Clinical scores for the prediction of esophageal varices in patients with liver cirrhosis

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Abstract

Introduction : **Esophageal bleeding is one of the most important and dramatic complications of liver cirrhosis in our everyday practice. Considering the costs of repeated upper endoscopy (UE) there is an increasing number of studies focusing on noninvasive parameters for the assessment of esophageal varices (EV).**

Patients and methods : **Retrospective study included 74 patients with alcoholic and viral liver cirrhosis treated at Clinic of Gastroenterology and Hepatology, Clinical Center of Serbia. The data were obtained from patients medical records including history, biochemical, ultrasonography and UE findings.**

Results : **The average value of the RLLD/INR for patients who showed evidence of EV during UE and in those who didn't was 10.46 ± 3.09 and 12.24 ± 3.43, respectively ($p = 0.019$, $p < 0.05$). Cutoff value (11.5) of RLLD/INR showed a sensitivity of 64.15% and specificity of 66.67% (1.92LR+, and 0.54 LR-, AUROC 0.639) for the detection of EV. The average value of PC/SBD for patients who showed evidence of EV during UE and in those who didn't was 619.79 ± 492.96 and 1423.1 ± 908.2, respectively ($p = 0.0$, $p < 0.05$). The average value of RLLD/SA was 5.5 ± 0.17 and 4.57 ± 0.17 ($p = 0.015$, $p < 0.05$) for patients who showed evidence of EV during UE and in those who didn't, respectively.**

Conclusion : **Noninvasive assessment of EV using scores based on ultrasonography and laboratory is simple, inexpensive, and could be a useful tool in limiting the number of repeated UE.** (Acta gastroenterol. belg., **2016**, 79, **14-17**).

Key words : portal hypertension, esophageal varices, liver cirrhosis, and echosonography.

Introduction

Portal hypertension (PHT) is one of the most important complications of liver cirrhosis, therefore, one of the main factors determining it's course (1). For the assessment of portal pressure recent guidelines suggest measurement of hepatic venous pressure gradient (HPVG). Although safe, it is an invasive procedure only performed in specialized centers, leading to the necessity of other methods for the assessment of PHT (2). Clinically significant PHT leads to development of esophageal varices (EV), ascites, and other complications (3). From a clinician`s point of view, rupture of EV is one of the most dramatic events of PHT in everyday practice. The majority of bleeding episodes occur in the first year after varices detection with mortality rate up to 15% in the first episode of bleeding, and up to 33% in patients with recurrences. Pursuant to this, there is a need for annual screening upper endoscopy (UE) (4).

Considering the costs of repeated UE there is an increasing number of studies focusing on non-invasive parameters for the assessment of clinically significant EV. The most commonly used noninvasive parameter is ratio of platelet count and spleen diameter (5-7).

According to Baveno V consensus workshop on methodology of diagnosis and therapy in PHT further studies are required in the field of non-invasive techniques to identify patients with clinically significant PHT (8).

Aim

The aim of our study was to determine and evaluate non-invasive parameters of clinically significant portal hypertension in patients with liver cirrhosis.

Patients and methods

We conducted a retrospective study which included 74 patients with liver cirrhosis, examined and treated in period from January till December 2011.

Cirrhosis was diagnosed on the basis of clinical, biochemical, and ultrasonography parameters. In a number of cases where the patient's general condition allowed liver biopsy, the diagnosis was also based on the histopathology findings. The diagnosis of alcoholic cirrhosis was made in patients with a history of daily alcohol consumption > 80g/day in the period of 5 years (6). The diagnosis of hepatitis C cirrhosis was seropositivity for HCV antibodies and detectable HCV RNA. The diagnosis of hepatitis B cirrhosis was seropositivity for HBs antigen, HBe antigen, and antibodies for HBe and HBc.

All studied subjects underwent ultrasonographic examination (Toshiba Core Vision, with Doppler duplex convex probe, 3.5MHz) of the upper abdomen. The right liver lobe diameter in the medioclavicular line (RLLD), as well as the spleen bipolar diameter (SBD) was measured for three times and the mean value was recorded. In

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Submission date : 02/02/2015
Acceptance date : 18/09/2015

order to reduce errors in the assessment of the diameters, one investigator performed all measurements. Three ratios were observed : RLLD/serum albumin concentration (RLLD/SA), RLLD/INR, and platelet count/SBD (PC/SBD).

A single experienced endoscopist performed all UE (Olympus exera II CV-165, type Q165) and for classification of EV used Paquet (9) grading system (I-IV).

The established exclusion criteria were : previous bleeding episode from EV, endoscopic band ligation or sclerosation, portosystemic shunts operation as well as verified hepatocellular carcinoma, hematological disease and treatment with nonselective beta blockers, nitrates, anticoagulant therapy and interferon therapy.

All patients were classified according to Child-Tourqote-Pugh classification.

Statistical analysis was performed using SPSS 15.0 for Windows (Student's t test, chi square test, Mann-Whitney test). Basic descriptive statistics included means, standard deviations, ranges and percentages. Normality of distribution was examined by the Kolmogorov-Smirnov test. Differences were considered statistically significant if the two-tailed *p* value was less than 0.05. Sensitivity and specificity, as well as the best cut-off value for the diagnosis of EV were calculated using ROC curves.

Study was preformed according to the regulations of The Ethic Committee of our institution. The study was conducted according to principles of Helsinki Declaration (1989).

Results

Clinical and demographic characteristics of patients are presented in Table 1.

The average value of PC/SBD for patients who showed evidence of EV during UE and in those who didn't was 619.79 ± 492.96 and 1423.1 ± 908.2, respectively ($p = 0.0$, $p < 0.05$). The PC were 97.37 ± 59.39 and 181.14 ± 95.99, respectively ($p = 0.001$, $p < 0.05$), and SBD values were 162.71 ± 3.72 and 134.12 ± 3.5 respectively ($p = 0.003$, $p < 0.05$) (Table 2).

For detection of EV, PC/SBD with the cut-off of 1300, showed sensitivity of 92.45% and specificity of 52.38%, 1.94 LR+, and 0.13 LR- with AUROC 0.784 (Table 3).

The average value of RLLD/SA was 5.5 ± 0.17 and 4.57 ± 0.17 ($p = 0.015$, $p < 0.05$) for patients who showed evidence of EV during UE and in those who didn't, respectively.

The respective RLLD values were 157.33 ± 2.57 and 152.21 ± 1.67 ($p = 0.40$, $p > 0.05$), and SA values were 30.23 ± 7.14, and 36.14 ± 8.62 respectively ($p = 0.003$, $p < 0.05$) (Table 2).

For detection of EV, RLLD/SA with the cut-off 3.5 showed sensitivity 92.45%, specificity of 47.52%, 1.77LR+, and 0.16 LR-, with AUROC 0.687 (Table 3).

The average value of the RLLD/INR for patients who showed evidence of EV during UE and in those who didn't was 10.46 ± 3.09 and 12.24 ± 3.43, respectively ($p = 0.019$, $p < 0.05$). The respective INR values were 1.61 ± 0.41 and 1.34 + 0.39 ($p = 0.02$, $p < 0.05$) (Table 2).

For detection of EV, RLLD/INR with the cut-off 11.5 showed sensitivity 64.15%, specificity of 66.67%, 1.92LR+, and 0.54 LR-, with AUROC 0.639 (Table 3).

Table 1. — **General characteristics of patients**

Characteristics	Value
Patients (*n*)	74 (100%)
Male	39 (52.7%)
Female	35 (47.3%)
Age (yr)	55.32+13.6
Cirrhosis etiology	
Alcoholism	46 (62.16%)
Viral hepatitis	28 (38.84%)
Grading of varices	
I	21 (28%)
II	13 (18%)
III	17 (23%)
IV	2 (3%)
Child–Pugh classification	
A	37 (50%)
B	20 (27%)
C	17 (23%)

Discussion

The most commonly used noninvasive parameter is the ratio of PC/SBD, because of it's high sensitivity and specificity in patients with liver cirrhosis (5-7).

Gianinni *et al*. showed, retrospectively as well as prospectively, that the PC/SBD ratio is sensitive enough to predict the presence and size of EV. These authors indicate the cut-off value of 909 (10,11).

In our study, PC/SBD with a cutoff of 1300, produced sensitivity and specificity of 92.45%, and 52.38%, respectively, which correlated with the existence of EV. The PC/SBD cutoff in our study group was higher than reported by Giannini et al, which can be explained by the fact that the majority of patients were classified as Child Pugh A (mean 7.2 range 5-12) rendering a better general condition in comparison to Giannini *et al*. who had patients with Child Pugh of 8.5 (5-14). Consequently, our patients had higher PC in comparison to Giannini *et al*. group of patients (97 370 range 38 000-156000 vs 79 820 range 13 000-121 000) also pointing out the higher cutoff values in our study.

On the other hand, Gonzales *et al*. reported an even lower cutoff value (884) than Giannini et al, reporting that such low values could be due to ethnical difference. Compared to our results Gonzales *et al*. group had a significantly lower percent of Child Pugh A patients (17% vs 50%) which could be the reasons of such low

Table 2. — **Correlation of clinical results with presence of varices**

	EV present	EV absent	p value
platelets/μL	97.37 ± 59.39	181.14 ± 95.99	0.001
serum albumin	30.23 ± 7.14	36.14 ± 8.62	0.003
INR	1.61 ± 0.41	1.34 ± 0.39	0.02
RLLD	157.33 ± 2.57	152.21 ± 1.67	0.40
SBD	162.71 ± 3.72	134.12 ± 3.5	0.003
PT/SBD ratio	619.79 ± 492.96	1423.1 ± 908.2	0.0
RLLD/SA ratio	5.5 ± 0.17	4.57 ± 0.17	0.015
RLLD/INR ratio	10.46 ± 3.09	12.24 ± 3.43	0.019

Table 3. — **Predictive values of scores**

	PC/SBD	RLLD/SA	RLLD/INR
Cutoff ratio	1300	3.5	11.5
Sensitivity	92.45%	92.45%	64.15%
Specificity	52.38%	47.52%	66.67%
Positive likelihood ratio	1.94	1.77	1.92
Negative likelihood ratio	0.13	0.16	0.54
AUROC	0.784	0.687	0.639

cutoff value for PC/SBD (12). Also these differences could be explained due to methodological discrepancies among our study and Gonzales *et al*. (single non-blinded radiologist vs blinded radiologist)

Discrepancy in PC/SBD between our and previous studies (10,11,12) suggests that it is essential to determine a cutoff point for the PC/SBD ratio in every specific group of patients.

Zaman *et al*. (13) showed that patients with platelet count below 88000/mm^3 had a five time higher risk in developing large EV, in contrast to patients with a greater platelet count. Chalasani *et al*. (14) noted that thrombocytopenia and enlarged bipolar diameter of spleen are predictors for large EV and subsequent predictors of portal hypertension.

Thrombocytopenia is one of the most common hematological complication of liver cirrhosis. It can occur from splenic sequestration and platelets destruction, or damaged generation of bone marrow and moderation of hepatic thrombopoietin (15).

Results of our study showed that PC as well as SBD, as independent parameters correlate with the presence of EV. The difference in median values can be explained by various etiologies of cirrhosis, general patient condition, difference in Child-Pugh score, immunological mediators, and splenic sequestration.

Although, PC, SBD, as well as PC/SBD were the most commonly used predictors of PHT and EV, there are studies that indicate that the index of RLLD/SA also plays a role in the prediction of EV. Alempijević *et al*. (16) noted that the RLLD/SA index correlates significantly with presence of EV. These authors suggested a cutoff value of 4.425, with a sensitivity of 83.1% and specificity 73.9%. Our results differ from Alempijevic *et al*. with a lower RLLD/SA cutt-off value (3.5, sensitivity 92.45%, specificity 47.52%). This could be explained by higher serum albumin concentration in our patients, resulting a lower value. INR has been used as a standardization of prothrombin time (PT). It is also incorporated in MELD score and Child-Pugh classification which are commonly used in everyday practice in assessment of patients undergoing liver transplantation (17,18). The majority of patients with liver disease have alterations of components involved in hemostasis, so prothrombin time and partial thromboplastin time are constantly prolonged because of the compromised protein synthesis in cirrhotic liver, and are regarded as indicators of hepatocellular malfunction. Although some studies (19,20) have illustrated prothrombin time is related with presence of large EV, the majority of the studies suggested it is not a predictor of EV (20,21).

We attempted to evaluate whether RLLD/INR could predict the presence of EV in our patients with liver cirrhosis, considering the occurring pathophysiological changes in this disease. Our result showed significant correlation of this score with the presence of EV, however for the cut off value 11.5, sensitivity was 64.15%, and specificity was 66.67%. Searching the available literature we did not found a similar ratio.

We are aware of the limitations of our study, taking into consideration that it was not a prospective one and that echosonography measurements were not preformed blinded and done by a single radiologist.

At this time, literature data do not support replacement of upper endoscopy in process of identifying EV, with non-invasive parameters. However these non invasive parameters could be useful in patients with history data suggesting the presence of EV, but with general condition which does not allow the use of an invasive procedure. Also these ratios are simple, inexpensive, and could be useful tool in limiting the number of repeated upper endoscopies.

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