ORIGINAL ARTICLE

Observational Study

Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients

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Abstract

AIM

To assess "predictors" of esophageal varices (EV) and variceal bleeding using non-invasive markers in Albanian patients diagnosed with liver cirrhosis.

METHODS

One hundred thirty-nine newly diagnosed cirrhotic patients without variceal bleeding were included in this analysis. 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 were measured for all participants. All patients underwent endoscopic assessment within two days of hospitalization. The major end point was the first esophageal variceal bleeding (EVB) event. The diagnostic performance of "predictors" for the presence of EV and EVB were assessed by sensitivity and specificity values obtained from the receiver operating characteristics procedure.

RESULTS

FIB-4 was the only strong and significant "predictor" of esophageal varices (multivariable-adjusted OR = 1.57 for one unit increment; 95%CI: 1.15-2.14). Furthermore, a cut-off value of 3.23 for FIB-4 was a significant predictor of esophageal varices, with a sensitivity of 72%, a specificity of 58% and a proportion of area under the curve (AUC) of 66% (*P* = 0.01). During the

follow-up (median: 31.5 mo; interquartile range: 11-59 mo), 34 patients (24%) experienced a first EVB. FIB-4 was a poor predictor of EVB (the AUC was only 51%) for a cut-off value of 5.02. Furthermore, the AUC of AST/ALT, APRI, PC/SD, FI, MELD and King's Score ranged from 45% to 55%. None of the non-invasive markers turned out to be a useful predictor of EVB.

CONCLUSION
Despite the low diagnostic accuracy, FIB-4 appears the most efficient non-invasive liver fibrosis marker which can be used as an initial screening tool for cirrhotic patients.

Key words: Albania; Esophageal varices; Liver cirrhosis; Non-invasive biomarkers; Variceal bleeding

Core tip: Non-invasive markers of liver fibrosis constitute a simple and practical alternative to predict the presence of esophageal varices in cirrhotic patients. However, no single or a combination of non-invasive markers has been widely evaluated for predicting the variceal bleeding, to date. Our findings from a study conducted in Albania indicate that, despite the low diagnostic accuracy, fibrosis-4-index appears the most efficient non-invasive marker which can be used as an initial screening tool for cirrhotic patients in the areas with lacking endoscopy facilities. Yet, none of the non-invasive markers was a useful predictor of esophageal variceal bleeding in Albanian cirrhotic patients.

INTRODUCTION

Liver cirrhosis is the 13th leading cause of death globally, with increasing mortality rate worldwide[1]. Portal hypertension is a frequent consequence in the progression of liver cirrhosis and plays a crucial role in the clinical manifestations of disease[2,3]. One of the most serious complications of portal hypertension is the development of esophageal varices (EV) caused by increased hepatic vascular resistance related to hepatic fibrosis and regenerative nodules[3]. In addition, the variceal bleeding due to the rupture of varices is still the most common lethal complication of cirrhosis[4]. Therefore, assessing the presence of esophageal varices in cirrhotic patients is clinically important in prevention of their bleeding. To date, the

upper gastrointestinal endoscopy remains the golden diagnostic methods for EV and the recent Baveno VI Meeting Consensus recommends the endoscopy screening for all cirrhotic patients at the time of their diagnosis and periodical endoscopy examination in patients with EV[4]. However, routine endoscopy screening may not be cost-effective, as less than 50% of all patients with cirrhosis have EV[5]. Furthermore, there is a low prevalence of varices which requires primary prophylaxis[5]. Also, the upper endoscopy is an invasive and uncomfortable procedure which may not be acceptable for the patients. Hence, predicting the presence of EV through non-endoscopic and non-invasive markers is important in order to identify the patients who benefit from routine endoscopy screening and may reduce considerably the number of avoidable endoscopies[6].

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 a simple, non-invasive and easier practical alternative to predict the presence of EV in cirrhotic patients[7-14]. However, the findings of these previous studies are controversial and their utility in clinical practice is uncertain. The conclusions of these studies vary in different populations and in different etiologies of liver cirrhosis[13-16]. In this context, our prospective study aimed to assess the non-invasive markers, composed on routine laboratory parameters that could predict the presence of EV in liver cirrhosis patients in Albania, an endemic area of hepatitis B virus infection in Southeastern Europe and a Mediterranean country with a high consumption of domestic alcoholic beverages[17,18].

Despite the large number of studies, to date, no single or combination of non-invasive markers has been widely evaluated for predicting the first variceal bleeding in patients with cirrhosis[19,20]. Therefore, the second objective of our study was to identify the cirrhotic patients with a high risk for variceal bleeding using non-invasive markers.

MATERIALS AND METHODS

Study design

This was a prospective study conducted at the University Hospital Center "Mother Teresa" in Tirana, which constitutes the only academic and tertiary hospital center in Albania. Our study included all consecutive patients newly diagnosed (first time hospitalized) with liver cirrhosis hospitalized at the University Clinic of Gastro-Hepatology during 2005-2007 who were followed-up for five years (or, until an adverse event occurred during the follow-up period). The study was approved by the Department of

Internal Medicine of the University of Medicine, Tirana, Albania; all participants gave written informed consent after being explained in detail the aim and procedures of the study.

Study population and patients' follow-up

One hundred and thirty-nine newly diagnosed cirrhotic patients (Child-Turcotte-Pugh of at least 5-13) aged 18-70 years without variceal bleeding were enrolled in the study. Liver cirrhosis was diagnosed based on clinical data, laboratory test, liver imaging and/or histological criteria.

The exclusion criteria were as follows: (1) previous upper gastrointestinal hemorrhage; (2) using beta blockers or nitrates therapy; (3) current or past history of treatment for chronic B or C hepatitis (because these conditions may alter the hematological and biochemical parameters); (4) previous portosystemic shunt; (5) presence of gastric varices at endoscopy; (6) history of gastrointestinal surgery and/or gastrointestinal malignancies including hepatocellular carcinoma (HCC); (7) thrombosis of portal or splenic vein; (8) current or previous history of lympho-proliferative diseases; and (9) severe diseases of other organs or infections that could affect liver or spleen size.

After enrollment, all patients were treated according to the recent recommendations[21]. Patients with high risk EV (large, medium or small varices with red signs or in Child-Pugh class C) were administered non-selective beta blockers (propranolol), if not contraindicated[4]. Treatment compliance of the patients was monitored by measuring the resting pulse rate and interviewing them periodically if any side effects occurred. During the follow-up period, none of the patients were prescribed antiplatelet or anticoagulant agents. All patients were followed up for five years (or, until an adverse event occurred during the follow-up period). Adverse events were considered one of the following complications: the occurrence of severe ascites or hepatic encephalopathy requiring hospitalization ($n = 5$), a diagnosis of HCC ($n = 9$), upper gastrointestinal hemorrhage from variceal bleeding confirmed by endoscopy ($n = 34$), as well as deaths ($n = 2$). Ten patients were lost during the follow-up period. The outcome of interest was the occurrence of upper gastrointestinal hemorrhage from variceal bleeding confirmed by endoscopy and requiring hospitalization. We aimed to assess whether the non-invasive markers could predict the risk of first variceal bleeding.

Laboratory and endoscopic evaluation

All patients underwent detailed clinical and laboratory evaluation, ultrasonography and endoscopic assessment within two days of hospitalization. For each patient, data on age, sex, medical history, and use of medication, etiology of cirrhosis, and presence or absence of ascites, pedal edema, jaundice and

hepatic encephalopathy were collected. Laboratory data included hemoglobin, platelet count, AST and ALT level, serum albumin, total serum bilirubin, gamma glutamyltranspeptidase (GGT), gamma globulin, prothrombin time with international normalized ratio (INR) and serum creatinine. In addition, all patients were classified according the Child-Turcotte-Pugh (CTP) class.

Also, the following non-invasive markers were calculated for each patient: AST/ALT, APRI, PC/SD, FIB-4, FI and King's score[9,12]. MELD score was determined by using the UNOS Internet site MELD calculator (http://www.unos.org/). At endoscopy, the presence and size of varices were classified as large, medium or small according to the proposed guidelines by a single experienced endoscopist who was unaware (blinded) of the values of non-invasive markers[5]. Presence of red signs was also recorded in all patients.

Statistical analyses

Fisher's exact test was used to compare the distribution of sex, etiology of cirrhosis, type of disease and CTP between patients with and without esophageal varices and, subsequently, between patients with and without esophageal variceal bleeding.

Conversely, Mann-Whitney *U*-test was employed to compare mean values of age, biochemical parameters (hemoglobin, creatinine, AST, ALT, GGT, gamma-globulin, INR and albumin) and "predictors" of esophageal varices and esophageal variceal bleeding (FIB-4, fibrosis index, APRI, PL/SD, AST/ALT, King's score and MELD).

Binary logistic regression was used to assess the association between non-invasive markers and esophageal varices. Initially, crude (unadjusted) models were run. Crude ORs, their respective 95%CI and *P*-values were calculated. Subsequently, multivariable-adjusted logistic regression were run, with demographic characteristics (age and sex), etiology of cirrhosis, type of disease, CTP, biochemical parameters (hemoglobin, creatinine, AST, ALT, GGT, gamma-globulin, INR and albumin) and "predictors" of esophageal varices (FIB-4, fibrosis index, APRI, PL/SD, AST/ALT, King's score and MELD) introduced all in a backward stepwise elimination procedure with a *P*-value to exit set at > 0.10. Multivariable-adjusted ORs and their respective 95%CIs were calculated.

The diagnostic performance of "predictors" (FIB-4, fibrosis index, APRI, PL/SD, AST/ALT, King's score and MELD) for the absence or presence of esophageal varices and/or esophageal variceal bleeding was assessed by sensitivity and specificity values and area under the curve (AUC) obtained from the receiver operating characteristics procedure (ROC curve).

In all cases, a *P*-value $\leqslant 0.05$ was considered as statistically significant. All the statistical analyses were conducted in SPSS (Statistical Package for Social Sciences), version 19.0. The statistical review of the study was performed by a biomedical statistician (GB,

Table 1 Distribution of baseline characteristics by esophageal variceal status

Variable	Total (n = 139)	Without EV (n = 26)	With EV (n = 113)	P value
Upper panel: Categorical variables[2]				
Sex				
Men	109 (78.4)[1]	18 (69.2)	91 (80.5)	0.289
Women	30 (21.6)	8 (30.8)	22 (19.5)	
Etiology of cirrhosis				0.005
Alcoholic	67 (48.2)	10 (38.5)	57 (50.4)	
HBV	32 (23.0)	5 (19.2)	27 (23.9)	
HCV	8 (5.8)	-	8 (7.1)	
Alcoholic + viral	11 (7.9)	1 (3.8)	10 (8.8)	
Other	21 (15.1)	10 (38.5)	11 (9.7)	
EV				-
None	26 (18.7)	26 (100.0)	-	
SEV	44 (31.7)	-	44 (38.9)	
MEV	39 (28.1)	-	39 (34.5)	
LEV	30 (21.6)	-	30 (26.5)	
Red signs				0.034
Without varices	26 (18.7)	22 (21.0)	4 (11.8)	
Yes	19 (13.7)	10 (9.5)	9 (26.5)	
No	94 (67.6)	73 (69.5)	21 (61.8)	
CTP				0.047
A (5-6)	43 (30.9)	13 (50.0)	30 (26.5)	
B (7-9)	63 (45.3)	10 (38.5)	53 (46.9)	
C (10-15)	33 (23.7)	3 (11.5)	30 (26.5)	
Lower panel: Numerical variables[3]				
Age (yr)	51.5 ± 13.1	47.6 ± 15.4	52.3 ± 12.4	0.106
Hemoglobin (mg/dL)	11.8 ± 2.3	11.6 ± 2.4	11.8 ± 2.3	0.916
Creatinine (mg/dL)	0.89 ± 0.34	0.89 ± 0.44	0.89 ± 0.31	0.141
AST (UI/L)	107.6 ± 156.1	153.5 ± 331.6	97.0 ± 69.9	0.412
ALT (UI/L)	73.1 ± 161.9	125.5 ± 336.7	61.0 ± 78.9	0.742
GGT (UI/L)	264.9 ± 302.7	282.0 ± 389.7	261.0 ± 280.9	0.709
Gama globulin (g/L)	27.1 ± 10.3	26.9 ± 15.3	27.2 ± 8.8	0.310
INR	1.65 ± 0.47	1.38 ± 0.34	1.71 ± 0.47	< 0.001
Albumin	3.19 ± 0.65	3.27 ± 0.71	3.17 ± 0.64	0.058
FIB-4	5.83 ± 5.33	3.98 ± 3.06	6.26 ± 5.64	0.011
Fibrosis index	3.15 ± 1.30	2.83 ± 1.08	3.22 ± 1.33	0.012
King score	82.9 ± 135.2	66.5 ± 137.4	86.7 ± 135.1	0.002
APRI	2.63 ± 3.79	2.52 ± 4.74	2.66 ± 3.57	0.014
PL/SD	1146 ± 780	1395 ± 784	1089 ± 771	0.028
AST/ALT	2.18 ± 1.62	1.93 ± 1.47	2.23 ± 1.66	0.339
MELD	15.7 ± 5.2	13.6 ± 4.8	16.1 ± 5.2	0.027

[1]Absolute numbers and *column* percentages (in parentheses); [2]P values from Fisher's exact test; [3]P values from Mann-Whitney's *U*-test. AST/ALT: Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; APRI: AST to platelet ratio index; CTP: Child-Turcotte-Pugh score; EV: Esophageal varices; FIB-4: Fibrosis-4-index; GGT: Gamma glutamyltranspeptidase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; LEV: Large esophageal varices; MEV: Medium esophageal varices; MELD: Model for end-stage liver disease; PC/SD: Platelet count to spleen diameter; SEV: Small esophageal varices.

the senior author of this article).

RESULTS

Table 1 presents the distribution of baseline characteristics in patients with (n = 113) and without (n = 26) esophageal varices. Among patients with esophageal varices, 19 (17%) presented red signs compared with 94 (83%) patients without red signs. There was no sex-difference in the prevalence of esophageal varices between the two groups (upper panel). An alcoholic and/or viral etiology of cirrhosis was significantly more prevalent among patients with esophageal varices compared with their counterparts without esophageal varices. Conversely, grade A of

CTP was significantly more prevalent among patients without varices than those with esophageal varices (50% *vs* 27%, respectively).

Mean age was not significantly different between patients with and without esophageal varices (Table 1 - lower panel). Likewise, there were no group differences regarding mean levels of hemoglobin, creatinine, AST and ALT, GGT and gamma globulin. Conversely, mean value of INR was significantly higher among patients with varices than in those without varices (1.7 *vs* 1.4, respectively; P < 0.001). Similarly, mean levels of most of the non-invasive markers were significantly higher in patients with varices than in those without variances (FIB-4: 6.3 *vs* 4.0, respectively; fibrosis index: 3.2 *vs* 2.8, respectively; King's score: 87 *vs*

Table 2 Association of non-invasive markers with presence of esophageal varices in liver cirrhosis

Non-invasive markers	Left panel: Unadjusted models		Right panel: Multivariable-adjusted models[2]	
	OR (95%CI)[1]	*P*[1] vaule	OR (95%CI)	*P* vaule
FIB-4	1.18 (1.01-1.38)	0.032	1.57 (1.15-2.14)	0.005
Fibrosis index	1.25 (0.90-1.74)	0.177		
King score	1.00 (0.99-1.01)	0.501		
APRI	1.01 (0.90-1.14)	0.866		
PL/SD	1.00 (0.99-1.00)	0.078		
AST/ALT	1.15 (0.84-1.57)	0.395		
MELD	1.11 (1.01-1.22)	0.026		

[1]Odds ratios (OR: Esophageal varices *vs* no esophageal varices), 95%CI and *P* values from binary logistic regression. [2]Models adjusted for age, sex, etiology of liver cirrhosis, CTP, VPT, hemoglobin, creatinine, AST, ALT, GGT, gama globulin, INR, albumin, FIB 4, fibrosis index, king score, APRI, PL/SD, AST/ALT and MELD. All variables were entered in a backward stepwise elimination procedure with a p-value to exit set at > 0.10. Empty cells refer to the variables excluded from the multivariable-adjusted logistic regression models. AST/ALT: Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4-index; MELD: Model for end-stage liver disease; PC/SD: Platelet count to spleen diameter.

Table 3 Performance of fibrosis-4-index for prediction of esophageal varices (*n* = 139; esophageal varices: *n* = 113)

Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (95%CI)[1]	*P* value
3.23	72%	58%	88%	32%	0.66 (0.54-0.78)	0.011

[1]AUC (area under the curve) obtained from the receiver operating characteristic. FIB-4: Fibrosis-4-index; NPV: Negative predictive value; PPV: Positive predictive value.

67, respectively; APRI: 2.7 *vs* 2.5, respectively; and MELD index: 16.1 *vs* 13.6, respectively). On the other hand, mean level of PL/SD was lower in patient with varices than in those without varices (1089 *vs* 1395, respectively; *P* = 0.03) (Table 1 - lower panel).

In crude (unadjusted) binary logistic regression models (Table 2 - left panel), there was a significant association between esophageal varices and FIB 4 (OR = 1.18 for one unit increment; 95%CI: 1.01-1.38), and MELD score (OR = 1.11 for one unit increment; 95%CI: 1.01-1.22). On the other hand, there was no evidence of any significant association of esophageal varices with the other non-invasive markers (fibrosis index, King's score, APRI, PL/SD and AST/ALT). Upon adjustment for demographic characteristics, clinical parameters and all the biomarkers in a backward stepwise elimination procedure (right panel), FIB 4 was the only strong and significant "predictor" of esophageal varices (OR = 1.57 for one unit increment; 95%CI: 1.15-2.14). Furthermore, a cut-off value of 3.23 for FIB 4 was a significant predictor of esophageal varices (Table 3), with a sensitivity of 72%, a specificity of 58% and a proportion of area under the curve of 66% (*P* = 0.01).

During follow-up (median: 31.5 mo; interquartile range: 11-59 mo), 34 patients (24%) experienced first esophageal variceal bleeding. Of these, 4 (11.8%) patients were without EV upon enrollment, but experienced EV in the course of the follow-up. There was no evidence of any significant differences in the distribution of baseline characteristics in patients with (*n* = 34) and those without (*n* = 105) hemorrhagic events (Table 4).

The performance of the non-invasive markers for prediction of esophageal variceal bleeding is presented in Table 5, as an additional objective of our analysis was to identify the cirrhotic patients with high risk for variceal bleeding employing these non-invasive markers. Yet, none of the non-invasive markers turned out to be a useful predictor of esophageal variceal bleeding in this sample of Albanian patients. The area under the curve was pretty close to 50% for all of the non-invasive markers. For PL/SD there was evidence of a poorer prediction than even by chance (the area under the curve was 45%). FIB-4, which was shown a powerful predictor of esophageal varices, was nevertheless a very poor predictor of esophageal variceal bleeding (the area under the curve was only 51%) for a cut-off value of 5.02. The analysis was also restricted to individuals with variceal prophylactic therapy (VPT) (*n* = 83); similarly though, none of the non-invasive markers appeared to be a useful predictor of esophageal variceal bleeding (Table 6).

DISCUSSION

Nowadays, clinicians are interested to identify some "ideal" non-invasive biochemical markers which may be cheaper and easy to obtain, but with a high sensitivity and specificity for reducing the number of upper endoscopy needed for screening and management of EV in patients with liver cirrhosis. Such non-invasive tools are especially needed in developing countries with shortage of endoscopy, limited resources and a strong appeal for rationalization of funding. Therefore, we tried to explore whether any of the non-invasive markers (including AST/ALT, APRI, PC/SD, FIB-4, FI and King's Score) could predict the presence

Table 4 Baseline characteristics of patients with esophageal variceal bleeding during follow-up *n* (%)

Categorical variables	Total (*n* = 139)	No EVB (*n* = 105)	EVB (*n* = 34)	*P* value
Upper panel: Categorical variables[2]				
Sex				
Men	109 (78.4)[1]	80 (76.2)	29 (85.3)	0.341
Women	30 (21.6)	25 (23.8)	5 (14.7)	
Etiology of cirrhosis:				0.762
Alcoholic	67 (48.2)	49 (46.7)	18 (52.9)	
HBV	32 (23.0)	23 (21.9)	9 (26.5)	
HCV	8 (5.8)	6 (5.7)	2 (5.9)	
Alcoholic + viral	11 (7.9)	9 (8.6)	2 (5.9)	
Other	21 (15.1)	18 (17.1)	3 (8.8)	
EV				0.176
None	26 (18.7)	22 (21.0)	4 (11.8)	
SEV	44 (31.7)	36 (34.3)	8 (23.5)	
MEV	39 (28.1)	25 (23.8)	14 (41.2)	
LEV	30 (21.6)	22 (21.0)	8 (23.5)	
Red signs				0.034
Without varices	26 (18.7)	22 (21.0)	4 (11.8)	
Yes	19 (13.7)	10 (9.5)	9 (26.5)	
No	94 (67.6)	73 (69.5)	21 (61.8)	
CTP				0.968
A (5-6)	43 (30.9)	33 (31.4)	10 (29.4)	
B (7-9)	63 (45.3)	47 (44.8)	16 (47.1)	
C (10-15)	33 (23.7)	25 (23.8)	8 (23.5)	
Lower panel: Numerical variables[3]				
Age (yr)	51.5 ± 13.1	52.1 ± 13.5	49.7 ± 11.6	0.402
Hemoglobin (mg/dL)	11.8 ± 2.3	12.0 ± 2.2	10.9 ± 2.5	0.017
PL (n/mm[3])	165539 ± 101181	168742 ± 107419	155647 ± 79459	0.801
Creatinine (mg/dL)	0.89 ± 0.34	0.88 ± 0.34	0.92 ± 0.32	0.336
AST (UI/L)	107.6 ± 156.1	112.2 ± 175.7	93.4 ± 65.8	0.852
ALT (UI/L)	73.1 ± 161.9	80.3 ± 189.9	50.6 ± 34.5	0.930
GGT (UI/L)	264.9 ± 302.7	267.1 ± 311.4	258.2 ± 278.1	0.737
Gama globulin (g/L)	27.1 ± 10.3	26.6 ± 9.0	28.6 ± 13.6	0.555
INR	1.65 ± 0.47	1.65 ± 0.48	1.65 ± 0.43	0.862
Albumin	3.19 ± 0.65	3.17 ± 0.72	3.25 ± 0.38	0.608
FIB-4	5.83 ± 5.33	5.93 ± 5.80	5.50 ± 3.56	0.881
Fibrosis index	3.15 ± 1.30	3.13 ± 1.41	3.22 ± 0.84	0.901
King score	82.9 ± 135.2	89.6 ± 152.2	62.1 ± 53.7	0.978
APRI	2.63 ± 3.79	2.80 ± 4.25	2.13 ± 1.70	0.550
PL/SD	1146 ± 780	1189 ± 826	1014 ± 605	0.398
AST/ALT	2.18 ± 1.62	2.17 ± 1.64	2.23 ± 1.57	0.628
MELD	15.7 ± 5.2	15.5 ± 5.3	16.2 ± 4.8	0.435

[1]Absolute numbers and *column* percentages (in parentheses); [2]*P* values from Fisher's exact test; [3]*P* values from Mann-Whitney's *U*-test. AST/ALT: Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; APRI: AST to platelet ratio index; CTP: Child-Turcotte-Pugh score; EV: Esophageal varices; FIB-4: Fibrosis-4-index; GGT: Gamma glutamyltranspeptidase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; LEV: Large esophageal varices; MEV: Medium esophageal varices; MELD: Model for end-stage liver disease; PC/SD: Platelet count to spleen diameter; SEV: Small esophageal varices.

of EV in cirrhotic patients in Albanian, a transitional Mediterranean country. We found that among all clinical and biochemical features assessed in univariate analyses, FIB-4 and MELD score significantly correlated with the presence of EV. However, in multivariable-adjusted logistic regression models, only FIB-4 remained a significant independent predictor of EV. It is interesting that only FIB-4, a fibrosis marker based on parameters linked to liver dysfunction or advanced diseases (AST and ALT), linked to portal hypertension (platelet count) and age could predict the EV despite the non-invasive markers that we included in our analysis. One plausible explanation for the lack of prediction of the other markers may consist of the age of the patients included in our study. Considering that

liver fibrosis is a dynamic process and there is a close relationship between liver fibrosis, portal hypertension and development of EV, older patients are more likely to have EV. Indeed, mean age of our patients was relatively high and most of the patients were admitted in an advanced liver failure stage. Furthermore, previous studies investigating FIB-4 as a predictor of EV in liver cirrhosis patients showed similar results. In another prospective studies, for a cut-off value of 3.98 and 2.8, the AUC for predicting the EV was 62% and 78%, respectively[22,23], whereas Sebastiani *et al*[10] showed an AUC of 64% for the prediction of EV at a cut-off value of 3.5 in a retrospective study. However, their sensitivities and specificities were relatively low, ranging from 66% to 76% and from

Table 5 Performance of non-invasive markers for prediction of esophageal variceal bleeding (*n* = 34)

Non-invasive markers	Cut-off value	Sensitivity	Specificity	AUC (95%CI)[1]	*P* value
FIB-4	5.02	53%	54%	0.51 (0.40-0.62)	0.881
Fibrosis index	3.12	53%	45%	0.52 (0.40-0.61)	0.901
King score	37.16	65%	44%	0.50 (0.40-0.60)	0.978
APRI	1.66	59%	54%	0.53 (0.43-0.64)	0.550
PL/SD	828	53%	39%	0.45 (0.34-0.56)	0.398
AST/ALT	1.71	59%	54%	0.53 (0.42-0.64)	0.628
MELD	15.5	56%	52%	0.55 (0.44-0.65)	0.436

[1]AUC (area under the curve) obtained from the receiver operating characteristic. AST/ALT: Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4-index; MELD: Model for end-stage liver disease; PC/SD: Platelet count to spleen diameter.

Table 6 Performance of non-invasive markers for prediction of esophageal variceal bleeding among patients with variceal prophylactic therapy (*n* = 83; esophageal variceal bleeding: *n* = 23)

Non-invasive markers	Cut-off value	Sensitivity	Specificity	AUC (95%CI)[1]	*P* value
FIB-4	5.02	57%	42%	0.42 (0.28-0.56)	0.257
Fibrosis index	3.43	57%	40%	0.41 (0.28-0.55)	0.215
King score	46.15	57%	28%	0.39 (0.26-0.52)	0.112
APRI	1.65	57%	58%	0.45 (0.32-0.57)	0.439
PL/SD	736	52%	43%	0.49 (0.34-0.63)	0.843
AST/ALT	1.79	57%	58%	0.53 (0.42-0.64)	0.628
MELD	16.5	57%	58%	0.49 (0.35-0.63)	0.879

[1]AUC (area under the curve) obtained from the receiver operating characteristic. AST/ALT: Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4-index; MELD: Model for end-stage liver disease; PC/SD: Platelet count to spleen diameter; VPT: Variceal prophylactic therapy.

54% to 80%, respectively. Similarly, a recent meta-analysis demonstrated that AUC of FIB-4 for prediction the presence of EV was 77%[24]. In our study, a cut-off value of 3.23 of FIB-4 was proposed for diagnosis of esophageal varices. At this cut-off, the sensitivity was 72%, specificity was 58%, PPV was 88%, NPV was 32% and the AUC was 66%.

Esophageal variceal bleeding is the most important complication of liver cirrhosis and the major cause of death in cirrhotic patients. Therefore, prevention of esophageal variceal bleeding by using prophylactic treatment is an important goal to be achieved in cirrhotic patients with high risk esophageal varices. In our study, the prophylactic treatment with non-selective beta blockers was introduced in almost 60% of cirrhotic patients based on endoscopic criteria and liver dysfunction. Nonetheless, during the five years of follow-up, 11 patients (20%) among 56 cases without VPT and 23 patients (28%) among 83 cases who underwent VPT experienced upper gastrointestinal hemorrhage from variceal bleeding confirmed by endoscopy. Thus, these patients may require other prophylactic treatments such as band ligations of esophageal varices. Furthermore, identifying the non-invasive markers to predict EVB during the follow-up may be an important tool for a better management of cirrhotic patients. From this point of view, we conducted the present study under the assumption that progression of EV and ultimately EVB is caused directly by portal hypertension which correlates with

liver fibrosis and may be assessed by non-invasive markers. Our study demonstrated insufficient accuracy of AST/ALT, APRI, PC/SD, FIB-4, FI and King's score for the prediction of EVB which ranged from 0.45 to 0.55. These findings suggest that none of the non-invasive markers is a useful predictor of esophageal variceal bleeding in this sample of Albanian patients.

To our knowledge, this is the first study exploring the role of non-invasive biomarkers as predictors of EVB in a longitudinal study. These non-invasive biomarkers are based on regular laboratory data, require no extra cost, specialized devices or additional biochemical tests and differ from other noninvasive markers which may not be easily accessible[25]. This fact may be very important in developing and transitional countries with rather limited resources. However, only FIB-4 turned out to be a useful predictor in this sample of Albanian patients and, therefore, the usefulness and applicability of these noninvasive markers should be considered cautiously. Furthermore, our data were collected at a single center in which the standard of care did not change substantially during the period under study. Also, the study participants were representative of the population of cirrhotic patients with different etiologies of liver cirrhosis avoiding selection bias pertinent to different etiologies or subgroups. In addition, the relatively large number of participants and the reasonable follow-up period constitute other strength of this study.

Multivariate modeling is frequently used to predict

the risk or prognosis of diseases and treatment's response. In our study, the multivariate model allowed us to assess important variables most of which, nevertheless, did not predict the presence of EV and the risk of first variceal bleeding in cirrhotic patients. However, multi-center prospective studies are needed to confirm our findings and ensure that they are applicable to diverse populations with different etiologies of liver cirrhosis. In addition, we cannot exclude the possibility that other predictors could induce hematological changes such as antiviral treatment or continued consumption of alcohol during the follow-up period - factors which were not accounted for in our analysis. Also, assessment of the sensitivity and specificity upon a second-time measurement would have provided an additional insight into the predictive power of the non-invasive parameters included in our analysis.

In conclusion, our results, based on cirrhotic patients with different etiologies, suggest that the FIB-4 is the most reliable predictor of esophageal varices in liver cirrhosis patients. Despite the low diagnostic accuracy, FIB-4 is the most efficient non-invasive liver fibrosis marker which can be used as an initial screening tool for cirrhotic patients in the areas with lack of endoscopy facilities. However, none of the non-invasive markers assessed in this sample of Albanian patients was a useful predictor of esophageal variceal bleeding. Thus, these markers may not be adequate for the replacement of upper endoscopy. Future large prospective studies are warranted to further define the diagnostic accuracy of non-invasive markers in the diagnosis of EV and prediction of EVB in countries where there is a shortage of endoscopy.

COMMENTS

Background

Portal hypertension is a frequent consequence in the progression of liver cirrhosis. Esophageal varices are one of the most serious complications of portal hypertension and variceal bleeding is the most common lethal complication. For this reason, assessing the presence of esophageal varices in cirrhotic patients is clinically important in order to prevent bleeding. This study aimed to assess the non-invasive markers, based on routine laboratory parameters, which could predict the presence of esophageal varices and first variceal bleeding in liver cirrhosis patients in Albania.

Research frontiers

Endoscopy screening for esophageal varices is currently recommended for all cirrhotic patients. On the other hand, the upper endoscopy is an invasive and uncomfortable procedure which may not be acceptable for the patients. Therefore, various non-invasive markers have been demonstrated as a simple and easier practical alternative to predict the presence of esophageal varices in cirrhotic patients. However, the findings of previous studies are controversial and their utility in clinical practice is uncertain. Furthermore, no single or a combination of non-invasive markers has been widely evaluated for predicting the variceal bleeding, to date.

Innovations and breakthroughs

They findings from a study conducted in Albania indicate that, despite the low diagnostic accuracy, fibrosis-4-index (FIB-4) appears the most efficient non-invasive marker which can be used as an initial screening tool for cirrhotic patients in the areas with lacking endoscopy facilities. Yet, none of the non-

invasive markers was a useful predictor of esophageal variceal bleeding in Albanian cirrhotic patients.

Applications

These non-invasive biomarkers are based on regular laboratory data, require no extra cost, specialized devices or additional biochemical tests and differ from other noninvasive markers which may not be easily accessible. This fact may be very important in developing and transitional countries with rather limited resources. Nevertheless, future large prospective studies are warranted to further define the diagnostic accuracy of non-invasive markers in the diagnosis of esophageal varices and prediction of esophageal variceal bleeding in countries where there is a shortage of endoscopy.

Peer-review

The paper by Kraja Bledar *et al* demonstrated FIB-4 was strong predictor of EV in patients with liver cirrhosis; however, there was no association between FIB-4 and esophageal variceal bleeding. They concluded that FIB-4 is useful for initial screening tool for cirrhotic patients in the areas with lack of endoscopy facilities.

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