Non-invasive laboratory, imaging and elastography markers in predicting varices with high risk of bleeding in cirrhotic patients

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Introduction. Upper digestive tract endoscopy remains the gold-standard for detecting esophageal or gastric varices and assessment of bleeding risk, but this method is invasive. The aim of the study was to identify non-invasive factors that could be incorporated into an algorithm for estimating the risk of variceal bleeding.

Methods. A prospective study was performed on 130 cirrhotic patients. Tests were performed on all patients which included liver enzymes, complete blood count and coagulation parameters, abdominal ultrasound, elastography of both the liver and the spleen. Upper gastrointestinal endoscopy was performed in all patients included in the study and the results were classified, in accordance with Baveno VI into 2 outcome groups: Group 1 – patients with low bleeding risk and Group 2 – patients with varices needing treatment.

Results. The study lot (130 patients) was divided into: Group I (low bleeding risk – 102 patients), and Group II (high bleeding risk – 28 patients). Parameters found to have significant differences in univariate analysis were transaminases, platelet count, spleen size, INR, portal vein diameter and both liver and spleen elastography. Calculating AUROC for each parameter identifies spleen elastography as having the best result, followed by INR, AST and platelet count. Liver elastography had the worst AUROC. Independent variables identified by logistic regression included spleen elastography, INR, platelet count, spleen diameter, ALT, age, and gender.

Conclusions. Spleen stiffness is the best single parameter predicting the presence of high-risk esophageal varices.

Key words: liver cirrhosis, esophageal and gastric varices, gastrointestinal hemorrhage, elasticity imaging techniques.

What is new? What is important?

- Spleen elastography was the more accurate method in our study of predicting high risk esophageal varices.
- The accuracy of spleen elastography is significantly better than the more frequently known and used liver elastography.
- Other parameters tested, including AST, ALT, platelet count, spleen size, INR, portal vein diameter, liver elastography were much weaker in diagnosing the presence of varices with a high risk of bleeding.

INTRODUCTION

Upper gastrointestinal bleeding is one of the most important gastroenterological emergencies

and is a major cause of mortality. Esophageal, gastric and/or rectal varices are present in almost 50% [1] of patients diagnosed with liver cirrhosis and bleeding occurs in 25–40% of patients

diagnosed with liver cirrhosis. Each episode of variceal bleeding is associated with a mortality of 15–20%, and the risk of repeated bleeding at 1 year is 70% with a mortality of 33%, in the absence of treatment.

The risk of variceal bleeding depends mainly on three factors: the severity of liver disease (assessed by the Child-Pugh classification) [2, 3], the size of the varices and the presence of visible endoscopic stigmas of bleeding: “red wale marks” (longitudinal red streaks along the varices), “cherry red spots” (red spots, discrete, flattened), hemolytic spots (red, elevated) or diffuse erythema [4].

The latest Baveno consensus (VI) states that patients with hepatic elastography measured by transient elastography with a value under 20 kPa and a platelet count of over 150,000 cell/mm³ have a very low risk of having varices requiring treatment and can avoid screening endoscopy [5]. Unfortunately, the number of endoscopies avoided using the Baveno VI criteria is low [6].

Thus, the main objective of this study was to assess various non-invasive methods of screening patients with high-risk varices.

MATERIALS AND METHODS

Study design

Inclusion criteria were histologically or non-invasively determined liver cirrhosis (regardless of etiology) that has been either newly diagnosed or very recently diagnosed (< 3 months), age > 18 years old, willingness to participate in study (signed informed consent).

Exclusion criteria included acute hepatitis (regardless of etiology), acute on chronic liver disease, recent upper gastrointestinal bleeding, already established high risk varices and chronic treatment (beta-blockers), already established cirrhosis (> 3 months since initial diagnosis).

For each group of patients, demographic and epidemiological characteristics were noted – gender, age, etiology of cirrhosis. Laboratory blood tests were performed, which included liver enzymes (aspartate aminotransferase and alanine aminotransferase), complete blood count (thrombocyte count was noted) and coagulation parameters (prothrombin time, international normalized ratio).

Ultrasound was also performed, and parameters of interest included portal vein diameter, antero-posterior diameter of the spleen. The ultrasound

device used was Acuson S2000 (Siemens AG, Munich, Germany).

Upper gastrointestinal endoscopy was performed in all patients included in the study and the results were classified, in accordance with Baveno VI [7], into 2 outcome groups: Group 1 – patients with low bleeding risk and Group 2 – patients with varices needing treatment (high bleeding risk – either large varices or varices with red wales) [7]. In addition, the presence of stigmas associated with an increased risk of hemorrhage was noted [8, 9].

Acoustic radiation force impulse elastography

The ultrasound device had an elastography module implemented, and elastography of the liver and spleen was performed for each patient. Values noted in elastography were a ten-measurement average for each organ and standard deviation of the measurements. In the case of spleen elastography, the measurements were performed at 2 cm depth, under the capsule.

The acoustic wave elastography technique functions as follows: during standard abdominal ultrasound, the device creates an acoustic force wave that distorts the tissue through which it passes. The distortion causes the formation of lateral shear waves, that travel through the tissue more rapidly (stiff tissue) or more slowly (soft tissue). The shear waves are observed through the ultrasound, and the device calculates the speed of the shear waves as a proxy for tissue stiffness.

Statistical analysis

The statistical analysis was performed using SPSS Statistics (International Business Machines Corporation, Armonk, New York, USA) Version 20 and Python (Python Software Foundation, Delaware, United States) with the Pandas and Statsmodels libraries. The statistical significance threshold used was $\alpha = 0.05$ ($p < 0.05$). Statistical association was determined using Independent Samples T Test, Mann Whitney U Test, Fisher Exact Test and Chi Square Test. The validity of the tests was estimated using the area under the ROC curve (AUROC) with a confidence interval of 95% (95% CI). In addition, the data was analyzed by logistic regression models using the “Enter” method to estimate additional risk predicted by each individual variable.

RESULTS

According to the bleeding risk, the study lot (130 patients) was divided into: Group I (low bleeding risk), which included 102 patients, and Group II (high bleeding risk), which included 28 patients.

Parameters found to have statistically significant differences between the two groups were transaminases, platelet count, spleen size, INR, portal vein diameter and both liver and spleen elastography. Age, gender, hemoglobin, and body mass index parameters did not have a significant

statistical difference between the two groups in the initial univariate analysis.

Table 1 presents AUROC for each parameter found relevant in the initial univariate analysis and identifies spleen elastography as having the best result (Figure 1), followed by INR, AST and platelet count. Liver elastography had the worst performance out of all parameters analyzed.

Logistic regression was performed for all parameters and the following parameters were determined to be part of the model as independent variables: spleen elastography, INR, platelet count, spleen diameter, ALT, age, and gender (Table 2).

Table 1

Parameter accuracy

Parameter	AUROC ⁴ (95% CI ⁵)	P-value (statistic test)
AST ¹	0.769 (0.687 – 0.839)	0.005 (Independent Samples T-test)
ALT ²	0.657 (0.569 – 0.738)	0.01 (Mann-Whitney)
Platelet Count	0.740 (0.751 – 0.829)	< 0.001 (Mann-Whitney)
Spleen size	0.723 (0.638 – 0.798)	< 0.001 (Independent Samples T-test)
INR ³	0.776 (0.695 – 0.845)	< 0.001 (Mann-Whitney)
Portal vein diameter	0.695 (0.608 – 0.774)	0.002 (Independent Samples T-test)
Liver elastography	0.627 (0.538 – 0.710)	0.021 (Independent Samples T-test)
Spleen elastography	0.863 (0.791 – 0.917)	< 0.001 (Independent Samples T-test)

¹aspartate aminotransferase, ²alanine aminotransferase, ³International Normalized Ratio, ⁴area under receiver operating characteristic, ⁵95% confidence interval.

Figure 1. AUROC for spleen elastography.

Table 2

Logistic regression

Parameter	Odds ratio	95% Confidence Interval	p-value
Age	0.8465	0.7169 – 0.9995	0.0493
Gender = M	0.0121	0.0006 – 0.2377	0.0037
ALT ¹	1.0453	1.0071 – 1.0849	0.0198
Platelet Count	1.0000	0.9999 – 1.0000	0.0070
INR ²	320000	96.7650 – 10600000000	0.0022
Spleen elastography	42.2358	4.5733 – 390.0611	0.0010

¹ aspartate aminotransferase, ²International Normalized Ratio.

DISCUSSION

Our study showed that spleen stiffness was the best noninvasive method of identifying patients with high-risk varices. Logistic regression also shows significant accuracy for spleen stiffness. Other parameters like AST, ALT, platelet count, spleen size, INR, portal vein diameter, liver elastography were much weaker in diagnosing the presence of varices with a high risk of bleeding.

Variceal bleeding is one of the most important complications of portal hypertension. Thus, the need to identify patients with high-risk varices is crucial. The current gold standard methods of identifying these patients are hepatic venous pressure gradient (HVPG) and upper digestive endoscopy. Unfortunately, both methods are invasive, have a high cost and require specialized personal. Consequently, various non-invasive methods have been proposed to circumvent the need for upper digestive endoscopy or HVPG.

Current guidelines recommend usage of the Baveno VI criteria (liver stiffness measured by transient elastography with values under 20 kPa plus a platelet count of over 150,000) to identify patients with a low risk of having varices which require treatment [5]. With the Baveno VI criteria approximately 26% of endoscopies can be avoided in patients with high-risk varices [6]. Because the number of unnecessary endoscopies still being performed is high, the Expanded Baveno VI criteria were established (liver stiffness measured by transient elastography with values under 25 kPa plus a platelet count of over 110,000) [10]. With the Expanded Baveno VI criteria more endoscopies can be avoided in patients with high-risk varices (approximately 31%), but with a higher error rate compared to the classic Baveno VI criteria [6]. Hepatic elastography used as a single parameter showed poor results in predicting high risk varices [11–13]. Combining hepatic elastography with platelet count significantly increases diagnostic performance.

Spleen stiffness is a novel parameter that has shown promise in diagnosing both clinically significant portal hypertension (HVPG ≥ 10 mmHg) and severe portal hypertension (HVPG > 12 mmHg) in multiple studies [14–18]. Portal hypertension leads to activation of the mTOR (mammalian target of rapamycin) pathway which in turn activates fibrogenesis, angiogenesis, expansion of lymphatic compartment in the spleen [19, 20]. Thus, portal hypertension induces spleen fibrogenesis, and as a result portal hypertension correlates with spleen stiffness.

In a recent meta-analysis which evaluated 7 studies, spleen stiffness showed excellent performance in identifying clinical significant portal hypertension (AUROC 0.92) and severe portal hypertension (AUROC 0.91) [21]. The same meta-analysis showed that spleen stiffness (17 studies) was a good method of diagnosing patients with high-risk varices (AUROC 0.83) with a pooled sensitivity of 87% and a pooled specificity of 66% [21]. It is important to point out that this meta-analysis included multiple elastography techniques (transient elastography, point shear-wave elastography, two-dimensional shear wave elastography, magnetic resonance elastography), each with its advantages and disadvantages [21]. Another meta-analysis which included 7 studies also showed that spleen stiffness was a good predictor of high risk esophageal varices (AUROC 0.807) [22]. Studies which used point shear-wave elastography like in our study, showed that spleen stiffness was a good method of predicting high risk varices [13, 23–25]. The cut-off values and performance of spleen stiffness varied in studies because most studies included multiple etiologies, different measuring techniques and different protocols.

Other parameters like laboratory data, or scores that use laboratory values like aspartate aminotransferase-to-platelet ratio (APRI), aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), FIB-4, Lok have showed low to moderate diagnostic accuracy in predicting the presence of high-risk esophageal varices [26, 27].

In regard to platelet count, one large study shows that, as a standalone factor, it is not a significant predictor of unprovoked variceal bleeding [28]. However, both INR and platelet count should be treated in patients where high-risk procedures need to be performed as well as in patients with active bleeding [29].

Models that include age, platelet count (Fib-4 score) were found to be useful but not accurate in predicting variceal bleeding. Other models including the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AST/ALT), AST to platelet ratio index (APRI), platelet count to spleen diameter (PC/SD), fibrosis index (FI) and King's Score, were found to not be useful [30].

Some of the limitations of our study are the fact that we did not perform HVPG to properly assess portal hypertension and instead used upper digestive endoscopy which is a subjective technique. The number of patients included was small which led to wide confidence intervals. We also did not compare our results to other elastography techniques such as transient elastography.

CONCLUSIONS

Spleen stiffness is the best noninvasive method of predicting the presence of high-risk esophageal varices. Future studies need to be elaborated to assess the diagnostic performance of spleen stiffness.

Introducere. Endoscopia digestivă superioară rămâne standardul de aur pentru diagnosticarea varicelor esofagiene sau gastrice, dar procedura este invazivă și des însoțită de complianță scăzută din partea pacienților. Scopul studiului a fost identificarea parametrilor non-invazivi care pot fi încorporați într-un algoritm pentru estimarea riscului de hemoragie variceală.

Material și metode. S-a realizat un studiu prospectiv pe 130 pacienți cirofici. Pacienții au efectuat teste ce au inclus enzime hepatice, hemogramă completă, parametrii de coagulare, ecografie abdominală și elastografie a ficatului și splinei. Endoscopia digestivă superioară s-a realizat pentru toți pacienții incluși în studiu, rezultatele împărțind pacienții în două categorii, în concordanță cu clasificarea Baveno: Grupul 1 – pacienți cu risc de sângerare scăzut și Grupul 2 – pacienți care necesită tratament profilactic.

Rezultate. Lotul de studiu (130 pacienți) a fost împărțit în: Grupul 1 (risc scăzut de sângerare – 102 pacienți) și Grupul 2 (risc crescut de sângerare – 28 pacienți). Parametrii descoperiți cu diferențe semnificative în analiza univariată au fost transaminazele, trombocitele, axul lung al splinei, INR, diametrul venei porte și elastografia ficatului și splinei. Calculând AUROC pentru fiecare parametru, identificăm elastografia splenică ca având cel mai bun rezultat, urmat de INR, AST și trombocite. Elastografia hepatică a avut cel mai slab AUROC. Variabilele independente identificate prin regresia logistică au inclus elastografia splenică, INR, trombocitele, diametrul splinei, ALT, vârsta și sexul.

Concluzii: Elastografia splenică este cea mai bună metodă de a prezice varicele esofagiene cu risc înalt de sângerare.

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