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Nonalcoholic fatty liver scoring panels shortcut for fibro scanning results or not

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Abstract

Introduction: Liver steatosis has a wide range of conditions from simple steatosis to non-alcoholic steatohepatitis, fibrosis, and eventually cirrhosis. Several panels and scoring systems have been introduced to differentiate steatosis with or without advanced fibrosis and also the degree of fibrosis. This study aimed to evaluate eleven different scoring panels in patients with steatosis and compare their results with Fibro Scan.

Methods: The study was performed on 122 NAFLD patients who were confirmed by ultrasound. The patients were referred to the gastroenterologist in Razi hospital in the north of Iran from September 2017 to April 2018. All patients underwent Fibro Scan. Multiple scoring systems were calculated using the laboratory values. These results were compared with the results of Fibro Scan. AUC for each panel was calculated.

Results: In This study, 62 (50.8%) were men. The mean age of the patients was 47.1±11.7 years. There were significant differences between patients with or without advanced fibrosis in three panels of APRI, NIPPON, and FIB4 (p=0.03, p=0.01, p=0.005, respectively). AUROC for APRI, NIPPON, and FIB4 were, 0.695 (CI=0.58-0.8, p=0.001), 0.642 (CI: 0.5-0.74, p=0.015) and 0.684 (CI: 0.5-0.7, p=0.002), respectively. None of the other panels had enough sensitivity for the diagnosis of advanced fibrosis.

Conclusion: Given the cost-effectiveness of panels, their ease of calculation, and noninvasiveness, FIB4, NIPPON and APRI can be used as useful tools for following, and also for predicting progression to advanced fibrosis.

Keywords: Nonalcoholic Fatty Liver Disease, Scoring Panels, Predicting

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Introduction

Non-alcoholic fatty liver (NAFLD) is formed with the pathological accumulation of fat in the liver (1) which is defined as the accumulation of fat in more than 5% of hepatocytes (2). Over the past 3 decades, fatty liver has become one of the most important chronic liver diseases in the world (3, 4). The highest prevalence of this disease belongs to western countries (5, 6). The prevalence of NAFLD in Asia is variable between 12-24 %. The prevalence of NAFLD is 2.9- 7.1% in Iran (7). The incidence of fatty liver is about 20 out of every 10,000 people per year. This disease has a wide range of conditions from simple steatosis to non-alcoholic steatohepatitis, fibrosis, and eventually cirrhosis and hepatocellular carcinoma (9).

Liver biopsy is the gold standard method for evaluating inflammation and severity and ranking fibrosis in NAFLD and non-alcoholic steatohepatitis (10). The biopsy is an invasive and also a difficult procedure that is associated with pain, the risk of complications, measurement errors, high cost, and the patient's unwillingness (11); therefore, the biopsy is not realistic for all NFLD patients and it is impractical (12, 13).

Alternative methods, and various tools for NAFLD are magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), ultrasound (absence of steatosis only), the enhanced liver fibrosis (ELF) score, transient elastography and NAFLD fibrosis score (13). These methods have some limitations, thus non-invasive, and reliable tests for this highly prevalent disease is important(14). Several panels and scoring systems from a combination of laboratory and clinical variables have been introduced to differentiate NAFLD with and without advanced fibrosis and to determine the degree of liver fibrosis. Most of them, to a large extent, have acceptable accuracy in distinguishing NAFLD with and without advanced fibrosis (10, 15, 16).

Our study aimed to evaluate 11 different scoring panels such as FIB4 [Age, AST, ALT, Platelets], APRI [AST platelet ratio index], AAR [Age, ALT/AST ratio], NFS [NAFLD fibrosis score], AP [Age, Platelets], BAAT [BMI, Age, ALT, TG] Score, BARD [BMI, AST/ALT ratio, DM) score, PLALA [platelet, albumin, AST/ALT ratio] score, N [Nippon]Score, FI [Platelets, Albumin], Forns index [platelet count, GGT, Age, total cholesterol] in patients with NAFLD and compare their results with Fibro Scan.

Methods

Patient

The sample size of this cross-sectional study was set as 122 patients. All patients with age 13-69 years were referred to the gastroenterologist in Razi hospital in the north of Iran from September 2017 to April 2018. The protocol of this study was approved by a local ethical committee of Guilan University of Medical Sciences (No. IR.GUMS.1396.114) and was based on the Declaration of Helsinki. Informed consent was obtained from all patients and all securities were applied to their data.

Inclusion criteria were patients with NAFLD confirmed by ultrasound. People with viral hepatitis (hepatitis B and C), autoimmune hepatitis, drug-induced liver disease, consumption of hepatotoxicity drugs including glucocorticoid, methotrexate, amiodarone, isoniazid, and tamoxifen during 6 months, consumption of vitamin E or glitazon, primary biliary cirrhosis, sclerosing cholangitis, genetic, metabolic, and cholestatic liver diseases, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency related to liver disease, recent or past alcohol consumption of >21 standard drinks per week for men and >14 standard drinks per week for women, past and present alcohol side effects, evidence of HCC or liver cancers, and history of bariatric surgery were excluded.

Then, the patients underwent Fibro Scan (FibroScan; Echosens, Paris, France) to determine the degree of fibrosis (F0-F4) and steatosis (S1-S3) in the liver. All patients underwent Fibro Scan by one expert person.

Clinical and biochemical measurements

Clinical and biochemical parameters were assessed for each participant. Underlying comorbidities including diabetes, hypertension, dyslipidemia, hypothyroidism, and polycystic ovary syndrome (PCOS) were also recorded. The history of pharmacotherapy for diabetes, hypertension, hypothyroidism, dyslipidemia, and other drugs was also reviewed .

Laboratory tests including white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), hematocrit (Hct), platelet (Plt), aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, albumin (Alb), ferritin, total iron-binding capacity (TIBC), gamma-glutamyl transpeptidase (GGT), ceruloplasmin, transferrin saturation, fasting blood glucose (FBS), and alpha-fetoprotein (AFP) were checked.

Then the scores of multiple scoring systems including AAR, APRI, FIB4, NFS, AP index, FI, Forms Index, BARD, BAAT, N Score, PLALA Score were calculated using the laboratory values, and the diagnostic value of the clinical indicators and the scoring systems was compared with the results of Fibro Scan. To determine the diagnostic value of each panel, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated.

Statistical analysis

Information on patients was classified, and the demographic data were analyzed in two groups with or without advanced fibrosis in SPSS 22. The qualitative parameters were analyzed through the Chi-Square test and the quantitative parameters through t-test in both groups. The results of Fibro Scan were divided into two groups without fibrosis (F0)/with mild fibrosis equivalent (F0F1) and advanced fibrosis (F2, F3, F3F4, and F4).

The results of the 11 panels were analyzed using a t-test in both groups. In addition, considering the cutoff point, the results of each panel were divided into two groups of no advanced fibrosis (no fibrosis or slight fibrosis) and advanced fibrosis. These results were compared with the results of Fibro Scan (no advanced fibrosis (F0 and F0F1) and advanced fibrosis (F2, F3, F3F4, F4), and then sensitivity, specificity, PPV, NPV, and accuracy of each panel were calculated. The area under the receiver operating characteristic (AUROC) curve and the confidence interval were also calculated for each panel. P-values less than 0.05 were considered significant. Finally, sensitivity, specificity, PPV, NPV, and accuracy of all panels were compared and the ROC curves of all panels were plotted on a single chart to compare the AUROCs. The formula and cutoff point for each panel are as follows in Table 1.

Table 1. The formula and cutoff point for each panel were as follows.

	Panel	Formula	cutoff point
1	FIB4 panel	(Age(year) × AST(IU/L))/(PLT(10^9/L) × √ALT(IU/L))	1.45 and 3.25 (21)
2	APRI panel	([AST/ULN]/PLT(10^9/L)) × 100	0.88 (17)
3	AAR panel	AST(IU/L)/ALT(IU/L)	0.8 (22)
4	NAFLD fibrosis score(NFS) panel	-1.675 + (0.037×Age(year)) + (0.094×BMI(Kg/M^2)) + (1.13×diabetes/IFG (yes=1, no=0)) + 0.99×(AST/ALT) - (0.013 × PLT (×10^9/L)) - (0.66 × ALB(g/dl))	-1.455 and 0.676 (23)
5	AP Panel	PLT(10^9/L) Age (years)	6 (24)

		>225-0 point 200-224-1 point 175-199-2 point 150-174-3 point 125-149-4 point <125-5 point	<30-0 point 30-39-1 point 40-49-2 point 50-59-3 point 60-69-4 point ≥70-5 point
		Score is the sum of two (0-10)	
6	BAAT Score panel	Sum of the items: BMI(Kg/M^2) ≥28, 1 point Age ≥50 years, 1 point ALT ≥ twice upper limit normal (80 U/L), 1 point TG ≥150 mg/dL, 1 point	2 (25)
7	BARD Score panel	Sum of the items: Diagnosis of Diabetes, 1 point BMI(Kg/M^2) ≥28, 1 point AST/ALT ≥0.8, 2 point	2 (26)
8	PLALA panel	Sum of the items: PLT <15.3(10^4/μL), 1 point Alb <4 (g/dl) 1 point AST/ALT> 0.9, 1 point	2 (3)
9	Nippon(N Score) Panel	Sum of the items: Female sex, 1 point Age >60, 1 point Type 2 Diabetes, 1 point Hypertension, 1 point	2 (27)
10	FI Panel	8.28 - (PLT(10^9/L) × 0.01) - (Alb(g/dl) × 1.08)	2.1 (28)
11	Forns index panel	7.811 - 3.131× In(PLT(10^9/L)) + 0.781× In(GGT(IU/L)) + 3.467× In(Age) - 0.014 × Cholesterol(mg/dl)	4.2 and 6.9 (29)

AST: aspartate aminotransferase, PLT: platelet count, ALT: alanine aminotransferase, ULN: upper limit of normal, BMI: body mass index, IFG: impaired fasting glucose, ALB: albumin, TG: triglyceride, GGT: gamma glutamyl transpeptidase

Results

Out of 122 samples, 62 (50.8%) were men. The mean age of the patients was 47.1±11.7 years. The mean BMI and waist circumferences were 31.3±4.9 kg/m2 and 105.3±11.4 cm, respectively. The demographic and disease characteristics of NAFLD patients with and without advanced fibrosis are compared in Table 2. The only significant difference between the two groups with and without advanced fibrosis was the presence of diabetes in these groups (p=0.001).

Table 2. Comparison of some different characteristics in NAFLD patients with and without advanced fibrosis.

Variable	Total	No fibrosis or slight fibrosis (F0, F0F1) (n=88)	Advanced fibrosis (F2, F3, F3F4, F4) (n=34)	*p*-value
Age (years) [Mean ± SD]	47.1±11.7	46±11	50±10	NS*
Gender: Male/Female [N (%)]	62 (50.8) / 60 (49.1)	45/43	17/17	NS**
BMI (kg/m^2) [Mean ± SD]	31.3±4.9	31.2±4.6	31.5±5.5	NS*
Waist circumference (cm) [Mean ± SD]	105.3±11.4	104.5±11	107.4±12	NS*
Diabetes [N (%)]	29 (23.8)	12	17	0.001**
Hypertension [N (%)]	17 (13.9)	12	5	NS**
Dyslipidemia [N (%)]	67 (54.9)	44	23	NS**
Hypothyroidism [N (%)]	6 (4.8)	2	4	NS**
Polycystic Ovary Syndrome (PCO) [N (%)]	1 (0.8)	1	0	NS**

* Analyzed with *t*-test

** Analyzed with Chi-square test

The mean fibrosis among the patients was 6.4±2.5 kPa, with the highest and lowest fibrosis of 16.1 kPa and 2.6 kPa, respectively. Regarding the fibrosis grade, 50 (41%) were F0, 38 (31.1%) were F0F1, 15 (12.3%) were F2, 13 (10.7%) were F3, 5 (4.1%) were F3F4 and 1 (0.8%) was F4.

The mean steatosis among the patients was 308.8±36.3 dB/m2, with the highest and lowest steatosis of 400 dB/m2, and 241 dB/m2, respectively. Regarding the steatosis grade, 13 patients (10.7%) were S1, 26 patients (21.3%) were S2, and 83 patients (68%) were S3. The mean percentage of steatosis was 66.3±20.5%, with the highest and lowest rate of 100% and 13%, respectively (Table 3).

Table 3. The status of fibrosis and steatosis in the participants based on the Fibro Scan results.

Fibrosis Grade (Number (%)	F0	50 (41)
	F0F1	38 (31.1)
	F2	15 (12.3)
	F3	13 (10.7)
	F3F4	5 (4.1)
	F4	1 (0.8)
Fibrosis (kPa) Mean ± SD		6.4±2.5
Steatosis	S1	13 (10.7)
	S2	26 (21.3)
	S3	83 (68)
Steatosis (in terms of CAP) Mean ± SD		308.8±36.3
Steatosis percent Mean ± SD		66.3±20.5

According to Table 4, there were significant differences between the two groups of patients with and without advanced fibrosis in three panels of APRI, NIPPON, and FIB4 (p=0.03, p=0.01, p=0.005, respectively).

Table 4. Comparison of different types of NAFLD severity scoring panels based on the fibrosis severity in FibroScan.

Panel	No fibrosis or slight fibrosis (Mean ± SD)	Advanced fibrosis (Mean ± SD)	T	*p*-value
APRI	0.3±0.2	0.4±0.2	-2.2	0.03
BAAT	1.8±0.8	1.9±0.9	-0.3	NS
AP	2.8±1.5	3.4±1.7	-1.8	NS
BARD	1.7±1.1	2.2±1.3	-1.9	NS
PLALA	0.5±0.4	0.5±0.5	0.02	NS
NIPPON	0.9±0.8	1.3±1	-2.5	0.01
AAR	0.7±0.2	0.8±0.3	-1	NS
NAFLD fibrosis score	-1.9±1.1	-1.8±1.7	-0.3	NS
FIB4	0.8±0.3	1.1±0.5	-2.9	0.005
FORNS	4.5±0.7	4.2±1.3	0.8	NS
FI	1.2±0.6	0.8±0.7	1.6	NS

According to Table 5, sensitivity, specificity, PPV, NPV, and accuracy were 2.9, 95, 20, 69.7, and 67.5% for the APRI panel, 35.3, 78.4, 38.7, 75.8, and 66.3 for the NIPPON panel, 21.2, 92.5, 35, 74, and 71.6 for the FIB4 panel at cutoff point of 1.45, and 0, 100, 0, 70.7, and 70.7 for the FIB4 panel at cutoff point of 3.25.

Table 5. Comparison of the ability of each test to detect advanced fibrosis in patients with NAFLD.

Panel	Cutoff point	AUC	Confidence interval	Sensitivity*	Specificity*	PPV*	NPV*	Accuracy
APRI	0.88	0.695	0.58-0.8	2.9	95	20	69.7	67.5
FIB4	1.45	0.684	0.57-0.8	21.2	92.5	35	74	71.6
	3.25			0	100	0	70.7	70.7
NIPPON	2	0.642	0.5-0.74	35.3	78.4	38.7	75.8	66.3
BARD	2	0.607	0.48-0.7	66.7	53.8	37.9	79.2	57.6
AP	6	0.586	0.47-0.7	9.1	95.3	42.8	73.2	71.4
NAFLD fibrosis score	-1.455	0.569	0.39-0.7	0	100	0	65.3	65.3
	0.676			11.1	94.1	50	66.6	65.3
BAAT	2	0.529	0.4-0.6	72.7	32.4	33.3	71.8	45.2
AAR	0.8	0.521	0.4-0.63	48.5	59.3	32.6	73.8	56.1
PLALA	2	0.500	0.3-0.66	0	97.1	0	65.3	64.1
FORNS	4.2	0.402	0.19-0.6	46.2	27.3	27.2	46.1	34.2
	6.9			0	100	0	62.8	62.8
FI	2.1	0.383	0.2-0.54	5.3	94.4	25	64	61.1

*** Values are in percent**

In addition, AUC for each panel is shown in figure 1.

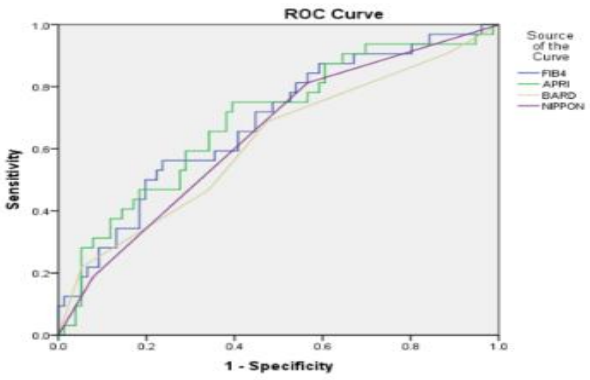

Figure 1. Comparison of the area under the ROC curve in panels with AUC >0.6.

Also, a diagnostic algorithm for clinical use of these panels is presented in Figure 2.

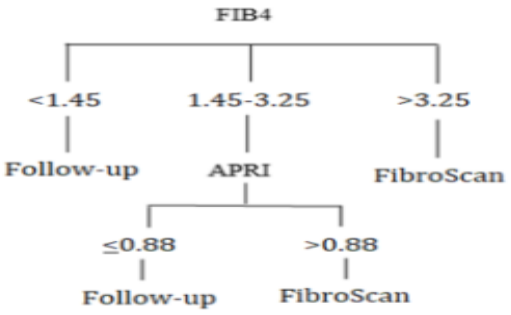

Figure 2. Proposed diagnostic algorithm for patients with NAFLD.

Discussion

This study aimed to compare the scoring panels of NAFLD with Fibro Scan. NAFLD is a common liver disease that may progress to steatohepatitis and cirrhosis. The liver biopsy is a gold standard but, invasive diagnostic procedure that is not without flaws. Therefore, there has been increasing interest in identifying non-invasive, surrogate diagnostic methods such as scoring panels and Fibro Scan.

Scoring panels can play an important role in the diagnosis of NAFLD along with Fibro Scan. There was no significant age difference between the two groups of patients with and without advanced fibrosis. However, in the study of Kessuko et al, Cichoz-Lach et al, Ratziu et al, McPherson et al, and Mohamed et al, the two groups had a significant age difference (17-21). In our study, there was no significant difference in BMI between patients with advanced fibrosis and patients without it, which is similar to the results of Kessuko et al and McPherson et al and in contrast to the results of Ratziu et al, A. Mohamed et al, and Cichoz-Lach et al (17-20).

APRI Panel

Sensitivity, specificity, PPV, NPV, and accuracy of the APRI panel were 2.9%, 95%, 20%, 69.7%, and 67.5%, respectively, indicating that the panel has a low sensitivity for the diagnosis of fibrosis, but high specificity of this panel with relatively good NPV indicates its high strength in ruling out advanced fibrosis. This panel was able to distinguish the two groups of the patient with and without advanced fibrosis (p=0.03). In addition, by calculating the area under the ROC curve, it was found that this panel had a relatively good diagnostic value (AUROC=0.695, CI=0.58-0.8, p=0.001). The cutoff point suggested by the ROC curve was 0.26 at which sensitivity and specificity were 73% and 62%, respectively.

According to the study of Atay et al, sensitivity, specificity, PPV, and NPV of the APRI panel at cutoff point of 0.61 were 35%, 95.7%, 85.7%, and 66.7%, respectively. Atay et al, stated that this panel is useful for ruling out rather than diagnosing advanced fibrosis (22). In a study by Shin et al on patients with chronic liver disease, sensitivity, specificity, PPV, and NPV of this panel were 93%, 48%, 75%, and 80% at the cutoff point of 0.5, and sensitivity, specificity, and PPV were 58%, 88% and 89% at the cutoff point of 1.5, respectively (23). In a study by Kruger et al, sensitivity, specificity, PPV, and NPV were 75%, 86%, 54%, 93%, respectively, at the cutoff point of 0.95 (24). While, in the study of Sumida et al, sensitivity, specificity, PPV, and NPV were 67%, 81%, 31%, and 95%, respectively (25). A cohort study showed that sensitivity and specificity of APRI score was 30 % and 92.8 % respectively (26).

Similar to the study of Mohamed, et al (p=0.001), the present study found a significant difference between two groups of patients with and without advanced fibrosis. In the study of Mohamed et al, sensitivity, specificity, PPV, NPV, accuracy, and AUROC were 21.1%, 93%, 50%, 77.9%, 75%, and 0.907, respectively, at the cutoff point of 1 (95%CI: 0.839-0.974). It was also stated that if the liver biopsy was considered only for individuals with a panel score of 1, 89.4% of unnecessary biopsies would be avoided (20). According to Macpherson's et al study, sensitivity, specificity, PPV, and NPV were 27%, 89%, 37%, and 84%, respectively, and AUROC was 0.67 at the cutoff point of 1 (95%CI: 0.54-0.8). Given that the NPV of this panel is suitable for ruling out advanced fibrosis. According to this study, the weak PPV of the panel indicates that it cannot replace liver biopsy (19). These were reported in the French cohort study as 66%, 90%, 72%, and 87%, respectively (27). The results of the Peres-Gutieierrez et al, were similar to those of McPherson et al, study (19, 28). According to Ding's study, AUROC was 0.795 and sensitivity, specificity, PPV, NPV, and accuracy were 80%, 73%, 33%, 96%,

and 65%, respectively (29). According to the study of Rath et al, sensitivity, specificity, PPV, NPV, and AUROC were 29.1%, 97.22%, 87.5%, 83.3%, and 0.36, respectively (10).

Similar to the results of Atay et al, and Rath et al, regarding the APRI panel, sensitivity was low and specificity was high in this study; sensitivity was much lower in our study than those studies (10, 22). On the other hand, there was a significant difference between the two groups of patients with and without advanced fibrosis; therefore, the low sensitivity of this panel may be attributed to the improper cutoff point. This cutoff point cannot properly diagnose patients with advanced fibrosis, but it can rule it out well. Therefore, using the ROC curve, 0.26 was selected as the cutoff point for the APRI panel in our study population. Assuming a new cutoff point for this panel, sensitivity and specificity were obtained 73% and 62%, respectively. As AST level in the group with advanced fibrosis was significantly higher than the other group (p=0.03), the significant difference between the two groups in the APRI panel is justifiable. But in general, given the low sensitivity and high specificity of the APRI panel, it is more useful to rule out than to diagnose advanced fibrosis.

NIPPON panel

Sensitivity, specificity, PPV, NPV, and accuracy of this panel were 35.3%, 78.4%, 38.7%, 75.8%, and 66.3%, respectively. This panel was able to make a significant difference between the two groups of patients with and without advanced fibrosis (p=0.01) (Table 4).

In addition, the area under the ROC curve showed that this panel had a good diagnostic value (AUROC=0.642, CI: 0.5-0.74, p=0.015). A limited number of studies have been performed on this panel. In a study by Sumida et al, this panel differentiated the groups of patients with and without advanced fibrosis (p<0.0001). The AUROC of this panel was 0.715 and sensitivity, specificity, PPV, and NPV were 80%, 58%, 19%, 96%, respectively. It was also stated that this panel can prevent 53% of unnecessary biopsies (25). Considering that diabetes was a parameter involved in this panel and also diabetes was differentiated in the two groups of patients with and without advanced fibrosis in this study (p=0), we could justify the ability of this panel to differentiate between these two groups.

FIB4 panel

Sensitivity, specificity, PPV, NPV and accuracy of this panel were 21.2%, 92.5%, 35%, 74%, and 71.6%, at the cutoff point of 1.45 and 0, 100%, 0, 70.7%and 70.7% at the cut point of 3.25, respectively.

This panel was able to significantly differentiate the two groups of patients with and without advanced fibrosis (p=0.005). In addition, the area under the ROC curve indicated that this panel has a good predictive value (AUROC=0.684, CI: 0.5-0.7, p=0.002). According to the ROC curve, the panel sensitivity and specificity will be 75% and 53% at the cutoff point of 0.82.

In the study of Atay et al, sensitivity, specificity, PPV, and NPV were 65%, 69.6%, 61.1%, and 72.7% at the cutoff point of 1.08, respectively. They stated that this panel has moderate sensitivity and specificity (22).

In a study by Shah et al, sensitivity, specificity, PPV, and NPV were 74%, 71%, 43%, and 90% at the cutoff point of 1.3 and 33%, 98%, 80%, and 83% at the cut point of 2.67, respectively (30). Sensitivity, specificity, PPV, and NPV in the study of Sumida et al, were 90%, 64%, 24%, and 98% at the cutoff point of 1.45, respectively. In addition, based on the ROC curve, sensitivity, specificity, PPV, and NPV were 48%, 95%, 53%, and 94% at the cutoff point of 3.25 in this study (25).

In the study of Mohamed et al, sensitivity, specificity, PPV, and NPV were 84.2%, 86.9%, 66.6%, and 94.2% at the cutoff point of 1.3 and 63.2%, 93%, 75%, and 88.3% at the cutoff point of 2.6, respectively. The accuracy and AUROC of this panel were 89.7 and 0.936 (95%CI: 0.884-0.898). The FIB4 panel was able to differentiate the two groups of patients with and without advanced fibrosis (p<0.001). It was also stated that this panel can prevent 68% of unnecessary biopsies at levels less than 1.3, and that it is suitable for both ruling out and diagnosis of advanced liver fibrosis [16]. In the study of McPherson et al, the FIB4 panel was able to differentiate the groups of patients with and without advanced fibrosis (p<0.001). In Cheah et al study FIB4 was introduced as available parameters to

identify fibrosis (6). AUROC for this panel was 0.86 (95%CI: 0.78- 0.94) and sensitivity, specificity, PPV, and NPV were 85%, 65%, 36%, and 95% at the cutoff point of 1.3 and 26%, 98%, 75%, and 85% at the cutoff point of 3.25, respectively. It was also stated that this panel can prevent 62% of unnecessary biopsies at levels less than 1.3, that this panel can rule out advanced fibrosis and its use can reduce unnecessary biopsy for people with mild fibrosis (19).

The panel's ability to differentiate the two groups of patients with and without advanced fibrosis and its good AUROC indicates the acceptable diagnostic power of this panel in the study population. Despite the panel's low sensitivity, its high specificity indicates that it can rule out rather than detecting advanced fibrosis.

In general, none of the panels had enough sensitivity for the diagnosis of advanced fibrosis. Given their relatively good specificity, these panels are generally better to rule out rather than to diagnose advanced fibrosis by comparison of the panels' diagnostic power (Table 5), the APRI and FIB4 panels are introduced as panels with high diagnostic power .

Conclusion

We concluded that the FIB4 panel is calculated first for the patient with NAFLD. For values less than 1.45, it is recommended to follow-up patients with other tests and examinations; for values greater than 3.25, it is recommended to perform more detailed investigations through Fibro Scan; and for values between 1.45 and 3.25, it is recommended to measure the APRI panel; in this regard, cases with APRI values of <0.88 and >0.88 are recommended to follow-up and perform Fibro Scan, respectively. Given the cost-effectiveness of these panels, their ease of calculation, and noninvasiveness, they can be used as useful tools for following up the patients and also for predicting progression to advanced fibrosis. It is recommended to develop a new and more accurate index for clinical use, based on the criteria of the three panels of FIB4, APRI, and NIPPON, and perform further studies on these panels. As a limitation of this study, the results of Fibro Scan were considered as the standard method, while the biopsy was the gold standard in other studies; this has somewhat diminished the accuracy of this study.

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Author contributions

Conception and design: **FMGh**, **ASh**; analysis and interpretation of the data: **FJ**, **SD**, **SY**, **SFA**;formal analysis: **FJ**, **ASh**; drafting of the article: **FJ**, **SD**, **SY**, **SFA**; critical revision of the article for important intellectual content: **FJ**, **ASh**; **KA** project administration: **FMGh**, **FJ**, **SFA**; final approval of the article: **ASh**, **FJ**, **SFA**. All authors approved its final version and agreed to be accountable for all aspects of the study.

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Ethical approval and consent to participate

This study was registered in the Research Department of Guilan University of Medical Sciences with the ethics code of IR.GUMS.1396.114. This manuscript has not been published in whole or in part. All authors have read the manuscript and have agreed that the work is ready for submission and accept responsibility for its contents. Before participation, all participants received oral and written study information and signed a written consent form.

Competing of interest

None to declare.

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