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Original Research Article **Gastroenterology**

FIB-4, APRI, and NFS Scores Compared to FibroScan for the Assessment of Liver Fibrosis in Patients with NAFLD

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Abstract

Background: NAFLD is a spectrum of liver disease ranging from fatty liver to steatohepatitis, fibrosis and cirrhosis. Due to the epidemic proportion of individuals with NAFLD worldwide, liver biopsy evaluation is impractical, and noninvasive assessment for the diagnosis of NASH and fibrosis is needed. In this study we aimed to compare FIB-4, APRI, and NFS score to FibroScan for the assessment of hepatic fibrosis in patients with NAFLD. ***Methods:*** This prospective study included 103 patients with NAFLD and was conducted in the Hepato-Gastroenterology Unit of Functional Digestive Explorations at CHU Ibn SINA in RABAT MOROCCO and covers the period from 01/2016 to 04/2023. A checklist was used to record the demographic features and biological data of the patients. Then, all patients underwent FibroScan using the FibroScan compact 530 device (Echosens, France). ***Results*:** Of the 103 patients with NAFLD included in this study, with a mean age of 54.4 ± 11.4 years, 35(34%) were male and 68 (66%) were female. Based on FibroScan results, 58 patients (56.3%) were classified as F1, 13 (12.6%) as F2, 5 (4.9 %) as F3, and 27 (26.2 %) as F4. A significant correlation was found between FibroScan and FIB-4 (r = 0.365), APRI (r = 0.376), and NFS score (r = 0.356) ($P < 0.001$). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of APRI at the 0.64 cut-off for the differentiation of F3F4 from F2F1 were 59.4, 84.5, 63.3, 82.2 and 76.7%. FIB-4 at the 1.8 cut-off 68.8, 83.1, 64.7, 85.5, 78.6% and NFS at the 0.89 cut-off 71.9, 69, 51.1, 84.5 and 69.9% respectively. Moreover, the area under the receiver operating curve of APRI, FIB-4, and NFS for the differentiation of F3F4 from F1F2 was 0.782, 0.779, and 0.723, respectively. ***Conclusions:*** Based on these results, APRI appears to be the most appropriate substitute of FibroScan for the detection of significant fibrosis in NAFLD patients.

Keywords: NAFLD, FibroScan, Fibrosis, FIB-4, APRI, NFS.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease globally [1]. The global prevalence has been increasing over time, NAFLD has a 24% estimated global prevalence rate, and it is >30% in the Middle East and South America what makes it an increasing public health problem, owing to its close association with type 2 diabetes mellitus, obesity, and metabolic syndrome. NAFLD encompasses a spectrum ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) [2]. The subtype of NAFLD that is histologically categorised as non-alcoholic steatohepatitis (NASH) has a potentially progressive course leading to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation.

Conventional ultrasonography is the most commonly used imaging method for the diagnosis of hepatic steatosis, with sensitivity and specificity of around 85% and 90%, respectively [3]; however, it has the limitation that detected only steatosis with >25% liver fat content and, therefore, a relevant number of patients with steatosis starting at 5% liver fat content can be missed. In addition, the accuracy of ultrasonography for diagnosis of liver steatosis is reduced in patients with obesity and coexistent renal disease [4]. For the assessment of hepatic steatosis, the controlled attenuation parameter (CAP), typically measured in conjunction with transient elastography (VCTE) , provides a point-of-care semi quantitative assessment of hepatic steatosis but does not accurately quantify or monitor changes in liver [5]. Liver biopsy is still the reference standard for the assessment of liver fibrosis

and allows for a detailed evaluation of the localisation and amount of fibrosis Liver biopsy in NAFLD patients but it is rarely used in clinical practice, due to its invasiveness, poor acceptability, sampling variability, and potential several complications. This, added to its relatively high cost, make non-invasive, repeatable and ideally cheaper alternative tools for the assessment of fibrosis highly desirable.

The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend the use of transient elastography by FibroScan for the evaluation of liver fibrosis in NAFLD patients [6, 7]. FibroScan is the most commonly used method to assess liver stiffness and can be used to exclude significant hepatic fibrosis. In addition, from FibroScan, several non-invasive biomarkers have been developed as valuable tools for estimate of the presence of advanced fibrosis, such as fbrosis-4 (FIB-4) score, NAFLD Fibrosis Score (NFS), AST Platelet Ratio Index (APRI).

Given the high prevalence of NAFLD and the potential complications of NASH, the screening of the liver fibrosis is highly recommended, especially at its early stages. Moreover, non-invasive methods are preferred over liver biopsy in this regard. However, although non-invasive, FibroScan is costly and may not be available at every center. Thus, we aimed to compare FIB-4, APRI, and NFS score to FibroScan for the assessment of hepatic fibrosis in patients with NAFLD.

METHODS

Participants

This study included patients with NAFLD or non-alcoholic steatohepatitis (NASH) diagnosed based on US findings according to the recommendations of the EASL.

Exclusion criteria were alcoholic liver disease, the use of hepatotoxic medications such as chronic intake of methotrexate, congestive heart failure, other chronic liver diseases, including hepatitis B, hepatitis C, or autoimmune hepatitis, any condition interfering with FibroScan evaluation such as major cytolysis > 5N or ascites based on clinical or US evidence.

Study design

This is a retrospective study including 103 NAFLD patients. The study was conducted in the Hepato-Gastroenterology Department of Functional Digestive Explorations at CHU Ibn Sina in RABAT and covers the period from 2016 to 04/2023.

A checklist was used to record the data. First demographic features and biological data of the patients. Then, all patients underwent FibroScan using the FibroScan compact 530 device (Echosens, France). All FibroScans were performed according to the manual of the manufacturer. Based on the previous studies and the recommendations of the manufacturer, FibroScan results were classified as:

F0-1:<7 kPa
F2: 7.1–8.5 kPa
F3: 8.6–10.2 kPa
F4: ≥ 10.3 kPa

Controlled attenuation parameter (CAP) score, showing the amount of liver with fatty change, was also determined in FibroScan for each patient.

NFS score, APRI and FIB-4 were calculated for each patient based on the following formulas:

$$Fib4 = (Age \times ASAT) / (Plaquettes \times \sqrt{[ALAT]})$$ [8]

$$APRI\ Score = (ASAT * 100 / RefAsat) / Plaquettes$$ [9]

$$NAFLD\ fibrosis\ score : -1{,}675 + 0{,}037 \times age\ (années) + 0{,}094 \times BMI\ (kg/m2) + 1{,}13 \times diabète\ (oui=1,\ non=0) + 0{,}99 \times ASAT/ALAT - 0{,}013 \times plaquettes\ (\times 10^9/l) - 0{,}066 \times albumine\ (g/l)$$ [10]

Data Analysis

The application JAMOVI 2.2.5 was used for data analysis. Mean, standard deviation, median, interquartile range (IQR), frequency, and percentages were used to describe the results. Distribution normality of quantitative variables were determined using the Shapiro-Wilk normality test. Accordingly, Spearman's correlation was used to determine their correlations. The receiver operating characteristic (ROC) curves were drawn to determine the diagnostic value of FIB-4, NFS, and APRI for the differentiation of F1-F2 of liver fibrosis from F3-F4 (in FibroScan). The area under the ROC (AUROC) curve was calculated for each non-invasive index. The optimal cut-off of all three indices was also determined for this purpose using the ROC curves. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were calculated for these cut-offs as well. p values ≤ 0.05 were regarded as statistically significant.

RESULTS

Of the 103 patients with NAFLD or NASH included in this study, with a mean age of 54.4 ± 11.4 years, 35(34%) of patients were male and 68 (66%) were female.27(26.2%) of patients have Type 2 diabetes and 31(30.1%) have Hypertension. General characteristics of the study participants are shown in Table 1. Based on FibroScan results, 58 patients (56.3%) were classified as F1, 13 (12.6%) as F2, 5 (4.9 %) as F3, and 27 (26.2 %) as F4. A significant correlation was found between FibroScan and FIB-4 (r = 0.365), APRI (r = 0.376), and NFS score (r = 0.356) (P < 0.001). Nonetheless, this correlation was moderate. Among different indices, only FIB-4 was significantly correlated with age (r = 0.190, P = 0.05); however, the correlation was weak (Table 2).

Figure 1 demonstrates the ROC curves of APRI, FIB4 and NFS score for detection of F3F4 of liver fibrosis from the lower stages F1F2.based on these curves, the best index to diagnose F3F4 from the lower stages of liver fibrosis was APRI with an AUROC curve of 0.782 (95% confidence interval). The optimal cut-off of APRI was 0.64 for this purpose, with a sensitivity of 59.4%, specificity of 84.5%, PPV of 63.3%, NPV of 82.2% and DA 76.7%. Results for other indices are shown in Table 4.

Table 1: General characteristics of the study participants

Variables	**Values (N=103)**
Age (years) #	54.4 ± 11.4
Gender **§**	
Male	35 (34)
Female	68 (66)
Type 2 diabetes §	27(26.2)
Hypertension §	31(30.1)
CAP score (dB/m) #	290± 44
FibroScan score (kPa) †	6.3 (4.6 ;10.6)
APRI†	0.34(0.22;0.70)
FIB-4†	1.26(0.78;2.26)
NFS †	-1.12(-2.51; -0.28)
FibroScan results **§**	
F0-1	58 (56.3)
F2	13 (12.6)
F3	5 (4.9)
F4	27 (26.2)
N number, # means ± standart deviation **§** effectif (pourcentage), † median and interquartile interval	

CAP controlled attenuation parameter, ***APRI*** AST to platelet ratio index, *FIB-4* fibrosis-4, NFS NAFLD fibrosis score

Table 2: Correlation of different indices with FibroScan, CAP scores, and age

First variable	**Second variable**	**Correlation coefficient**	***P* value***
FIB-4	CAP score	-0.067	0.502
	FibroScan score	0.365	< 0.001
	Age	0.190	**0.05**
APRI	CAP score	-0.026	0.796
	FibroScan score	0.376	< 0.001
Age		— 0.071	0.475
NFS	CAP score	— 0.076	0.447
	FibroScan score	0.356	< 0.001
	Age	0.144	0.148
FibroScan score	Age	− 0.024	0.809

CAP controlled attenuation parameter, *FIB-4* fibrosis-4, **NFS** NAFLD fibrosis score
*Analyzed by Spearman's correlation

Table 4: Diagnostic performance of the indices for the differentiation of F3 and F4 from lower stages

Indices	**AUC**	***P* value**	**Optimal cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**DA(%)**
APRI	**0.782**	< 0.001	0.64	59.4	**84.5**	63.3	82.2	76.1
FIB-4	0.779	< 0.001	1.8	68.8	83.1	**64.7**	**85.5**	**78.6**
NFS	0.723	< 0.001	-0.89	**71.9**	69.0	51.1	84.5	69.9

FIB-4 fibrosis-4, NFS NAFLD fibrosis score, *AUC* area under the curve, PPV positive predictive value, *NPV* negative predictive value, DA diagnostic accuracy

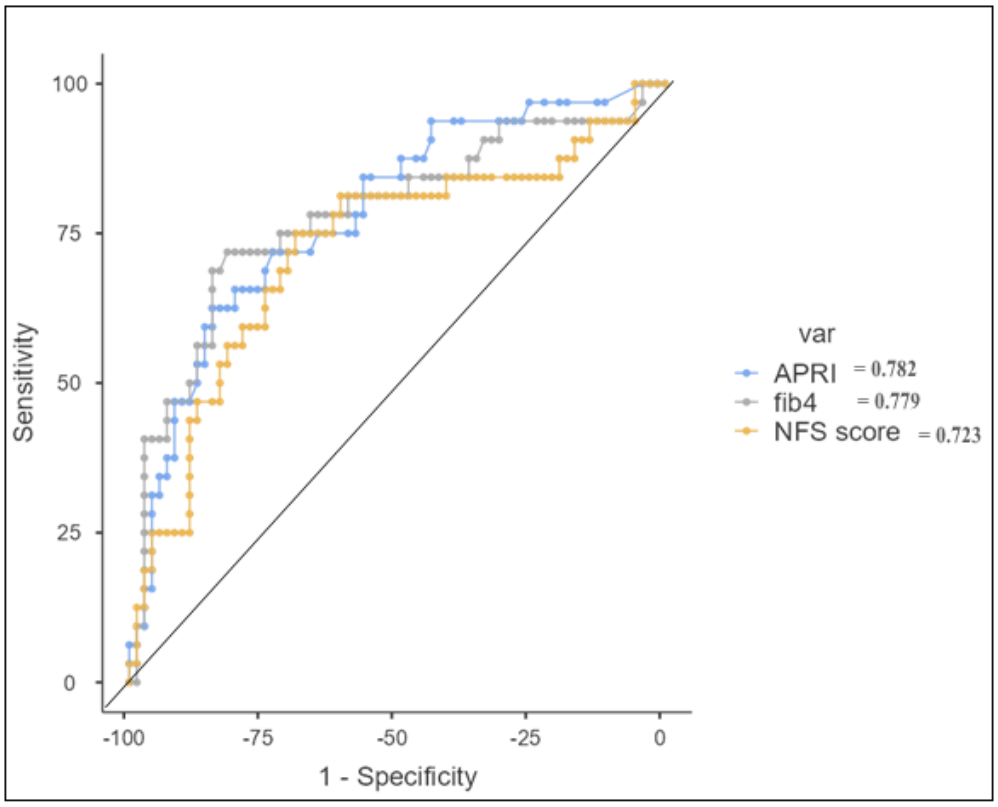

Fig 1: ROC curves of APRI, FIB-4, and NFS for the detection of F3-F4 of liver fibrosis from the lower stages F1-F2

DISCUSSION

In the management of NAFLD, it is important to identify patients with NASH and higher risk of progression to end stage liver disease, hepatic/extrahepatic complications and death. Liver biopsy is considered the gold standard and required to identify fibrosis status and patients with NASH. However, liver biopsy is invasive, costly, less suitable for population-level screening, and has some limitations that has made its use questionable. One limitation is that the liver biopsy does not efficiently reflect the fibrotic changes occurring in the entire liver because an optimally sized biopsy contains 5–11 complete portal tracts and reflects only 1/50000 the volume of the liver. Another limitation is that the process of hepatic fibrosis is not linear, and biopsies from different areas have shown different stages of fibrosis. Moreover, Disagreements between pathologists occur, which may correlate with the experience of the pathologist [11].

Therefore, to identify NASH in patients with NAFLD, various noninvasive fibrosis methods have been used. One of the scores, the NFS, is specific to NAFLD. Studies have suggested that higher NFS may be associated with increased mortality from cardiovascular disease [12]. In some studies, have been shown that the Fib-4 score have good predictive accuracy for advanced fibrosis in patients with chronic hepatitis C virus (HCV) infection [13]. In another study, it performed better than other serological markers for predicting advanced fibrosis in patients with NAFLD. The APRI has firstly been evaluated in patients with HCV and human immunodeficiency virus or alcoholic liver disease. The ability of the APRI to predict outcomes in patients with NAFLD was examined in a retrospective series with 320 patients and it was determined that only the high-risk group was at greater risk of death or liver transplantation [14].

The results of the current study revealed APRI as the best index to differentiate F3-F4 of liver fibrosis from F1-F2 compared to FIB-4 and NAFLD fibrosis score. APRI, with an AUROC curve of 0.782 at a cut-off of 0.64, had 59.4% sensitivity, 84.5% specificity, 63.3% PPV, 82.2% NPV and 76.7% DA for this purpose. Meanwhile, for FIB-4, the AUROC curve was 0.779 and the corresponding diagnostic values at a cut-off of 1.8 were 68.8, 83.1, 64.7,85.5 and 78.6%, respectively. As for NAFLD fibrosis score, the AUROC curve was 0.723 with an optimal cut-off of - 0.89, having 71.9% sensitivity, 69.0% specificity, 51.1% PPV, 84.5% NPV and 69.9% DA. The higher diagnostic performance of APRI in our study, contrary to previous findings, can be due to the measurement accuracy of laboratory parameters in the APRI formula, as well as NAFLD as the etiology of fibrosis in our study, and taking FibroScan results instead of biopsy findings as the reference of fibrosis staging, while we used FibroScan results. However, FibroScan has been recommended by the EASL and the AASLD for the assessment of liver fibrosis in NAFLD patients because it is the most widely

available and best evaluated point-of-care technique [10]. The only limitation of FibroScan appears to be obesity [15]. Yet, a recent study reported that FIB-4 and APRI are valuable for excluding advanced fibrosis in morbidly obese patients with NAFLD [16].

CONCLUSIONS

We found APRI to be the best index to predict advanced liver fibrosis compared to FIB-4 and NAFLD fibrosis score, with this index having the strongest correlation with FibroScan results.

As NAFLD is largely asymptomatic and the optimal timing of treatment depends on the accurate staging of fibrosis risk, screening at the primary care level is critical. Therefore, APRI is an appropriate index for the predicting of significant liver fibrosis and for determining which patients require fibroscan.

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