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Serum biomarkers predictive of cirrhosis in alcoholic liver disease as an alternative to ARFI-SW elastography

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Abstract. – OBJECTIVE: Aspartate aminotransferase to platelet ratio index (APRI) and fibrosis 4 (FIB-4) index are noninvasive biomarkers that evaluate liver stiffness in patients with chronic viral hepatitis and are able to detect advanced hepatic fibrosis and cirrhosis. However, their usefulness in alcoholic liver disease (ALD), when compared with Acoustic Radiation Force Impulse- Shear Wave (ARFI-SW) elastography, is debatable.

PATIENTS AND METHODS: We sifted the files of all enrolled patients with ALD that were admitted to our Emergency hospital between January 2019 and December 2020. All patients had undergone ARFI-SW elastography, and APRI and FIB-4 scores were calculated. The performance of APRI and FIB-4 scores in the prediction of cirrhotic patients according to ARFI-SW elastography was evaluated.

RESULTS: In total, 120 patients with ALD were evaluated. All of them were male and Caucasian, with a mean age of 55.54±12.4 years. The mean ARFI-SW elastography score was 1.57±0.7 m/s, the median APRI score was 0.68 (0.1-11.6) and the median FIB-4 score was 1.8 (0.2-19.4). Stages of liver fibrosis according to ARFI-SW elastography were evaluated as F0-1 in 21 (10.5%), F2 in 35 (26%), F3 in 52 (17.5%), and F4 in 92 (46%) patients. Based on ARFI-SW elastography fibrosis stage classification, we estimated the optimal APRI and FIB-4 scores to predict the presence of liver cirrhosis (F4) by using ROC curve analysis and the Youden index. The optimal APRI score for F4 patients was calculated as >1.52 [area under the curve (AUC) 0.875, 95% CI 0.809-0.919; $p<0.001$], giving sensitivity (Se) 81.2%, specificity (Sp) 81.4%, positive predictive value (PPV) 76%, and negative predictive value (NPV) 86.1%. The optimal FIB-4 score for F4 patients was calculated as >2.77 (AUC 0.916, 95% CI 0.814-0.922; $p<0.001$), giving Se 83.8%, Sp 77%, 81.4 77%, and NPV 84.3%.

CONCLUSIONS: APRI and FIB-4 scores can be used as screening tools in ALD for predicting cirrhosis instead of ARFI-SW elastography measurement, which is neither widely available nor an affordable method. Additional prospective studies are required in the future to confirm this finding.

Key Words:
Alcoholic liver disease, APRI, FIB-4, ARFI-SW elastography, Fibrosis, Cirrhosis.

Introduction

Nowadays, chronic alcoholism and its health implications represent a global concern. Over three million deaths are linked to chronic alcohol intake every year[1]. Even though ethanol is known for having a negative impact on almost every part of the body, the liver still remains the organ that suffers the most extensive tissue injury. Liver steatosis, steatohepatitis, fibrosis, and ultimately cirrhosis are the usual histologic findings observed in chronic alcoholism[2]. Taking into consideration the above-mentioned, when it comes to the therapeutic management and prognosis of alcoholic liver disease (ALD), staging liver fibrosis is crucial. To date, liver biopsy is still considered the gold standard for grading hepatic fibrosis, but due to its invasive character, alternative methods have been developed[3].

Our study reviewed three of these alternative methods that assess liver stiffness in a noninvasive manner. These methods are represented by the biochemical markers and scoring systems aspartate aminotransferase (AST) to platelet ratio in-

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dex (APRI) and fibrosis 4 index (FIB-4) together with Acoustic Radiation Force Impulse- Shear Wave (ARFI-SW) elastography[4].

APRI and FIB-4 scores are easy to calculate using clinical parameters introduced in specific formulas, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and age. Furthermore, these noninvasive biomarkers are widely available and are quite affordable[5]. However, these biomarkers were developed mostly for the detection of significant fibrosis and cirrhosis in patients with chronic viral hepatitis C, and little is known about their applicability in evaluating hepatic fibrosis in patients with alcoholic liver disease[6].

Meanwhile, ARFI-SW elastography, a relatively new ultrasound-based diagnostic technique that evaluates the wave propagation speed through the examined tissue, is able to detect every stage of liver fibrosis, regardless of the underlying pathology that leads to hepatic injury in the first place[7]. The main disadvantage of this imaging technique is that it is not generally available, mostly because of its high cost and also due to technical and practical reasons[8].

The aim of this study is to compare the diagnostic performance of APRI and FIB-4 scores with the diagnostic performance of ARFI-SW elastography in detecting F4 (liver cirrhosis) patients in a Romanian ALD cohort. Also, an approximation of best cut-offs for APRI and FIB-4 scores that can predict cirrhosis precisely (with the use of the Youden index and ROC curve analysis), in order to reduce the need for ARFI-SW elastography, especially in low socio-economic areas, where this method is not available or unaffordable.

Patients and Methods

The records of all patients with alcoholic liver disease who were admitted to an emergency hospital in Bucharest between January 2019 and December 2020 were reviewed. Basic demographic information was collected. Each patient was assessed with a pulmonary x-ray and electrocardiogram. Moreover, routine automated methods were used for measuring coagulation profiles (international normalized ratio, activated partial thromboplastin time), biochemical parameters (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, urea, creatinine), hemogram (hemoglobin, white blood cell count, platelet count, and detailed red blood cell indices) and urinalysis.

APRI and FIB-4 scores were calculated by following the standard formulas:

1. APRI=[AST level (IU/L)/AST-upper limit of normal (IU/L)]/Platelet count (10^9/L) X100.

2. FIB-4=age (y) X AST level (U/L)/Platelet count (109/L) X [ALT $(U/L)^{1/2}$], in which the age of the patient was the age at the time of the hospital admission.

Also, serologic markers such as hepatitis B s antigen (HBs Ag), antibodies to hepatitis C virus (HCV Ab) and antibodies to human immunodeficiency virus (HIV Ab) were assayed with the use of commercial enzyme immunoassays.

Further on, all patients underwent an ARFI-SW hepatic elastography which was executed in a resting respiratory state and a dorsal decubitus position, with the right arm above the head for adequate intercostal access. In the right lobe of the liver, the region of interest (ROI) (a rectangle of 0.5×1.0 cm), was placed by the operator at approximately 2.0 cm beneath the Glisson's capsule, with the major local vessels bypassed. Ten valid measurements were taken, and their median was used for grading liver stiffness. Optimal ARFI-SW velocity cut-off values, as suggested by Friedrich-Rust et al[9] were used: 1.51 m/s for $F \geq 3$ (advanced fibrosis) and 1.87 m/s for $F=4$ (cirrhosis), respectively.

Exclusion criteria comprised of patients that were chronically infected with hepatitis B or C virus and/or human immunodeficiency virus; patients with laboratory findings of acute hepatitis [alanine aminotransferase (ALT) levels ≥10 upper limits of normal (ULN)]; patients with any type of ongoing infection (e.g., urinary, pulmonary); patients with any other chronic illness (e.g., cardiac failure, diabetes mellitus, chronic kidney disease).

The database included medical history, clinical and laboratory data. The study was performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the hospital's ethics committee.

Statistical Analysis

All data were analyzed using the statistical package MedCalc, version 20.116 (Ostend, Belgium). Continuous variables were defined by their mean±standard deviation and/or by their median (min-max). Correlation analysis was performed in order to compare the stage of liver fibrosis that was detected by both APRI and FIB-4 scores with the stage of liver fibrosis that was detected through ARFI-SW elastography. Diagnostic performances for APRI and

FIB-4 scores versus ARFI-SW elastography were analyzed separately, according to sensitivity (Se), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV), and area under the receiver operating characteristic (ROC) curve. Optimal cut-off values for APRI and FIB-4 scores were determined by using the Youden index criterion [Youden index=Sensitivity (%)+Specificity (%)-100]. Youden Index represents a summary measure of the ROC curve that estimates the effectiveness of a diagnostic marker and enables the selection of an optimal threshold value (the cut-off point)[10]. A two-tailed *p*-value <0.05 was considered to be statistically significant.

Results

In total, 120 patients with ALD were evaluated. Their mean age was 55.54±12.4 years and all of them were male and Caucasian. The mean ARFI-SW elastography score was 1.57±0.7 m/s, the median APRI score was 0.68 (0.1-11.6) and the median FIB-4 score was 1.8 (0.2-19.4). Stages of liver fibrosis according to ARFI-SW elastography were evaluated as F0-1 in 21 (10.5%), F2 in 35 (26%), F3 in 52 (17.5%), and F4 in 92 (46%) patients.

Based on ARFI-SW elastography fibrosis stage classification, we estimated the optimal APRI and FIB-4 scores to predict the presence of liver cirrhosis (F4) by using Youden index and ROC curve analysis[11].

The optimal APRI score for F4 patients was calculated as >1.52 [area under the curve (AUC) 0.871, 95% CI 0.809-0.919; *p*-value<0.001], giving Se 81.2%, Sp 81.4%, PPV 76%, and NPV 86.1% (Figure 1).

The optimal FIB-4 score for F4 patients was calculated as >2.77 (AUC 0.875, 95% CI 0.814-0.922; *p*<0.001), giving Se 83.8%, Sp 77%, 81.4 77%, and NPV 84.3% (Figure 2) (Table I).

Discussion

Nowadays, liver biopsy, due to its invasive character, is more likely to be replaced by noninvasive methods. ARFI-SW elastography (together with transient elastography) is one of the most valid methods for the assessment of liver fibrosis in ALD[12]. Unfortunately, due to its expensive cost, this method is not commonly used in low-income re-

Table I. Performance indicators of APRI and FIB-4 scores in F4 patients.

Score	APRI (F4)	FIB-4 (F4)
Cut-off value	>1.52	>2.77
Sensitivity, %	81.2	83.8
Specificity, %	81.4	74.4
PPV, %	76	73.6
NPV, %	86.1	84.3

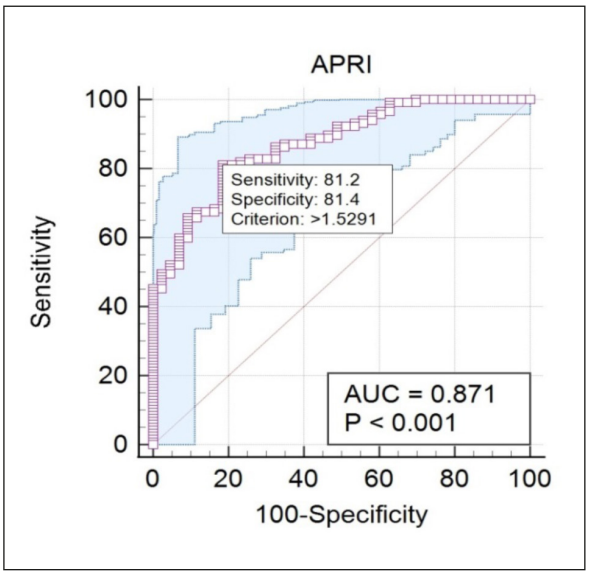

Figure 1. Performance of APRI score in the prediction of F4 patients according to ARFI-SW elastography. ARFI-SW: Acoustic Radiation Force Impulse-Shear Wave elastography; AUC: area under the curve.

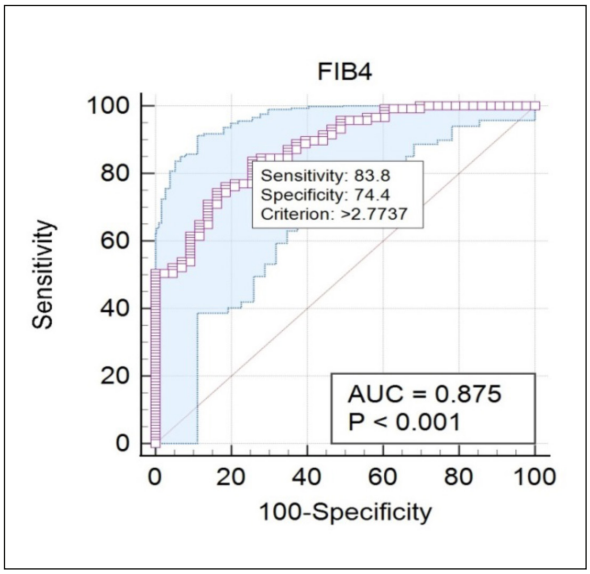

Figure 2. Performance of FIB-4 score in the prediction of F4 patients according to ARFI-SW elastography. ARFI-SW: Acoustic Radiation Force Impulse-Shear Wave elastography; AUC: area under the curve.

gions[13]. On the contrary, APRI and FIB-4 index are 2 scoring systems very facile to use for liver fibrosis and have been proven to achieve high precision for the diagnosis of cirrhosis in chronic C hepatitis patients when compared to transient elastography and liver biopsy[5]. However, there is little information when it comes to comparing the diagnostic accuracy of both APRI and FIB-4 scores with that of ARFI-SW elastography in ALD patients.

Separating non-cirrhotic patients from those with cirrhosis is very important in everyday practice. Patients with cirrhosis need further evaluation, such as abdominal ultrasound and upper digestive endoscopy, in order to be screened for ascites, splenomegaly, and esophageal varices. Also, they may require lifesaving treatment such as vasoconstrictors for portal hypertension and prophylactic endoscopic variceal band ligation[14].

Our study concluded that both scores predicted F4 (cirrhotic) patients adequately. The optimal cut-off values for APRI and FIB4 were determined using the Youden index criterion - a summary measure of the ROC curve that estimates the effectiveness of a certain diagnostic marker and enables the selection of an optimal threshold value known as cutoff point[15].

The Area Under the Receiver Operating Characteristic curve (AUROC) we detected were 0.871 and 0.875 for the APRI and FIB-4 scores, respectively. A cut-off of >1.52 for APRI score was 81.2% sensitive and 81.4% specific in detecting F4 patients. The PPV of this threshold was as high as 76%, with an NPV of 86.1%. A cut-off of >2.77 for FIB-4 score was 83.8% sensitive and 74.4% specific in the diagnosis of F4 patients. The PPV of this threshold was 73.6% and the NPV was 84.3%. Both APRI and FIB-4 are satisfactory tools for ruling out non-cirrhotic patients.

It is not uncommon for the threshold values of APRI and FIB4 score systems to vary between studies. Differences in reference ranges used for AST and ALT levels and differences in patient populations, including the prevalence of cirrhosis, may explain these inconsistencies[16-18]. Several APRI and FIB-4 cut-off values predictive of cirrhosis have been mentioned in literature[19].

For APRI, in one systematic review done by Shaheen and Myers[20], the lower threshold value of 1 was 76% sensitive and 76% specific, with an overall AUROC of 0.76. The PPV of this threshold was 32%, while NPV was 94%. The higher threshold value of 2 was more specific (91%), but less sensitive (49%), with PPV 50% and NPV 91%, indicating its efficacy in excluding cirrhosis.

In regard to the FIB-4 score, its diagnostic performance was evaluated by Vallet-Pichard et al[21] on a large number of patients with chronic C hepatitis in comparison to liver biopsy. FIB-4 with a threshold <1.45 had an NPV of 94.7% to exclude significant fibrosis, with a Se of 74.3%, while a threshold higher than 3.25 had a PPV to confirm the existence of a significant fibrosis of 82.1%, with a Sp of 98.2%.

When set side by side with other similar papers, the main difference is that our study compares the diagnostic performance of APRI and FIB-4 scores to that of ARFI-SW elastography in patients with alcoholic liver disease, whereas other studies[22,23] compare the diagnostic performance of APRI and FIB-4 scores to that of liver biopsy in patients with chronic viral hepatitis.

In this post-pandemic era of economic crisis, the need to simplify the assessment of ALD patients, especially those from low-income areas, where liver elastography and biopsy are not available, is crucial[24]. Our study determined that the use of biochemical scores such as APRI and FIB-4 may represent a cheaper and easier method to separate non-cirrhotic patients from cirrhotic patients.

Limitations

As for the limitations of our study, the most important ones would be the retrospective nature of our study and the use of a noninvasive procedure such as ARFI-SW elastography for liver fibrosis assessment. Another limitation would be the reduced number of patients with low-grade fibrosis that made the cut-off values we suggested significant only for patients with severe fibrosis/cirrhosis. On the other hand, the large number of well-documented cases that fulfilled our inclusion criteria allowed us to fulfill the aim of the study accurately.

Conclusions

Hence, it can be concluded that both the scores APRI and FIB-4 scores predicted F4 (cirrhotic) patients adequately and can be considered reliable tools for excluding non-cirrhotic patients. And can minimize the use of expensive methods like Acoustic Radiation Force Impulse- Shear Wave elastography.

Informed Consent

Written informed consent was obtained from all patients at the time of their admission to the hospital.

Ethics Approval
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (Ethics Committee No. 11607/16.02.2019) of the Bucharest Emergency Clinical Hospital.

Data Availability
Data will be made available on request.

Conflicts of Interest
The authors declare no conflict of interest.

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Authors' Contributions
Study design: C-N.R. A.S.; data collection: C-N.R.; data analysis: N.R.K, S.I.; supervision and drawing conclusions: A.V., S.I.; writing the draft: N.R.K, A.S. revising the draft: D.N. accuracy check: S.I.; literature research: M.E., D.N.

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