as the culprit lesion only when recent bleeding stigmata were present on the varices.

The standard endoscopic treatment for VB with active bleeding or recent bleeding stigmata was esophageal variceal ligation (EVL) for EV and cyanoacrylate glue injection for GV whereas the standard endoscopic treatment for NVB with active bleeding or recent bleeding stigmata was mechanical clipping or bipolar coaptation, with or without adrenaline injection. Complications were defined as unwanted events which occurred during hospitalization including shock, rebleeding, sepsis, encephalopathy, and acute kidney injury (AKI). Shock was defined as all class of hemorrhagic shock according to ATLS® classification. Rebleeding was defined as any recurrent UGIB during hospitalization as well as bleeding episodes less than 30 days after discharge. Acute kidney injury was defined in accordance with the specifications of KDIGO. In-hospital mortality was defined as any death which occurred, irrespective of cause, during hospitalization.

Data collection

The present study collected the following data from patients and electronic medical records: age, sex, previous medical history, history of previous UGIB, history of alcohol consumption, current medications, presence of cirrhosis and its etiology, Child-Turcotte-Pugh (CTP) classification, presenting symptoms, physical examination including vital signs, presence of ascites, splenic dullness, palmar erythema and spider nevi, stool characteristics, nasogastric (NG) tube findings, laboratory values including white blood cell (WBC), hemoglobin (Hb), hematocrit (Hct), platelet count, prothrombin time (PT), international normalized ratio (INR), blood urea nitrogen (BUN), creatinine (Cr), electrolytes, total protein, albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Glasgow-Blatchford score (GBS) was calculated for risk stratification and need for interventions,[14] and endoscopic findings and therapeutic modalities as well as treatment outcomes were also recorded. The authors calculated several NIFTs using basic laboratory values recorded as follows:

- APRI (aspartate aminotransferase-to-platelet ratio)[15] = AST(/ULN)/platelet(10^9/L) x 100
- AAR (aspartate aminotransferase-to-alanine aminotransferase ratio)[16] = AST/ALT
- Fibrosis-4 (FIB-4) score[17]

$$= \frac{\text{Age (years) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x square root of ALT (U/L)}}$$

- Fibrosis Index (FI)[18] = 8 - 0.01 x platelet count

(10^3/uL) - albumin(g/dL)

- King Scores[19] = age x AST x INR/PLT

- Lok index[20] = -5.56-0.0089 x PLT+1.26 x AST/ALT+ 5.27xINR

- Goteborg University Cirrhosis Index (GUCI)[21] = AST x prothrombin - INR x 100/platelet

Statistical analysis

Patients' demographic and clinical characteristics were reported using descriptive statistics. Categorical data were reported as frequencies (percentages) and compared using Chi-square tests. Continuous data were reported as mean and standard deviation and compared using independent sample t-tests. Receiver operating characteristic (ROC) curves were performed to evaluate and compare the diagnostic accuracy of GUCI, APRI, AAR, FIB-4, FI, Kings scores, Lok index, and platelet count for the prediction of VB as a cause of upper gastrointestinal bleeding (UGIB). Diagnostic performances were expressed as area under curve (AUC), sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, PPV, and NPV. Optimal cut-off values were chosen with the best sensitivity and specificity. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS software version 22.0®.

Results

Patient characteristics

A total of 215 patients with UGIB were included (2 patients had repeated admission more than 30 days after discharge). Detailed patient characteristics and laboratory values are shown in Table 1. Of all UGIB patients, 159 were male (74%), the mean age was 56.4 years, 83 (38.6%) were known to have cirrhosis, mean Glasgow-Blatchford score was 9.8, and 85 patients (39.5%) were classified into the VB group.

Hematemesis (57.6%) was the main presentation in the VB group while melena (28.5%) was the most prevalent in the NVB group. The most common stool characteristics and NG lavage findings of both groups were melena and coffee-ground respectively. Patients with VB were significantly more likely to have a history of heavy alcohol consumption (>40 gram/day), stigmata of chronic liver disease, and signs of portal hypertension than those in the NVB group. Laboratory values in the VB group also showed statistically significantly higher levels of PT, INR, TB, DB, and significantly lower platelet count.

Endoscopic findings and outcomes

Endoscopic treatment was performed in 27 patients (20.8%) and 48 patients (56.5%) in the NVB and VB groups respectively. Either octreotide or terlipressin was administered to 65 patients (76.5%) with VB and 9 (6.9%) with NVB. Pack red cells transfusion tended to be higher in the VB group, but without statistical significance. Detailed endoscopic findings, treatment modalities and outcomes are described in Table 2.

Primary outcomes

Results of NIFTs in patients in the VB and NVB groups are shown in Table 3. In overall analysis, the AUCs of NIFTs-scoring systems for predicting VB ranged between 0.686 and 0.867. The detailed AUCs, sensitivity, specificity, PPV, NPV, positive likelihood ratio, negative likelihood ratio, and accuracy are shown in Table 4. Receiver operating characteristic (ROC) curves for diagnostic accuracy of APRI, AAR, FIB-4, FI, Kings scores, Lok index, GUCI, and platelet count are displayed in Figure 1. Among evaluated NIFTs-scoring systems, GUCI and APRI (both at the cut-off of 0.5) showed the best performance in predicting VB with sensitivity of 95.3% and 90.6%, and specificity of 73.1% and 75.4% respectively.

In patients without previously-known cirrhosis status (n = 132), the AUCs of GUCI and APRI in predicting VB were 0.860 and 0.895 respectively.

Secondary outcomes

Incidence of shock, rebleeding, AKI, and in-hospital mortality were higher in the VB group than in the NVB one, but without statistical significance. Length of hospital stay tended to be longer in NVB group, but again, the differences were not statistically significant.

Discussion

VB is known to be associated with higher morbidity and mortality than NVB. Notably, early identification of VB is crucial in clinical practice as prompt specific treatment can significantly reduce VB-associated complications and mortality. In out-patient settings, NIFTs (e.g. platelet count and transient elastography) have shown acceptable accuracy in predicting the presence of EV, particularly to rule out high-risk EV in patients with compensated cirrhosis[5]. However, there have been no specific signs or laboratory values that reliably predict VB among patients presenting with UGIB, and the benchmark for the diagnosis of VB is still EGD which has become increasingly available; however, in the current real-world situation, even in large referral centers, limitations still exist and the door-to-EGD timing is still far from ideal. Therefore, precise NIFTs, using simple laboratory parameters at presentation, in predicting VB would be very helpful in the context of UGIB. Nevertheless, one may speculate that the performance of NIFTs in patients with UGIB may be different from that in stable patients in out-patient clinics for several reasons, such as the presence of hemodynamic instability, AKI, sepsis, massive blood loss, coagulopathy and acute-on-chronic liver failure, which may interfere with the predicting parameters included in the NIFTs-scoring systems.

In the present study, the authors evaluated the performance of various NIFTs-scoring systems comprising simple clinical and laboratory parameters that are easily obtained in not more than 1 hour after presentation such as age, AST, ALT, platelet count, INR and albumin, in acute

Table 1. Baseline patient characteristics, laboratory values, and treatment outcomes in patients with upper gastrointestinal bleeding

Variables	All patients	NVB group (n = 130)	VB group (n = 85)	*p*-value
Age, year, mean (SD)	56.1 (16.1)	60.3 (17.5)	50.5 (11.4)	<0.001
Male gender, n (%)	159 (74)	130 (69.2)	85 (81.2)	0.051
Comorbidity, n (%)				
Hypertension	63 (29.3)	57 (43.8)	6 (7.1)	<0.001
Diabetes mellitus	24 (11.2)	39 (30)	8 (9.4)	<0.001
Dyslipidemia	24 (11.2)	22 (16.9)	2 (2.4)	0.001
Chronic kidney disease	29 (13.5)	27 (20.8)	2 (2.4)	<0.001
Coronary artery disease	13 (6)	10 (7.7)	3 (3.5)	0.211
Previous UGIB, n (%)	45 (20.9)	8 (6.2)	37 (43.5)	<0.001
Alcohol >40 g/day, n (%)	58 (27)	20 (15.4)	38 (44.7)	<0.001
Cirrhosis, n (%)	83 (38.6)	13 (10)	70 (82.4)	<0.001
HBV	15 (7)	1 (0.8)	14 (16.5)	<0.001
Alcoholic	24 (11.2)	4 (3.1)	20 (23.5)	
HCV	23 (10.7)	2 (1.5)	21 (24.7)	
NAFLD	8 (3.7)	4 (3.1)	4 (4.7)	
Cryptogenic	7 (3.3)	1 (0.8)	6 (7.1)	
Others	3 (1.4)	1 (0.8)	5 (7.14)	
CTP class, n				<0.001
A	44	7	37	
B	32	5	27	
C	7	1	6	
Chief complaint, n (%)				<0.001
Hematemesis	83 (38.6)	34 (26.2)	49 (57.6)	
Hematochezia	8 (3.7)	6 (4.6)	2 (2.4)	
Coffee ground	15 (7)	11 (8.5)	4 (4.7)	
Syncope	6 (2.8)	6 (4.6)	0 (0)	
Melena	50 (23.3)	37 (28.5)	13 (15.3)	
Others	52 (24.2)	36 (27.7)	17 (20)	
Physical Examination, n (%)				
SBP, mmHg, mean (SD)	114 (23)	115 (24)	113 (20)	0.652
Unstable vital signs	86 (40)	55 (42.3)	31 (36.5)	0.393
Ascites	33 (15.3)	4 (3.1)	29 (34.1)	<0.001
Splenic dullness	33 (15.3)	4 (3.1)	29 (34.1)	<0.001
Palmar erythema	7 (3.3)	0	7 (8.2)	0.001
Spider nevi	13 (6)	1 (0.8)	12 (14.1)	<0.001
Stool characteristics, n (%)				
Hematochezia	24 (11.2)	14 (10.77)	10 (11.76)	0.963
Melena	103 (47.9)	61 (46.9)	42 (49.4)	
Yellowish/greenish	88 (40.9)	55 (42.3)	33 (38.8)	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CTP = Child-Turcotte-Pugh; EGD = esophagogastroduodenoscopy; GBS = Glasgow-Blatchford score; HBV = hepatitis B virus; Hct = haematocrit; HCV = hepatitis C virus; INR = international normalized ratio; Na = sodium; NAFLD = non-alcoholic fatty liver disease; NVB = non-variceal bleeding; PT = prothrombin time; SBP = systolic blood pressure; UGIB = upper gastrointestinal bleeding; VB = variceal bleeding

Table 1. Cont.

Variables	All patients	NVB group (n = 130)	VB group (n = 85)	*p*-value
NG tube findings, n (%)				<0.001
Fresh blood	49 (22.8)	14 (10.8)	35 (41.2)	
Coffee-ground	121 (56.3)	80 (61.5)	41 (48.2)	
Clear	45 (20.9)	36 (27.7)	9 (10.6)	
Laboratory values, mean (SD)				
Hct, (%)	26.1 (8.4)	26.0 (8.7)	26.3 (7.8)	0.75
Platelets, (/$mm^{3)}$	194,316 (112,296)	238,061 (114,181)	127,411 (67,925)	<0.001
PT, (second)	14.6 (4.1)	13.3 (2.4)	16.7 (5.2)	<0.001
INR	1.24 (0.30)	1.12 (0.20)	1.42 (0.34)	<0.001
BUN, (mg/dL)	30.2 (24)	34.8 (25.7)	23.1 (19.3)	<0.001
Cr, (mg/dL)	1.6 (2.2)	1.4 (2.3)	1.9 (2.0)	0.087
Na, (mEq/L)	136 (10)	136 (5)	135 (14)	0.313
Total protein, (g/dL)	6.6 (1.1)	6.4 (1.1)	7.0 (1.0)	<0.001
Albumin, (g/dL)	3.2 (0.8)	3.3 (0.8)	3.0 (0.7)	0.001
AST, (U/L)	59 (67)	47 (73)	77 (53)	0.001
ALT, (U/L)	34 (39)	31 (45)	40 (26)	0.1
ALP, (U/L)	108 (92)	99 (106)	122 (66)	0.068
GBS, (point)	9.8 (4.3)	10.6 (4.2)	8.6 (4.1)	0.001

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CTP = Child-Turcotte-Pugh; EGD = esophagogastroduodenoscopy; GBS = Glasgow-Blatchford score; HBV = hepatitis B virus; Hct = haematocrit; HCV = hepatitis C virus; INR = international normalized ratio; Na = sodium; NAFLD = non-alcoholic fatty liver disease; NVB = non-variceal bleeding; PT = prothrombin time; SBP = systolic blood pressure; UGIB = upper gastrointestinal bleeding; VB = variceal bleeding

UGIB patients. Based on the location of Rajavithi Hospital and the centralized referral system of the Ministry of Public Health of Thailand, the authors believe that the clinical characteristics of patients in the present study can be a good representation of acute UGIB patients presenting at secondary/tertiary medical centers in the center of Thailand. All evaluated NIFTs-scoring systems have shown acceptable performance (AUC ranged 0.823 to 0.867), with the exceptions of FI (AUC 0.788) and AAR (AUC 0.686). Of note, GUCI and APRI scores showed the best performance in predicting VB as etiology of bleeding in patients presenting with UGIB regardless of known cirrhosis status. The accuracy of GUCI and APRI were 81.9% and 81.4% respectively. GUCI showed the best NPV (96%) while APRI showed the best PPV (70.6%). In comparison with APRI, Kings Score and Lok Index showed similar NPV (92.0%).

Despite the limited amount of previous data, the results of the authors' study were in line with a previous retrospective study by Rockey et al[22] which evaluated the performance of NIFTs (platelet count, AAR, APRI, and Lok index) in 2,025 UGIB patients in the United States (24.8% bled from VB). In the present study, APRI (cut-off 2.6) showed the best sensitivity (92%) with 21% specificity while Lok index (cut off 0.9) showed the best specificity (63%) with 70% sensitivity for predicting EV as a cause of bleeding in UGIB patients. Despite different cutoffs between Rockey et al and the authors' study, both APRI and Lok index appeared to have good accuracy in predicting VB (AUC 0.77 to 0.857 for APRI and AUC 0.73 to 0.85 for Lok index). Notably, GUCI was the best VB predictor in the authors' study, and, to the authors' knowledge, has never been investigated as a predictive tool for presence of EV or VB in the setting of UGIB.

Both GUCI and APRI are calculated from basic laboratory values (AST, platelet count and PT) that are commonly included in standard care for UGIB patients. Routine application of GUCI and/or APRI, using GUCI score (with an easily-memorized cutoff level of 0.5 for both) in the initial assessment and triage of patients with UGIB should be considered in current practice for justification of specific interventions for VB including prompt administration of intravenous vasoactive agents, antibiotic prophylaxis, and more urgent endoscopy. For example, if GUCI <0.5, the likelihood of VB being a cause of UGIB is less than 4% and specific interventions for VB may not be required; on

Table 2. Endoscopic findings, cause of bleeding, and treatment modalities in patients with upper gastrointestinal bleeding

Endoscopic findings, n (%)	NVB group (n = 130)	VB group (n = 85)	*p*-value
Gastric ulcer	48 (36.9)	4 (4.7)	<0.001
Duodenal ulcer	34 (26.2)	5 (5.9)	<0.001
Gastritis	94 (72.3)	35 (41.2)	<0.001
EV	11 (8.5)	72 (84.7)	<0.001
GV	2 (1.5)	24 (28.2)	<0.001
PHG	11 (8.5)	41 (48.2)	<0.001
Positive for *Helicobacter pylori*	36 (27.7)	10 (11.8)	0.005
Cause of bleeding, n (%)			
Gastric ulcer	32 (24.6)	0 (0)	<0.001
Duodenal ulcer	34 (26.2)	0 (0)	<0.001
Gastritis	39 (30)	0 (0)	<0.001
EV	0	60 (70.6)	<0.001
GV	0	15 (17.6)	<0.001
PHG	0	10 (11.8)	<0.001
Mallory Weiss Tear	10 (7.7)	0	<0.001
Bleeding tumor	9 (6.9)	0	<0.001
Esophagitis	5 (3.8)	0	<0.001
Treatment, n (%)			
Endoscopic treatment	27 (20.8)	48 (56.5)	<0.001
Proton pump inhibitors	130 (100)	85 (100)	0.1
Octreotide	9 (6.9)	59 (69.4)	<0.001
Terlipressin	0	6 (7.1)	0.002
PRCs transfusion	94 (72.3)	64 (75.3)	0.628
Mean of unit of transfusion	2.2	3.1	
Outcomes, n (%)			
Length of stay, (day), mean (SD)	7.7 (13.3)	6.9 (6.6)	0.618
Shock	24 (18.5)	25 (29.4)	0.061
Rebleeding	3 (2.3)	5 (5.9)	0.176
Acute kidney injury	19 (14.6)	14 (16.5)	0.712
In-hospital mortality	7 (5.4)	7 (8.2)	0.408

EV = esophageal varices; GV = gastric varices; NVB = non-variceal bleeding; PHG = portal hypertensive gastropathy; PRCs = packed red cells; VB = variceal bleeding

the other hand, if GUCI >0.5, the likelihood of VB being a cause of UGIB is 70% and specific interventions for VB should be provided pre-endoscopically. Notably, these cutoff levels of GUCI and APRI are much lower compared to previous studies, which could be explained by the different settings as the present study was performed to predict VB as the cause of bleeding in acute UGIB setting while previous studies with different cutoff levels were performed to predict the degree of liver fibrosis in stable cirrhotic patients. It should also be noted that the VB/NVB ratio of patients with UGIB in the present study was relatively high (39.5%). In other centers where VB/NVB ratios are lower, the NPV of GUCI and APRI will be higher, permitting greater confidence in excluding VB; however, the PPV will also be lower. Further studies to validate the authors' results in different populations may be required.

Fundamental skills of clinical practice such as presenting symptoms and physical signs, seemed to facilitate differentiating VB and NVB. Hematemesis, chronic liver stigmata and signs of portal hypertension were more

Table 3. Comparison of non-invasive liver fibrosis tests in patients with variceal- and non-variceal bleeding groups

NIFTs, mean (SD)	NVB group (n = 130)	VB group (n = 85)	*p*-value
APRI	0.88 (2.08)	2.02 (2.31)	<0.001
AAR	1.67 (1.23)	2.12 (1.06)	0.004
FIB-4	2.95 (5.37)	6.58 (7.16)	<0.001
FI	2.48 (1.74)	3.78 (1.01)	<0.001
Kings scores	25.96 (73.98)	59.76 (80.39)	0.002
Lok index	0.33 (2.29)	3.5 (2.58)	<0.001
GUCI	1.17 (3.39)	3.02 (4.02)	<0.001
Platelet count	238,061 (114,181)	127,411 (67,925)	<0.001

AAR = aspartate aminotransferase-to-alanine aminotransferase ratio; APRI = aspartate aminotransferase-to-platelet ratio; FI = fibrosis index; FIB-4 = fibrosis-4; GUCI = Goteborg University cirrhosis index; NIFTs = non-invasive liver fibrosis tests; NVB = non-variceal bleeding; VB = variceal bleeding

frequently observed in patients with VB. Interestingly, a single laboratory parameter such as platelet count also has a good performance in predicting VB in patients with UGIB. By using platelet count at the cutoff of 190,000/mm^3, the NPV and PPV for predicting VB was 90.4% and 62.8% respectively. Thus, when lowering the platelet count cutoffs to 150,000/mm^3 and 120,000/mm^3, the PPV for predicting VB increased to 69.7% and 72.9%, respectively.

Limitations of the present study included its small sample size, the fact that it was conducted in a single center, and the uncertain diagnosis of cirrhosis (not all cirrhotic patients' diagnoses were verified proven with biopsy).

Conclusion

NIFTs-scoring systems particularly GUCI and APRI showed good performance in predicting VB in patients presenting with UGIB regardless of known cirrhosis status, and they could be helpful in selecting patients for prompt administration of vasoactive agents, antibiotics and urgent EGD.

What is already known on this topic?

Various NIFTs have previously been studied as predictors of esophageal varices in patients with chronic liver disease. However, studies of NIFTs in predicting VB in patients with UGIB remain limited.

What this study adds?

NIFTs, particularly GUCI and APRI, showed good performance in predicting VB in patients presenting with UGIB regardless of known cirrhosis status.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Stanley AJ, Laine L. Management of acute upper gastrointestinal bleeding. BMJ 2019;364:l536.
2. Yavorski RT, Wong RK, Maydonovitch C, Battin LS, Furnia A, Amundson DE. Analysis of 3,294 cases of upper gastrointestinal bleeding in military medical facilities. Am J Gastroenterol 1995;90:568-73.
3. Masoodi M, Saberifiroozi M. Etiology and outcome of acute gastrointestinal bleeding in iran:a review article. Middle East J Dig Dis 2012;4:193-8.
4. Sung JJ, Chiu PW, Chan FKL, Lau JY, Goh KL, Ho LH, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. Gut 2018;67:1757-68.
5. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310-35.
6. Jun CH, Park CH, Lee WS, Joo YE, Kim HS, Choi SK, et al. Antibiotic prophylaxis using third generation cephalosporins can reduce the risk of early rebleeding in the first acute gastroesophageal variceal hemorrhage: a prospective randomized study. J Korean Med Sci 2006;21:883-90.
7. Augustin S, Gonzalez A, Genesca J. Acute esophageal variceal bleeding: Current strategies and new perspectives. World J Hepatol 2010;2:261-74.

Table 4. Performance of non-invasive liver fibrosis tests in predicting variceal bleeding as bleeding etiology in patients with upper gastrointestinal bleeding

	GUCI	APRI	AAR	FIB-4	FI	Kings	Lok	Platelet
AUC	0.867	0.857	0.686	0.83	0.788	0.846	0.85	0.823
95% CI	0.817 to 0.918	0.805 to 0.909	0.614 to 0.758	0.776 to 0.885	0.726 to 0.851	0.793 to 0.899	0.797 to 0.903	0.765 to 0.881
Cut-off	0.5	0.5	1.2	1.8	3.2	11.5	0.85	190,000
Sensitivity, (%)	95.3	90.6	84.7	91.8	78.8	91.8	90.6	89.4
Specificity (%)	73.1	75.4	38.5	60.8	71.5	70.0	70.8	65.4
PPV (%)	69.8	70.6	47.4	60.5	64.4	66.7	67.0	62.8
NPV (%)	96	92.5	79.4	91.9	83.8	92.0	92.0	90.4
LR+	3.54	3.68	1.38	2.34	2.77	3.06	3.1	2.58
LR-	0.06	0.12	0.40	0.14	0.30	0.12	0.13	0.16
Accuracy (%)	81.9	81.4	56.7	73.0	74.4	78.6	78.6	74.9

AAR = aspartate aminotransferase-to-alanine aminotransferase ratio; APRI = aspartate aminotransferase-to-platelet ratio; AUC = area under curve; CI = confidence interval; FI = fibrosis index; FIB-4 = fibrosis-4; GUCI = Goteborg University cirrhosis index; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value

Figure 1. Receiver operating characteristic curves showing performance of noninvasive liver fibrosis tests in predicting variceal bleeding as an etiology of upper gastrointestinal bleeding.

8. Sridharan K, Sivaramakrishnan G. Vasoactive agents for the management of variceal bleeding: A mixed treatment comparison network meta-analysis and trial sequential analysis of randomized clinical trials. Drug Res (Stuttg) 2019;69:487-95.
9. Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014;80:221-7.
10. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.
11. Omran D, Zayed RA, Nabeel MM, Mobarak L, Zakaria Z, Farid A, et al. Evaluating diagnostic accuracy of noninvasive tests in assessment of significant liver fibrosis in chronic hepatitis C Egyptian patients. Viral Immunol 2018;31:315-20.
12. Gokcan H, Kuzu UB, Oztas E, Saygili F, Oztuna D, Suna N, et al. The predictive value of noninvasive serum markers of liver fibrosis in patients with chronic hepatitis C. Turk J Gastroenterol 2016;27:156-64.
13. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015;64:1680-704.
14. Laursen SB, Hansen JM, Schaffalitzky de Muckadell OB. The Glasgow Blatchford score is the most accurate

assessment of patients with upper gastrointestinal hemorrhage. Clin Gastroenterol Hepatol 2012;10:1130-5.e1.
15. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.
16. Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med 2003;163:218-24.
17. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007;46:32-6.
18. Ohta T, Sakaguchi K, Fujiwara A, Fujioka S, Iwasaki Y, Makino Y, et al. Simple surrogate index of the fibrosis stage in chronic hepatitis C patients using platelet count and serum albumin level. Acta Med Okayama 2006;60:77-84.
19. Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 2009;21:730-8.
20. Lok AS, Ghany MG, Goodman ZD, Wright EC, Everson GT, Sterling RK, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology 2005;42:282-92.
21. Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol 2005;40:867-72.
22. Rockey DC, Elliott A, Lyles T. Prediction of esophageal varices and variceal hemorrhage in patients with acute upper gastrointestinal bleeding. J Investig Med 2016;64:745-51.

ความสามารถของ non-invasive liver fibrosis tests ในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยที่มีภาวะเลือดออกในทางเดินอาหารส่วนบน

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ภูมิหลัง: การศึกษา non-invasive liver fibrosis tests (NIFTs) เพื่อทำนายภาวะหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยตับแข็งมีอย่างแพร่หลาย อย่างไรก็ดี ประสิทธิภาพของ NIFTs ในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยที่มีภาวะเลือดออกในทางเดินอาหารส่วนบน ยังไม่มีข้อมูลชัดเจน

วัตถุประสงค์: เพื่อศึกษาความสามารถของ NIFTs ต่างๆ ในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยที่มีภาวะเลือดออกในทางเดินอาหารส่วนบน

วัสดุและวิธีการ: เป็นการศึกษาแบบไปข้างหน้าในผู้ป่วยที่มาโรงพยาบาลด้วยเลือดออกในทางเดินอาหารส่วนบนและได้รับการส่องกล้องทางเดินอาหารที่โรงพยาบาลราชวิถี ตั้งแต่วันที่ 1 มิถุนายน พ.ศ. 2561 ถึงวันที่ 31 สิงหาคม พ.ศ. 2562 โดยเก็บข้อมูลพื้นฐานของผู้ป่วย อาการทางคลินิก ผลการตรวจทางห้องปฏิบัติการ และประเมินระบบ NIFTs ซึ่งประกอบไปด้วย APRI, AAR, FIB-4, Fibrosis index, Lok index, GUCI และ King's score

ผลการศึกษา: ผู้ป่วยที่มาโรงพยาบาลด้วยภาวะเลือดออกในทางเดินอาหารส่วนบนจำนวน 215 รายได้ถูกคัดเลือกเข้าการศึกษา โดยมีอายุเฉลี่ย 56.4 ปี คะแนนเฉลี่ย Glasgow-Blatchford 9.8 และมีผู้ป่วยที่มีภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารทั้งหมดร้อยละ 39.5 พื้นที่ใต้ ROC curve ของ NIFTs ในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยที่มีภาวะเลือดออกในทางเดินอาหารส่วนบนอยู่ในช่วง 0.686 ถึง 0.867 โดย GUCI และ APRI (ที่จุดตัด 0.5) มีประสิทธิภาพในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารได้ดีที่สุด โดยมีค่าความไวร้อยละ 95.3 และ 90.6 และความจำเพาะร้อยละ 73.1 และ 75.4 ตามลำดับ

สรุป: ระบบ NIFTs โดยเฉพาะ GUCI และ APRI มีความสามารถดีในการทำนายภาวะเลือดออกจากหลอดเลือดดำขอดในทางเดินอาหารในผู้ป่วยที่มีภาวะเลือดออกในทางเดินอาหารส่วนบน ซึ่งอาจมีประโยชน์ในเวชปฏิบัติในการเลือกผู้ป่วยที่ต้องได้รับยากลุ่ม vasoactive, ยาปฏิชีวนะ และการส่องกล้องทางเดินอาหารอย่างเร่งด่วนต่อไป