Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers

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Objective To determine whether Model for End-stage Liver Disease (MELD) Child–Turcotte–Pugh (CTP) classification, AST to platelet ratio index (APRI), and laboratory tests could predict the presence of esophageal varices (EV) or varices which need prophylactic therapy (medium or large size EV).

Methods Three hundred patients with cirrhosis (193 men; mean age 53.1 years; majority with chronic C hepatitis) were prospectively analyzed. The presence of EV (any size and medium or large EV) was correlated with patients' characteristics (MELD, CTP classification, APRI, platelets count, and liver tests).

Results One hundred and seventy-one patients (57%) had EV, of whom 35% (105) had varices which need prophylactic therapy (VPT). The distribution of EV according to CTP classification was as follows: A, 49%; B, 75.3% and C, 80%. Independent predictors of EV were: MELD higher than 8 ($P=0.02$); APRI higher than 1.64 ($P=0.01$); platelet count lower than 93 000/mm^3 ($P<0.01$); aspartate aminotransferase higher than 1.34 × UNL ($P=0.01$), and total bilirubin higher than 1 mg/dl ($P=0.04$). MELD higher than 8 had the highest discriminative value for presence of EV (sensitivity = 80.1%; specificity = 51.2%; area under receiver operating characteristics = 0.68). Factors independently associated with VPT were: thrombocytopenia (< 92 000/mm^3; $P<0.01$) and aspartate aminotransferase higher than 1.47 × UNL ($P=0.03$). Platelet count lower than 92 000/mm^3 had sensitivity of 65.7%, specificity of 57.9%, and an area under receiver operating characteristics of 0.62 for the presence of VPT.

Conclusion High values on MELD are associated with EV and thrombocytopenia, with varices which need prophylactic therapy. As a result of their low sensitivity and specificity, it is suggested to maintain the recommendation of upper gastrointestinal endoscopy for all patients with cirhosis. *Eur J Gastroenterol Hepatol* 23:754–758 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Esophageal varices (EV) are one of the major complications of portal hypertension because of liver cirrhosis [1]. The annual incidence of variceal bleeding is 5% for small varices and 15–20% for large ones, both with mortality rates ranging from 20 to 25% in the first week [2]. The risk of death remains unchanged for up to 6 weeks after the bleeding and varies between 15 and 30% [3,4].

The American College of Gastroenterology and V Meeting of Baveno Consensus recommend upper gastrointestinal endoscopy (UGE) for all patients with cirrhosis at the time of their diagnosis [5]. However, routine endoscopic screening of all patients has cost implications [6].

The use of nonendoscopic predictors of EV is interesting because they allow the selection of a subgroup of patients that are most likely to be favored by UGE [7]. The aim of this study was to determine whether Model for End-stage Liver Disease (MELD) score, Child–Turcotte–Pugh (CTP) classification, AST to platelet ratio index (APRI), and laboratory tests could predict the presence of EV or varices which need prophylactic therapy (EV with medium or large size).

Patients and methods

Patients with liver cirrhosis were prospectively studied between March 2007 and December 2008. Etiology of cirrhosis, age, and sex of each patient were recorded. By the end of the study, 10 patients had not completed etiological investigation of their liver cirrhosis and were designed 'under investigation'.

Patients with previous endoscopic treatment for EV or gastric varices, portosystemic shunts or surgery, hepatocarcinoma, pregnancy, and those using β-blockers,

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nitrates, anticoagulants, diuretics, chemotherapy, and chronic C hepatitis treatment were excluded.

All patients underwent UGE and biochemical analysis, including total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase (AP), gamma-glutamyl transpeptidase, serum albumin, international normalized ratio (INR), creatinine, and platelet count. MELD score, APRI and CTP classification were determined. All laboratory analyses and UGE were obtained within a maximum of 30-day intervals. UGEs were performed by two experienced endoscopists (more than 10 years in clinical practice) of the Division of Gastroenterology of Federal University of São Paulo.

Varices were classified in: small (varices disappear with air insufflation), medium (varices did not disappear with air insufflation and occupied less than one-third of the esophageal lumen), and large (varices did not disappear with air insufflation and occupied more than one-third of the esophageal lumen). Medium and large varices were considered varices with indication for prophylatic therapy (VPT).

To evaluate if any of the clinical variables had correlation with the presence of EV, patients were divided into two groups: group A (without EV) and group B (with EV). After these analyses, the patients were rearranged into two other groups: group 1 (VPT) and group 2 (no or small EV), to evaluate if any variable could predict the presence of VPT. This study was approved by our local Ethics Committee and signed information consent was obtained from each patient.

Statistical analysis

SPSS version 14.0 (SPSS, Inc., Chicago, Illinois, USA) was applied for statistical analysis using the *t*-test for quantitative variables and χ^2 test for qualitative variables. Differences were considered to be statistically significant if *P* value was less than 0.05. The receiver operating characteristic curve was applied to determine the cutoff values with best sensitivities and specificities for the significant parameters.

Results

Three hundred patients with cirrhosis were evaluated (193 men; age: 53 ± 12 years). Table 1 shows the characteristics of the study population.

Patients were divided into two groups according to the presence of EVs: group A (129 patients without EV) and group B (171 patients with EV). Chronic C hepatitis was the leading cause of cirrhosis in both groups. There was no statistically significant difference regarding age, sex, and cirrhosis etiology between both groups. The CTP classification was higher in group B (6.51 ± 1.73 vs. 5.64 ± 1.23). In both groups, Child A patients prevailed (83.72% group A and 60.82% group B). In the group with EV, the percentage of Child B (32.16%) and C (7.02%) patients was higher compared with those without EV (13.95 and 2.33%, respectively). In multivariate analysis, MELD score (group A: 9.72 ± 3.46; group B: 11.92 ± 4.16; $P = 0.02$) and APRI (group A: 2.13 ± 3.64; group B: 3.04 ± 2.92; $P = 0.01$) were directly correlated with the presence of EV (Table 2).

Table 1 Clinical and endoscopic characteristics of 300 patients

Study population	*N*	Patients without EV	Patients with EV
All patients	300	129 (43%)	171 (57%)
Male	193	68 (52.71%)	125 (73.09%)
Female	107	61 (47.23%)	46 (26.91%)
Mean age	53.10 ± 12.15	53.59 ± 12.54	52.74 ± 11.87
Etiology of cirrhosis			
Alcoholic liver disease	72	24	48
Chronic viral hepatitis	147	72	75
Chronic viral hepatitis + alcoholic liver disease	16	1	15
Autoimmune diseases	22	11	11
Other causes	17	8	9
Cryptogenic	16	11	5
Under investigation	10	2	8
Esophageal varices			
Small		0	66
Medium		0	95
Large		0	10
Not present		129	0
Child–Turcotte–Pugh classification			
Child A	212	108 (83.72%)	104 (60.82%)
Child B	73	18 (13.95%)	55 (32.16%)
Child C	15	3 (2.33%)	12 (7.02%)
MELD	10.98 ± 4.02	9.72 ± 3.46	11.92 ± 4.16
APRI	2.65 ± 3.28	2.13 ± 3.64	3.04 ± 2.92

EV, esophageal varices.

Laboratory test results of groups A and B are presented in Table 2. In univariate analysis, AST, AP, TB, INR, albumin, and platelets count were directly correlated with the presence of EV. However, in multivariate analysis, only AST ($P = 0.01$), TB ($P = 0.04$), and platelets count ($P < 0.01$) were confirmed as predictors. All significant variables in multivariate analysis are presented in Table 3, with the respective cutoff point, sensitivity, specificity, and AUROC.

To study the second objective, patients were rearranged into two other groups: those with VPT (group 1) and those without or with small EV (group 2). There was no statistically significant difference regarding age, sex, and etiology of cirrhosis between the two groups.

Overall, VPT were found in 26.8% Child A, 52% Child B, and 66.6% Child C patients. Child A patients prevailed in group 2. In contrast, Child B (36.19%) and Child C (9.52%), higher values of MELD score (12.29 ± 4.37) and APRI (3.17 ± 3.03) were more frequent in group 1. In univariate analysis, the values of CTP classification, MELD score, and APRI were correlated with VPT, but these were not confirmed by multivariate analysis (Table 4).

Table 4 shows laboratory tests for groups 1 and 2. In univariate analysis, values of AST, AP, TB, INR, albumin, and platelets count showed correlation with VPT.

Table 2 Correlation between Child–Turcotte–Pugh classification, MELD score, APRI, laboratory tests, and the presence of esophageal varices

	Study population	Group A (without EV)	Group B (with EV)	*P* (uni)	*P* (multi)	OR (95% CI)
CTP	6.14	5.64 ± 1.23	6.51 ± 1.73	<0.01	NS	0.60 (0.30–1)
MELD	10.98	9.72 ± 3.46	11.92 ± 4.16	<0.01	0.02	0.70 (0.50–1)
APRI	2.65	2.13 ± 3.64	3.04 ± 2.92	0.02	0.01	0.80 (0.7–1)
AST	1.89	1.64 ± 1.49	2.08 ± 1.59	0.01	0.01	1.40 (1–1.90)
ALT	1.55	1.44 ± 1.32	1.63 ± 1.43	NS		
AP	0.61	0.50 ± 0.41	0.70 ± 0.72	<0.01	NS	2.20 (1–4.80)
GGT	5.13	4.84 ± 7.6	5.35 ± 7.75	NS		
TB (mg/dl)	1.78	1.23 ± 0.83	2.20 ± 2.63	<0.01	0.04	3.20 (1.40–7.20)
INR	1.24	1.19 ± 0.27	1.28 ± 0.22	<0.01	NS	7.40 (0.40–26.50)
Albumin (mg/dl)	3.73	3.94 ± 0.71	3.57 ± 0.69	<0.01	NS	0.40 (0.20–0.90)
Platelets (mm^3)	107 706	130 286 ± 78 438	90 672 ± 49 016	<0.01	<0.01	0.80 (0.80–0.90)
Creatinine	0.97	0.87 ± 0.36	1.05 ± 1.22	0.06	NS	4.60 (1.20–18.10)

AST, ALT, AP, GGT: expressed as times exceeding upper normal limit.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; 95% CI, confidence interval; CTP, Child–Turcotte–Pugh classification; EV, esophageal varices; GGT, gamma-glutamyl transpeptidase; multi, multivariate analysis; NS, not significant; OR, odds ratio; TB, total bilirubin; uni, univariate analysis.

Table 3 Predictors of the presence of esophageal varices

	Cutoff point	AUROC (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)	Accur (%)	*P*	OR (95% CI)
MELD	>8	0.68 (0.62–0.73)	80.10	51.20	41.30	85.72	67.67	0.02	0.70 (0.50–1)
APRI	>1.64	0.67 (0.62–0.73)	56.70	69.80	44.59	79.00	62.33	0.01	0.80 (0.70–1)
AST	>1.34	0.60 (0.54–0.66)	56.10	61.20	38.26	76.49	58.33	0.01	1.40 (1–2)
TB (mg/dl)	>1	0.66 (0.62–0.73)	72.50	58.10	42.58	83.14	66.33	0.04	3.20 (1.40–7.20)
Platelets (mm^3)	< 93 000	0.67 (0.61–0.72)	63.70	64.30	43.33	80.52	64.0	<0.01	0.80 (0.80–0.90)

AST expressed as times exceeding upper normal limit.
Accur, accuracy; AST, aspartate aminotransferase; AUROC, area under receiver operating characteristics; CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sen, sensitivity; Spec, specificity; TB, total bilirubin.

Table 4 Correlation between Child–Turcotte–Pugh classification, MELD score, APRI, laboratory tests and the presence of VPT

	Study population	Group 1 (with VPT)	Group 2 (without VPT)	*P* (uni)	*P* (multi)	OR (95% CI)
CTP	6.14	6.77 ± 1.86	5.79 ± 1.31	<0.01	NS	0.80 (0.50–1.30)
MELD	10.98	12.29 ± 4.37	10.27 ± 3.64	<0.01	NS	1 (0.90–1.10)
APRI	2.65	3.17 ± 3.03	2.37 ± 3.38	0.04	NS	0.90 (0.70–1)
AST	1.89	2.2 ± 1.74	1.73 ± 1.43	0.01	0.03	1.40 (1–1.9)
ALT	1.55	1.62 ± 1.44	1.51 ± 1.35	NS		
AP	0.61	0.74 ± 0.85	0.55 ± 0.42	0.02	NS	1.70 (1–2.80)
GGT	5.13	5.32 ± 8.01	5.03 ± 7.52	NS		
TB (mg/dl)	1.78	2.45 ± 3.06	1.42 ± 1.22	<0.01	NS	1.20 (0.90–1.70)
INR	1.24	1.31 ± 0.24	1.21 ± 0.25	<0.01	NS	1.20 (0,20–7,20)
Albumin (mg/dl)	3.73	3.47 ± 0.71	3.87 ± 0.69	<0.01	NS	0.60 (0.30–1.20)
Platelets (mm^3)	107 706	90 733 ± 52.214	116 846 ± 71120	<0.01	<0.01	0.90 (0.80–1)
Creatinine	0.97	0.97 ± 0.90	0.98 ± 0.99	NS		

AST, ALT, AP, GGT: expressed as times exceeding upper normal limit.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; CTP, Child–Turcotte–Pugh classification; GGT, gamma-glutamyl transpeptidase; multi, multivariate; NS, not significant; OR, odds ratio; TB, total bilirubin; uni, univariate analysis; VPT, varices with indication for prophylaxis.

However, in multivariate analysis only AST ($P = 0.03$) and platelets count ($P < 0.01$) sustained such correlation. Table 5 shows the cutoff point, sensitivity, specificity, accuracy, and AUROC associated with AST and platelets count.

Discussion

The study of nonendoscopic predictors of EV is interesting to avoid performing UGE in every patient with cirrhosis. Thabut *et al.* [8], in their review of noninvasive assessment of portal hypertension, emphasized that serum markers and/or radiological examinations will carry out important contribution at the diagnosis algorithm of EV in the future. Therefore, the ideal marker needs to be cheaper, with easy access, and high-clinical sensitivity and specificity.

Our study population was composed mainly of patients with liver cirrhosis due to chronic C hepatitis or alcohol abuse, which represent more than 50% of the causes of liver cirrhosis [9,10].

In multivariate analysis, there was no correlation between the presence of EV and CTP classification. These findings were also reported by other researchers

Table 5 Predictors of the presence of VPT

	Cutoff point	AUROC (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)	Accur (%)	*P*	OR (95% CI)
AST	>1.47	0.60 (0.54–0.65)	56.20	61	13.80	92.61	59.33	0.03	1.40 (1–1.90)
Platelets (mm^3)	<92 000	0.62 (0.56–0.68)	65.70	57.90	14.78	93.82	60.67	<0.01	0.90 (0.80–1)

AST expressed as times exceeding upper normal limit.
Accur, accuracy; AST, aspartate aminotransferase; AUROC, area under receiver operating characteristics curve; CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sen, sensitivity; Spec, specificity.

[6,10,11]. We expected that CTP classification would be a good marker of EV, because it takes into account the results of liver function tests (prothrombin time and albumin). Two reasons may explain this lack of correlation. First, the use of two subjective criteria (presence of ascites and degree of hepatic encephalopathy), which may under or over-score some patients. The second is the fact that this classification attributes the same amount of points for different laboratory values (bilirubin above 3.00 mg/dl; prothrombin time over 6 s, and albumin below 2.80 mg/dl), classifying similarly patients with different degrees of disease [12,13].

In this study the presence of EV could be predicted by MELD score higher than 8 points (sensitivity: 80.10%; specificity: 51.20%; $P = 0.02$) and APRI higher than 1.64 (sensitivity: 56.70%; specificity: 69.80%; $P = 0.01$). MELD score had the highest sensitivity to predict esophageal varices, among all the variables studied.

In 2007, Burton *et al.* [10] showed that MELD was not a good predictor of EV or large EVs (LEVs). A possible criticism to that study is the fact that they considered the presence of gastric varices in the series of LEV, giving equal status to different clinical situations. In addition, certain laboratory tests are incomplete and only 83% of UGE used the same classification system for EV.

MELD score was not a good predictor of the presence of EV in the group studied by Levy *et al.* [14], but these researchers selected only patients with primary biliary cirrhosis. Our sample was composed primarily by patients with chronic viral hepatitis, which represents the major cause of cirrhosis in Western countries [15].

APRI values higher than 1.64 were correlated with the presence of EV, maybe because they indicate more severe hepatic parenchyma architectural distortion (represented by fibrosis and sinusoidal capillarization) and increased intrahepatic circulatory resistance, resulting in portal hypertension. For a full understanding of this relationship, it would be ideal to determine hepatic venous pressure gradient, which was not performed.

In 2006, Sanyal *et al.* [16] studied 1016 clinically stable cirrhotic patients and reported a correlation between high values of APRI, low platelets count and elevated AST, and the presence of EV. However, in their cohort there were patients under β-blocker use, only patients with less than 7 points at CTP classification and the possibility that liver disease was underestimated or associated with presinusoidal portal hypertension (98 of 598 patients with advanced fibrosis had EV). Sebastiani *et al.* [17] found a weak correlation between APRI and the presence of any EV (APRI = 1.4; sensitivity 54%; specificity: 69%) and large varices (APRI = 1.5; sensitivity 54%; specificity: 63%).

Thrombocytopenia of 93 000/mm^3 or less (sensitivity: 63.70%; specificity: 64.30%; $P < 0.01$) and AST levels higher than 1.34 × UNL (sensitivity: 56.10%; specificity: 61.20%; $P = 0.01$) were associated with the presence of EV.

Thrombocytopenia and EV are associated because both resulted from deterioration of liver functional reserve, leading to hemodynamic changes. The values of thrombocytopenia related to the presence of EV were different among published studies, probably due to differences in samples. In our study, we excluded patients under treatment for chronic C hepatitis, because it could induce hematological changes, such as thrombocytopenia, which could influence the results.

With regard to the presence of VPT, the variables that presented correlation were: AST (> 1.47 × UNL; sensitivity: 56.2%; specificity 61%; $P = 0.03$) and thrombocytopenia (≤ 92 000/mm^3; sensitivity: 65.7%; specificity: 57.9%; $P < 0.01$).

The originality and simplicity of this study is based on the fact that examinations and scores easily found at doctor's rooms and patients' bedside were compared. At the end, someone could ask: 'what is the best screening strategy for EVs?'. According to our results, MELD score higher than 8 points was the best variable associated with the presence of EV and thrombocytopenia of 92 000/mm^3 or less, in the presence of VPT. Although we found an association between those variables, the AUROC for all of them still show that specificity and sensitivity are poor, and they cannot be indicated, at this moment, to safely replace UGE.

Examinations as transient elastography (TE), Fibroscan, and methods which evaluate modifications in the splanchnic circulation will be studied too. As an example, Castéra *et al.* [18] evaluated the accuracy of TE for the detection of cirrhosis and EV compared with noninvasive scores (AST/alanine aminotransferase ratio, APRI, Fibrotest and Lok index) and standard laboratory tests (platelet count and prothrombin index). Except for APRI, TE did not perform better than the other noninvasive serum

markers and scores for detection of EV or LEV, even considering high cutoff values.

In conclusion, it seems prudent to keep the recommendation of performing UGE in all patients with cirrhosis at the time of their diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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