

# A New and Simple Algorithm for the Noninvasive Assessment of Esophageal Varices in Cirrhotic Patients Using Serum Fibrosis Markers and Transient Elastography

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## Abstract

**Background and aim:** Noninvasive serum liver fibrosis markers and liver stiffness could be used as predictors of esophageal varices in cirrhotic patients because portal hypertension is related to liver fibrosis. The aim of this study was to compare the performance of common serum fibrosis scores and transient elastography in diagnosing esophageal varices and to propose a new algorithm for predicting large varices. **Methods:** 231 consecutive cirrhotic patients (58.4% males, mean age 55.9 years) were enrolled. Routine biological tests were performed, so that APRI, FIB-4, Forns Index and Lok Score could be calculated. All patients underwent transient elastography and eso-gastroscopy. The diagnostic performance of the methods was assessed using sensitivity, specificity, positive predictive value, negative predictive value, accuracy, likelihood ratios and receiver operating characteristic curves. **Results:** The Lok Score was the best among all the serum scores for diagnosing the varices. For a value higher than 0.8, it had a 45.5% positive predictive value, 86.4% negative predictive value and 67.72% diagnostic accuracy for prediction of large varices. For liver stiffness higher than 30.8KPa, the positive predictive value was 47.3%, negative predictive value 81% and diagnostic accuracy 68.32%. Using both tests simultaneously, the presence of large varices was predicted with a diagnostic accuracy of 78.12%, obtaining an increment in NPV and -LR up to 93.67% and 0.21, respectively. **Conclusion:** The Lok Score is a good predictor for excluding the presence of large varices in cirrhotic patients, similarly with liver stiffness. The two methods can be successfully combined into a noninvasive algorithm for the assessment of esophageal varices in cirrhotic patients.

## Keywords

Transient elastography – serum fibrosis scores – noninvasive – liver cirrhosis – esophageal varices.

## Introduction

Liver cirrhosis (LC) is the final evolutive stage of any chronic liver disease and it is a condition prone to multiple complications because of portal hypertension. Development of esophageal varices (EV) is a major complication that may occur in up to 90% of cirrhotic patients [1]. Variceal bleeding is a life-threatening event that has an incidence of 5% in patients with small EV and up to 15% in those with large esophageal varices (LEV). Mortality per bleeding episode is around 10-20% [2, 3], and one year survival is only 63% [4]. Therefore, screening for EV in LC patients is a strong recommendation in all consensus statements [5-7]. The current screening method is endoscopy at 2-3 years in patients without EV, and at 1-2 years in those with small EV. This approach is, however, invasive, poorly accepted by patients and expensive. This is why the selection of patients with LEV at high risk for bleeding has become an issue of growing importance. In this respect, several clinical, biological, ultrasonographic and elastographic (transient elastography - TE) methods have been proposed (and some of them validated) as noninvasive alternatives to endoscopy [8].

Based on the concept that the development of portal hypertension is due to liver fibrosis, as the most important factor contributing to the increased hepatic resistance, noninvasive serum markers of liver fibrosis have been tested as predictors of EV in cirrhotic patients with promising results. The most validated is the FibroTest®, which is not currently widely available because of its cost and complexity. Several algorithms, all including FibroTest, have already been proposed [9, 10], but they are still awaiting external validation.

The hypothesis behind our study that common tests previously validated as predictors of liver fibrosis, such as APRI, Fib-4, Forns Index and Lok Score can be used to

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predict the presence of EV, as well. Our aim was to compare the performance of the above mentioned fibrosis scores and of the TE in diagnosing EV and to propose a new prediction algorithm for LEV by combining them.

## Methods

### Patients

Consecutive patients with LC, admitted during an 18 month period (February 2009 - August 2010) were selected for a cross-sectional study, according to the following criteria:

- Inclusion criteria: male or female patients, aged 18-79 years, who had overt (HCV or alcohol related) LC proved by liver biopsy or by other clinical/imaging methods.

- Exclusion criteria: presence of perihepatic ascites; presence of other liver specific viral infections (HBV, CMV, etc); immuno-depression (HIV infection, malignancy); comorbidities (NASH, hemochromatosis, primary sclerosing cholangitis, primary biliary cirrhosis); antiviral therapy between liver biopsy and study inclusion; pacemaker or heart defibrillator; pregnancy or lactation; liver transplantation.

All selected patients underwent TE liver stiffness measurement (LSM) and were evaluated by endoscopy for the assessment of EV. The main endpoint of the endoscopic evaluation was the detection of LEV.

Routine biological tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bil), alkaline phosphatase (ALP), gammaglutamyltranspeptidase (GGT), international normalised ratio (INR), platelets count (Pl) were recorded according to the follow-up protocol and serum liver fibrosis scores were calculated.

The study was designed to respect all ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki. All patients were enrolled for the study after signing an informed consent that was previously revised and approved, together with the study protocol by the Ethical Committee of the Cluj-Napoca University of Medicine and Pharmacy.

### Calculation of serum liver fibrosis scores

Using generally available biological parameters, the following serum liver fibrosis scores were calculated in all patients, according to previously published formulas:

- AST to platelets ratio index (APRI) =  $[(AST/ULN) \times 100]/\text{platelet count } 10^9/L$  (ULN = the upper limit of normal) [11];

- FiB4 =  $[\text{age (years)} \times AST (IU/L)]/[\text{platelet count } (10^9/L) \times ALT (IU/L)^{1/2}]$  [12];

- Forns Index =  $7.811 - 3.131 \times \ln[\text{platelet count } (10^9/L)] + 0.781 \times \ln[\text{GGT}(IU/L)] + 3.467 \times \ln[\text{age (years)}] - 0.014 [\text{cholesterol (mg/dL)}]$  [13];

- Lok Score:  $\log \text{ odds} = -5.56 - 0.0089 \times \text{platelet count } (10^3/\text{mm}^3) + 1.26 \times (AST/ALT) + 5.27 \times \text{INR}$ ;  $\text{Lok} = [\exp(\log \text{ odds})]/[1 + \exp(\log \text{ odds})]$  [14].

Since all these scores were designed and validated as surrogate markers for liver fibrosis and not for portal hypertension or its complications, new cut-off values for

prediction of LEV were calculated using the area under the curve analysis.

### Liver stiffness measurement

Liver stiffness measurements were performed using TE (FibroScan, Echosens, Paris, France) following the technical background and examination procedure as previously described [15]. The medium probe was used for all patients. The results were expressed in kilopascals (kPa). The median value of 10 successful measurements was kept as a representative of the liver stiffness, according to the manufacturer's recommendations and previous evidence: interquartile range (IQR) lower than 30% of the median value and success rate of at least 60% [16, 17]. The success rate was calculated as the number of validated LSMs divided by the number of total measurements. All LSMs were performed by experienced operator (M.L., H.S.), with more than 500 examinations of patients with chronic liver diseases.

### Endoscopy

All LC patients underwent upper endoscopy, using a flexible EVIS EXERA video gastroscope (Olympus Europe Medical Systems, Hamburg, Germany). Esophageal varices were graded according to their size as follows: (i) grade 1: small, straight EV; (ii) grade 2: enlarged, tortuous EV occupying less than one third of the lumen; and (iii) grade 3: large, coil-shaped EV occupying more than one third of the lumen. The endoscopic evaluation was not always synchronous with LSM, but did not exceed 6 months, and it was not performed by the same examiner.

### Statistical analysis

The statistical analysis was performed using the SPSS software version 15.0 (SPSS Inc. Chicago, IL, USA). The continuous variables were presented as mean values and standard deviation. The data were compared using independent sample *t* test. The diagnostic performance of LSM and serum fibrosis scores was assessed using sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), accuracy, likelihood ratios (LR) and receiver operating characteristic (ROC) curves. Optimal cut-offs for the variables were chosen so that the sum of sensitivity and specificity would be maximal; PPVs and NPVs were computed for these values.

## Results

A total number of 231 LC patients were enrolled. Baseline characteristics are presented in Table I.

### Performance of serum fibrosis tests in diagnosing esophageal varices

APRI was the less efficient in predicting the presence of EV, with no significant statistical differences between classes. The Lok Score, however, was the best, showing better figures in sensitivity, specificity, PPV, NPV. A detailed view is shown in Table II. The AUROC value for the Lok Score was the highest, but showed statistical significance only in comparison with APRI (Fig. 1A). The diagnostic accuracy of the Lok Score for the proposed cut-off value was 67.72%.

**Table I.** Baseline characteristics of patients

Parameter	mean±SD or N(%)
Gender (males/females)	135 (58.4) / 96 (41.6)
Age (years)	55.66 (±9.519)
<b>Etiology and diagnosis</b>	
VHC/ alcohol/ VHC+alcohol	115 (49.78)/ 90 ( 38.96)/ 26 (11.26)
histologic/ clinical	67 (29) / 164 (71)
<b>Clinical aspects</b>	
BMI (kg/m <sup>2</sup> )	27.3 (±4.68)
Child-Pugh class (A/ B/ C)	175 (75.9)/ 43 (18.4)/ 13 (5.7)
<b>Laboratory findings</b>	
AST (U/l)	86.37 (±64.289)
ALT (U/l)	82.06 (±63.49)
GGT (U/l)	185.8 (±318.373)
ALP (U/l)	324.86 (±330.2)
Bil (mg/dl)	1.75 (±2.83)
Plateles (10 <sup>9</sup> /l)	119.94 (±62.9)
INR	1.279 (±0.3)
<b>Endoscopy findings</b>	
EV (absent/ grade1 /grade 2-3)	74 (32) /89 (38.5) /68 (29.5)
<b>LSM findings</b>	
successful measurements	231 (100%)
value (KPa )	35.47 (±18.53)
succes rate value (%)	86.29 (±23.89)

BMI = body mass index; AST = Aspartate amino transferase; ALT = Alanine amino transferase; GGT = Gamma glutamyl transpeptidase; ALP = Alkaline phosphatase; Bil = Total bilirubin; INR = International Normalised Ratio; EV = esophageal varices; LSM = liver stiffness measurement.

Lok Score was the best in predicting LEV too (Table III). The AUROC of Lok Score was again significantly higher compared with all other tests (Fig. 1B). For the proposed cut-off value, the Lok Score showed a diagnostic accuracy for LEV of 65.9%.

Based on these results, we chose the Lok Score for further analysis in combination with LSM.

### Performance of TE in diagnosing esophageal varices

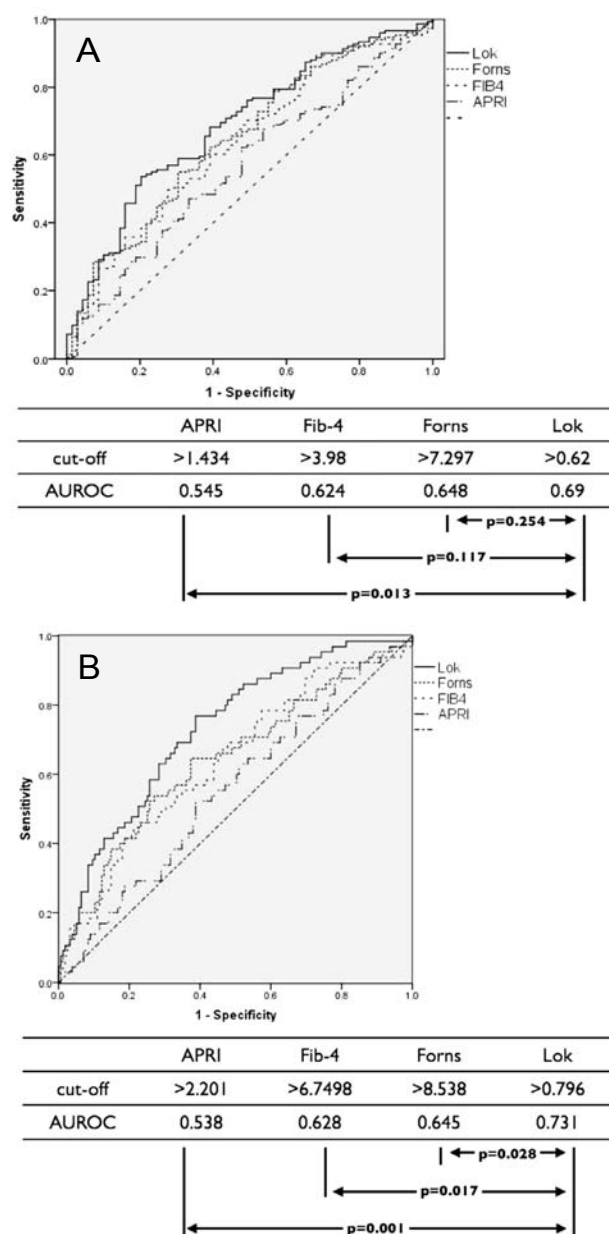
Liver stiffness was significantly higher in patients presenting EV as compared with those without and in patients with LEV compared with those with no LEV and showed a good performance in predicting the presence of any EV or only of the large ones (Table IV).

AUROC values obtained for LSM were acceptable (Figs. 2A, B) and they were comparable, with no significant differences with those obtained by the Lok Score in predicting the presence of EV ( $p=0.638$ ) or of LEV ( $p=0.419$ ).

Using the proposed cut-off values for LSM, the diagnostic accuracy was 66.96% for predicting the presence of EV and 68.32% for predicting the presence of LEV.

### Analysis of Lok Score and LSM in diagnosing esophageal varices

We combined the Lok Score and LSM and their proposed



**Fig 1.** Comparative AUROC analysis of APRI, Fib4, Forns Index and Lok Score in diagnosing the presence of esophageal varices (A) and large esophageal varices (B).

cut-off values trying to predict the presence of EV or of the LEV in our population. We managed to obtain better figures for sensitivity, specificity, PPV, NPV, +LR, -LR and we improved the diagnostic accuracy in both situations (Table V).

## Discussion

The development of EV is the most common complication that can occur in LC, therefore endoscopic screening for EV at the time of diagnosis is extremely important and is strongly recommended by all clinical guidelines [5-7]. This approach may identify those patients who can benefit from non-selective beta-blockers therapy or should start endoscopic

**Table II.** Performance of serum fibrosis scores to detect the presence of esophageal varices

parameter		APRI	Fig-4	Forns Index	Lok Score
mean value (±SD)	EV absent	2.42 (±2.7)	4.88 (±4.27)	7.67 (±1.79)	0.62 (±0.24)
	EV present	2.56 (±2.22)	6.40 (±4.69)	8.6 (±1.8)	0.77 (±0.22)
p		0.623	0.02	<0.0001	<0.0001
<b>cutoff value</b>		>1.434	>3.98	>7.297	>0.62
Se (%) [95% CI]		66.24 [58.3 - 73.6]	66.24 [58.3 - 73.6]	78.98 [71.8 - 85.1]	76.16 [68.6 - 82.7]
Sp (%) [95% CI]		44.59 [33 - 56.6]	54.05 [42.1 - 65.7]	44.59 [33 - 56.6]	50.72 [38.4 - 63.0]
+LR		1.2	1.44	1.43	1.55
-LR		0.76	0.62	0.47	0.47
PPV (%)		71.7	75.4	75.2	77.2
NPV (%)		38.4	43	50	49.3
<b>AUROC</b>		0.545	0.624	0.648	0.690
SE [95% CI]		0.04 [0.479 - 0.611]	0.038 [0.558 - 0.687]	0.037[0.583 - 0.709]	0.036 [0.624 - 0.750]
p		0.259	0.0011	0.001	<0.0001

EV: esophageal varices; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

prophylaxis. Endoscopy, however, is an invasive technique that is not easily accepted by the patients [18].

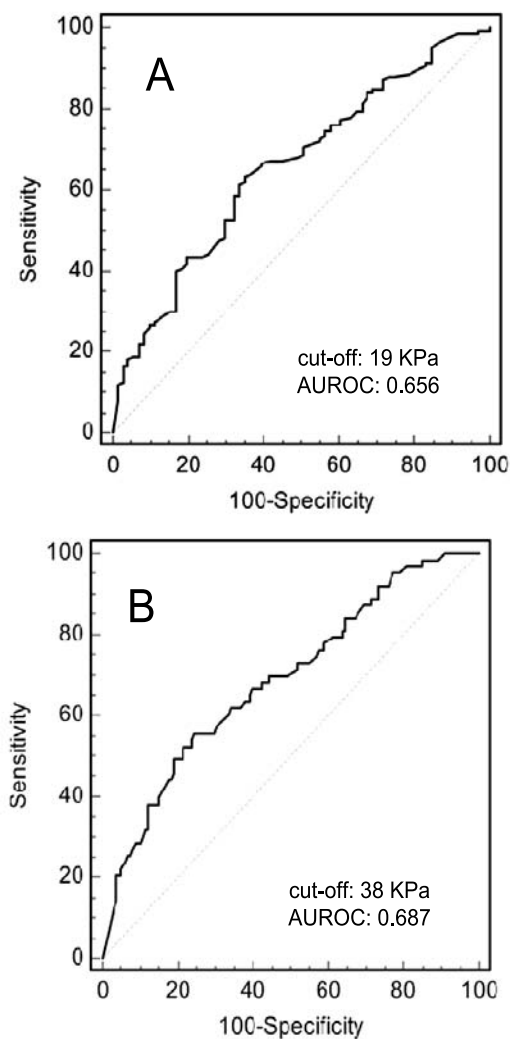
Noninvasiveness has become a major goal in hepatology in the latter years, since several serum markers and imaging methods have been demonstrated to correlate well with fibrosis stage and tend to replace liver biopsy. Several of these methods have been tried for the noninvasive assessment of portal hypertension or presence of EV. There is a close relationship between liver fibrosis, portal hypertension and EV. When cirrhosis is established, the progression of fibrosis is associated with increasing portal pressure and poorer outcomes [19] and, reversely, natural history and long term survival of LC patients depend closely on the decompensation of the disease [20].

Liver stiffness measurement using one-dimension TE was proven to accurately predict LC in a variety of clinical conditions [15, 21-24] and in some studies correlated also with the severity of portal hypertension [25-28]. The relationship between liver stiffness and EV was the subject

of several studies, with confusing results, varying from good correlation [9, 29] to no correlation at all [28]. Liver stiffness measurement was found to be a good predictor of EVs, with the area under the ROC curve ranging from 0.76 to 0.84 in some studies [9, 16, 29]. Depending on the cutoff value (13.9 kPa, 17.6 kPa or 21.3 kPa, respectively) the sensitivity for predicting the presence of EV decreased from 95% to 79%, and the specificity increased from 43% up to 70%. Using a higher cutoff value (30.5 kPa), it was possible to predict LEV ( $\geq$  grade 2) with an acceptable sensitivity and specificity (76% and 80%, respectively), but the positive predictive value did not exceed 54%. These results were critically analyzed in a review [30] that noticed that evaluation of the EV grade was subjective, and none of the above cited studies mentioned data on the quality of endoscopic evaluation. The cutoff value of liver stiffness for predicting EV is still a matter of debate since the results were not prospectively and independently validated and the specificity and PPV reported so far are too low to allow their use in current clinical practice.

**Table III.** Performance of serum fibrosis scores to detect the presence of large esophageal varices (see Table II for abbreviations)

parameter		APRI	Fib-4	Forns Index	Lok Score
mean value (±SD)	LEV absent	2.44 (±2.34)	5.29 (±4.07)	8.02 (±1.74)	0.67 (±0.24)
	LEV present	2.67 (±2.48)	7.41 (±5.6)	8.96 (±1.93)	0.85 (±0.17)
p		0.518	0.06	<0.0001	<0.0001
<b>cutoff value</b>		>2.201	>6.7498	>8.538	>0.796
Se (%) [95% CI]		51.47 [39 - 63.8]	45.59 [33.5 - 58.1]	63.24 [50.7 - 74.6]	76.92 [64.8 - 86.5]
Sp (%) [95% CI]		61.35 [53.4 - 68.9]	77.3 [70.1 - 83.5]	63.19 [55.3 - 70.6]	61.29 [53.1 - 69]
+LR		1.33	2.01	1.72	1.99
-LR		0.79	0.7	0.58	0.38
PPV (%)		35.7	45.6	41.7	45.5
NPV (%)		75.2	77.3	80.5	86.4
<b>AUROC</b>		0.538	0.628	0.645	0.731
SE [95% CI]		0.042 [0.472 - 0.609]	0.041 [0.563 - 0.691]	0.041 [0.579 - 0.706]	0.039 [0.667 - 0.788]
p		0.361	0.002	0.0004	0.0001



**Fig 2.** AUROC analysis of Liver Stiffness Measurement in diagnosing the presence of esophageal varices (A) and of large esophageal varices (B).

In our study, for a cut off value of 19 KPa, the AUROC for predicting EV presence was only 0.656, while the sensitivity was 84% and PPV was 72.4%. Using a cutoff value of 38 KPa, the AUROC for predicting LEV was 0.687, the specificity 75.32% and NPV 81%. Our rather modest performance may be explained by: the subjective assessment of the size of EVs on endoscopy [31]; the unequal distribution of patients according to the EV grade and the asynchronism between endoscopic and LSM evaluations.

On the other hand, almost all serum markers that showed a correlation with liver fibrosis were tried as predictors of EVs. From very simple tests such as platelets count or prothrombin index [32] to more specific ones such as hyaluronic acid [33] or type IV collagen [34], all correlated with the presence of EV in various degrees. In order to increase the diagnostic accuracy of EVs, combinations of markers were imagined, tested and some of them validated, such as AST/ALT ratio [35], AST to platelets ratio index (APRI) [11], or platelets count to spleen diameter ratio [36, 37].

Later on, complex scores, of which some were patented, were also tried as noninvasive predictors of EV in LC patients. After its extensive validation in predicting fibrosis stages, FibroTest® was tried as a surrogate marker for both HVPG and EV in patients with LC. Although the team that developed the score found a very high NPV (100%) for a cut-off of 0.75 [38], FibroTest could not be internally validated, showing a diagnostic value for EVs similar with the one of platelets count or of the Child-Pugh score [39]. However, at the moment FibroTest® is not widely used in clinical practice for the assessment of EVs because of its high cost.

APRI was initially developed for the noninvasive prediction of fibrosis stage in patients with chronic hepatitis C and showed good performance (AUROC of 0.88 and 0.94 for significant fibrosis and cirrhosis, respectively) [11]. When used for predicting EVs in cirrhotic patients, APRI did not perform so impressively: AUROC of 0.62 for predicting EV and 0.71 for LEV in one study that enrolled a limited number of patients [32]. In a larger cohort, APRI performed even worse, showing an AUROC of only 0.57 for EV and 0.6 for LEV [10]. In our study, for a cutoff value similar with the one validated in the literature (1.4) we found an AUROC of 0.545 for the prediction of EV; in the case of LEV, even using a higher cutoff value than the ones proposed in the literature (2.2 vs 1.5), we found an AUROC of only 0.538.

Fib-4 was confirmed as a good noninvasive marker of liver fibrosis for chronic hepatitis C, with performances similar to the FibroTest [12, 40]. For the diagnosis of severe fibrosis an AUROC of 0.85 was evidenced, while for predicting cirrhosis the AUROC was 0.91. Fib-4 was also tried for the prediction of EV in patients with cirrhosis, having an AUROC of 0.64 for the prediction of EV at a cutoff value of 3.5, while for the diagnosis of LEV the AUROC was 0.63 and the cutoff value 4.3 [10]. In our cohort of patients, Fib-4 performed better than APRI, and it was concurrent with the data previously reported. For predicting EV, we used a cutoff value of 3.98 and the AUROC was 0.624; for the diagnosis of LEV we used a higher cutoff value (6.75), but the AUROC remained as low as 0.628.

Forns Index is another noninvasive score that was developed for the assessment of liver fibrosis, it involves some simple serum variables (GGT, cholesterol and platelets count) and the patient's age. The prediction accuracy for significant fibrosis was reported to be between 50 and 85% [13, 41]. The value of this test was lower than that of the FibroTest in the diagnosis of significant fibrosis [42] and failed to predict cirrhosis [43]. It was, however, tried as a predictor for EVs in LC patients. For a cutoff value of 8.5, the AUROC for predicting EVs was 0.74. For diagnosing LEV, its performance was not so good: 0.61 AUROC for a cutoff value of 8.8 [10]. As far as our study is concerned, for a cutoff of only 7.3 we obtained an AUROC of 0.648 for the diagnosis of any grade EV, while using a cutoff value of 8.5, the AUROC for predicting LEV was 0.645.

The Lok score was proposed during the Halt-C trial [14]. According to the authors, for a cutoff value smaller than 0.2 to exclude cirrhosis, only 7.8% of patients had

**Table IV.** Performance of liver stiffness measurement in diagnosing esophageal varices

LSM	prediction of EV			prediction of LEV		
	EV absent	EV present	p	LEV absent	LEV present	p
mean value ( $\pm$ SD)	28.81 ( $\pm$ 15.05)	38.63 ( $\pm$ 19.22)	<0.0001	31.8 ( $\pm$ 16.53)	44.68 ( $\pm$ 20.1)	<0.0001
cutoff value	>19 KPa			>38 KPa		
Se (%) [95% CI]	84 [77.1 - 89.5]			55.56 [42.5 - 68.1]		
Sp (%) [95% CI]	32.39 [21.8 - 44.5]			75.32 [67.8 - 81.8]		
+LR	1.24			2.25		
-LR	0.49			0.59		
PPV (%)	72.4			47.3		
NPV (%)	48.9			81		
AUROC	0.656			0.687		
SE [95% CI]	0.038 [0.589 - 0.718]			0.041 [0.662 - 0.748]		
p	0.0001			0.0001		

**Table V.** Performance of the association between Lok Score and liver stiffness measurement in predicting esophageal varices

Lok + LSM	prediction of EV	prediction of LEV
	Lok > 0.62 LSM >19 KPa	Lok > 0.8 LSM > 38 KPa
cutoff value		
Se (%)	91.42	83.8
Sp (%)	35.55	76.28
+LR	1.41	3.53
-LR	0.24	0.21
PPV (%)	76.8	53.06
NPV (%)	64	93.67
Diagnostic accuracy (%)	74.66	78.12

been wrongly classified, while for values higher than 0.5 to confirm cirrhosis, 14.8% of patients had been misclassified. When tried as a predictor of EV, it also performed extremely satisfactory. In a large cohort [10], for a cutoff value of 0.9 the Lok Score had an AUROC of 0.77 for the diagnosis of EV, while for a cutoff value of 1.5 the AUROC was 0.69 for the prediction of LEV and NPV was 92%. In another smaller study [9], the AUROC was 0.81 for the presence of EV (cutoff value 0.6, NPV 96%) and 0.87 for LEV (no data about the cutoff or other performance indices). In our prospective study the Lok score performed the best from all tested serum markers. For a cutoff value of 0.62 we obtained 77.2% PPV for the presence of EV and an acceptable AUROC of 0.69. In the case of LEV, the best cutoff value was 0.8, with an AUROC of 0.731 and a NPV of 86.4%.

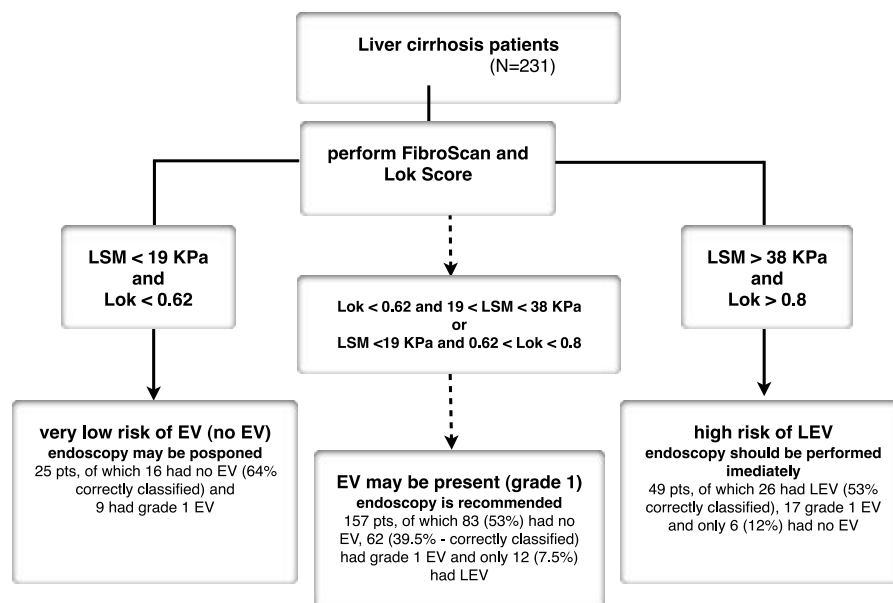
In the above mentioned study, Castera et al indirectly suggested by analyzing the discrepancies between LSM and serum markers that the association between TE and Lok score would be valuable for increasing the diagnostic performance. This approach meets the principle announced by Pinzani et al, according to which a concordance between two distinct noninvasive tests is required for an accurate diagnosis [44].

In this study, we tested the association between LSM and Lok Score for the prediction of EV. Used together, they lead to an increase in diagnostic accuracy and NPV for both

EV or LEV. Using a cutoff value for LSM of 19 KPa and of 0.62 for Lok score, we managed to predict the presence of EV with 74.66% diagnostic accuracy and 76.8 PPV. The figures are more impressive in the case of LEV when using the cutoff values of 38 KPa and 0.8, the diagnostic accuracy reaches 78% and the NPV 93%. In these conditions, the -LR remained as low as 0.24 (in the case of EVs) and 0.21 (for LEV), suggesting that a person without the specified condition is not likely to have this association of values.

In every day clinical practice the multitude of noninvasive methods available for patients with chronic liver diseases might be confusing. This is why the need for clear diagnostic algorithms was raised. Until now, several such algorithms were proposed, some combining FibroTest with APRI [45], either with Forns index (called FibroPaca) [46] or with Hepascore - another combination of serum markers used for the prediction of liver fibrosis [47]. Other two were extensively validated in the case of fibrosis stage diagnosis. One is the "SAFE" (Sequential Algorithms for Fibrosis Evaluation) biopsy proposed by Sebastiani et al [48] that combined the APRI and FibroTest. Using this approach, the authors managed to correctly classify almost 75% of the patients as cirrhotics/noncirrhotics; for the remainder of cases a liver biopsy was needed for a correct diagnosis. The other algorithm was proposed by the Bordeaux group [49] and it was based on the concordance between FibroScan and FibroTest. Using this approach, LC could be diagnosed with an accuracy of 93% and liver biopsy could be avoided in almost 80% of cases. By comparing the two algorithms [50], the Bordeaux algorithm seems to be more powerful in correctly diagnosing LC, but the SAFE biopsy may be more cost-efficient, since it uses APRI which is virtually costless.

Only very recently an algorithm combining the Lok score and the Forns Index was proposed for the noninvasive diagnosis of EV in patients with LC [10]. Using the cutoff values of 1.5 (for Lok Score) and 8.8 (for Forns Index), the diagnostic accuracy for LEV varied between 73.3% and 79.8%, depending on the aetiology of liver disease, values that are comparable with our data.



**Fig 3.** A noninvasive algorithm for the assessment of esophageal varices in patients with liver cirrhosis.

The above mentioned algorithm does not satisfy the need for an accurate noninvasive prediction of EV in cirrhotic patients. Based on our data, we propose an alternate algorithm, that combines the LSM and Lok Score (Fig. 3). Evidently, this approach needs extensive further internal and external validation, before it can be recommended in current clinical use.

In **conclusion**, we may safely state that among the tested serum markers, the Lok Score is the best in predicting the presence of EV and LEV in patients with cirrhosis. Using a combined approach (Lok Score and LSM), the diagnostic accuracy increases up to 78%. The Lok Score and LSM can be used together as a noninvasive algorithm for the prediction of esophageal varices in cirrhotic patients.

### Conflicts of interest

None to declare.

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