European Review for Medical and Pharmacological Sciences 2024; 28: 3104-3111

The diagnostic utility of FIB-4 as a non-invasive tool for liver fibrosis scoring among NAFLD patients: a retrospective cross-sectional study

J. AMER[1], M. ALNEES[2,3], M. SALAMEH[2], A. DARAGHMEH[2], A. KABHA[2], Y. ALHABIL[2], A. DARWISH[2], D. NAJAJRA[2], M. AWWAD[2], N. ABU HAMDEH[2], Q. ABDOH[1,4]

[1]Department of Allied Sciences, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[2]Department of Medical Sciences, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[3]Harvard Medical School Postgraduate Medical Education, Global Clinical Scholars Research Training Program, Boston, USA
[4]Department of Internal Medicine, GI and Endoscopy Unit, An-Najah National University Hospital, Nablus, Palestine

J. Amer and M. Alnees contributed equally

Abstract. – OBJECTIVE: Liver biopsy is the gold standard method to evaluate patients with non-alcoholic fatty liver disease (NAFLD). However, due to its several limitations and complications, a reliable and non-invasive marker is required to assess liver fibrosis. In this study, we compared the performance of the FIB-4 index [based on age, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels and platelets count] with the Scheuer scoring system of liver biopsies to evaluate the diagnostic utility of FIB-4 among NAFLD patients with different liver fibrosis severities.

PATIENTS AND METHODS: A cross-sectional study was conducted at An-Najah National University Hospital (NNUH) in Palestine. The FIB-4 index was calculated using laboratory data for 128 NAFLD patients who underwent liver biopsies between November 2014 and July 2022. The results of FIB-4 were compared with the Scheuer scoring system of liver biopsies (using F0, F1+F2, F3+F4) to determine the sensitivity and specificity of FIB-4 in detecting and staging liver fibrosis.

RESULTS: Out of 128 patients involved in our study, 49 of them had advanced fibrosis according to liver biopsy (F3+F4), where their FIB-4 indices showed 87% sensitivity at 1.45 cut off point and 87% specificity at 3.25 cut off point.

CONCLUSIONS: The FIB-4 index may be used as a screening tool in the primary care setting. To raise awareness of liver diseases, this non-invasive, inexpensive, simple, and quick marker could identify people in need of further liver fibrosis evaluation and diagnosis.

Key Words:
FIB-4, NAFLD, Liver fibrosis, Liver biopsy.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by an inflammatory fatty liver without secondary causes such as drug use, excessive alcohol intake, or other metabolic issues[1]. Yet, it is thought to be associated with impaired insulin function, metabolic disorders, obesity, and diabetes[2]. Additionally, NAFLD remains largely symptomless most of the time. Still, it can progress to non-alcoholic steatohepatitis (NASH) or cirrhosis, or even liver cancer (HCC), which is more severe and devastating[3,4]. For this reason, liver transplantation is expected to become necessary in the next decade[5]. Early detection and effective treatment of liver fibrosis in NAFLD are crucial. Because it is associated with other undesirable outcomes, for example, cardiac arrests, ischemic strokes, and metabolic abnormalities. That is why its importance extends beyond its effect on liver function[6].

Nowadays, it is considered the leading cause of chronic liver disease in developed countries due to its epidemic-status development[1]. Globally, 6% to 35% of individuals are thought to already have

Corresponding Authors: Qusay Abdoh, MD; e-mail: qusayabdoh@najah.edu; Mohammad Alnees, MD; e-mail: a2011z2012z2013@gmail.com

NAFLD[7]; on the other hand, the Middle East seems to have the highest prevalence of NAFLD (32%)[8]. In response to this huge, constantly growing prevalence, which causes a significant economic and clinical burden, we must optimize its prevention, diagnosis, and treatment[9]. It was always necessary to execute a liver biopsy to diagnose the progressive form of the disease (NASH). Nevertheless, its invasiveness and involvement of sampling and interobserver variability made scaling up impossible for the 1 billion people affected[10]. This has led to the development of alternative noninvasive approaches, which have been the topic of intensive research over the previous decade[11].

One of these non-invasive techniques we used in our research is the fibrosis index based on 4 factors (FIB-4), which was developed to pinpoint liver fibrosis in HIV/hepatitis C virus (HCV) coinfection by combining age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet counts. It was calculated by the formula of [age (years) × AST (U/L)] / (platelet (10^9/L) × (ALT (U/L))1/2][12]. Its low cost and accessibility in routine clinical practice made the fibrosis-4 (FIB-4) tool one of the most widely validated and advised tests. Among NAFLD patients, these scores are most convincing at identifying advanced fibrosis (F3-F4) and excluding significant fibrosis[1]. This index is valuable because it is based on simple, reachable test values that are routinely measured in health checkups. Moreover, it is not influenced by body mass index (BMI) as in any other screening tests[13].

In this cross-sectional study, we evaluated the diagnostic utility of FIB-4 as a non-invasive method of scoring liver fibrosis among NAFLD patients at An-Najah National University Hospital and determined an optimal cutoff to rule out fibrosis. This will help us in the early detection of liver fibrosis among NAFLD patients and, on the other hand, enable us to use the most appropriate methods for its evaluation, progression, management, and treatment.

Patients and Methods

Ethical Consideration

The Ethical Committee of the Institutional Review Board (IRB) at An-Najah National University (ANNU)-Palestine has approved the study and protocols in accordance with ethical standards. Before participating, every participant signed informed consent.

Data privacy and confidentiality were highly assured for all participants. All data were collected, treated confidentially, and kept in a strictly safe place; moreover, they were available for and accessible by the researchers. Personal information is not mentioned in the manuscript. Participants were provided with written information about the study. They were informed that they had the right to participate or leave the study at any time without consequences.

Study Design and Population

This is a cross-sectional, non-interventional, retrospective study that mainly aims to identify liver fibrosis using the FIB-4 index in already diagnosed NAFLD patients by liver biopsy between November 2014 and July 2022. The study included 130 NAFLD patients who underwent liver biopsies at the Department of Gastroenterology, An-Najah National University Hospital.

Inclusion and Exclusion Criteria

Patients >18 years old who had risk factors for developing liver fibrosis and who showed fatty liver infiltrates (NAFLD) were enrolled in our research. Patients who consume alcohol and patients diagnosed with chronic hepatitis B or C were excluded from our research.

Liver Histological Examination

A minimum of 15 mm of liver tissue with at least 6 portal tracts is considered sufficient. For histological scoring, the Scheuer scoring system was adopted as the histological standard of liver fibrosis. Liver fibrosis was classified into 5 stages: F0, no fibrosis; F1, enlarged fibrotic portal tracts; F2, periportal or portal-portal septa but intact architecture; F3, fibrosis with architectural distortion but no obvious cirrhosis; and F4, cirrhosis, probable or definite (Table I)[14].

Patients were categorized into three groups. The first group, named minimal fibrosis, included patients with the F0 stage on the Scheuer scoring system; the second group, named mild fibrosis, included patients with stages F1 and F2, and the third group, named advanced fibrosis, included patients with stages F3 and F4.

FIB-4 Score

FIB-4 score was calculated using laboratory data based on the following formula (Table II): FIB-4 = [age (year) × AST (IU/L)]/ [PLT (10^9/L) × (ALT (U/L))1/2].

Table I. Liver histological examination.

	F0	F1	F2	F3	F4
Scheuer system[14]	No fibrosis	Enlarged, fibrotic portal tracts	Periportal or portal – portal septa but intact architecture	Fibrosis with architectural distortion but no obvious cirrhosis	Cirrhosis, probable or definite

Statistical Analysis

Descriptive statistics and Fisher's exact statistical test are performed. A *p*-value lower than 0.05 was considered significant. Results were analyzed using IBM SPSS Statistics Version 26 (IBM Corp., Armonk, NY, USA) predictive analytics software[15]. Data was expressed as means ± SD continuous variables and as frequencies (percentages) for categorical variables. Variables not normally distributed were expressed as medians (lower-upper quartiles). Variables were tested for normality using Kolmogorov-Smirnov test. The chi-square test was used to test the significance between categorical variables. The Kruskal-Wallis test, followed by the Mann-Whitney test, was used to test for differences in the means between categories.

Results

Patients (n=128) (ages ranging from 18 to 79 - the mean age was 44) with NAFLD had undergone liver fibrosis testing by liver biopsy during the study period. In the study population, there were more females than males (51.9% *vs.* 48.1%). We divided the study population into three groups based on liver fibrosis stages by the Scheuer system, i.e., minimal fibrosis (F0), mild fibrosis (F1+F2), and advanced fibrosis (F3+F4). Patients with different stages of liver fibrosis were found as follows: 40 (31.2%) patients with stage F0, 39 (30.5%) patients with stages F1 and F2, and 49 (38.3%) patients with stages F3 and F4. FIB-4 results were divided into 3 groups (the mean FIB-4 index was 2.69), as seen in Table III.

The FIB-4 score results were compared to liver fibrosis stages, as shown in Table IV. Of 54 patients with a FIB-4 score lower than 1.45, 23 had F0 fibrosis stage, 25 had F1 or F2 fibrosis stage, and only six patients had advanced fibrosis (F3, F4). 29 of 39 patients who had FIB-4 scores higher than 3.25 were concordant with liver biopsy results.

Table II. Liver histological examination.

<1.45	1.45-3.25	>3.25
No or minimal fibrosis	Mild or moderate fibrosis	Advanced fibrosis

To evaluate the efficacy of FIB-4 as a tool for detecting liver fibrosis, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FIB-4 for mild and advanced fibrosis (Table V). For mild fibrosis, we used 1.45 as a cutoff point, and any patient who had an FIB-4 score of more than 1.45 was considered positive for mild fibrosis. Two cutoff points were used for advanced fibrosis: 1.45 and 3.25.

We conducted further analysis to see if there was a cause for the mismatch between the FIB-4 score and liver biopsy results for some patients. We discovered that 40% of patients with mild to moderate fibrosis (F0, F1/F2) and a FIB-4 score higher than 3.25 had diabetes mellitus, and 40% had hypertension. On the other hand, from 31 patients with mild to advanced fibrosis (F1/F2, F3/F4) with FIB-4 scores lower than 1.45, 9 (29%) patients were found to have diabetes mellitus, and 7 (22.5%) patients had hypertension as shown in Table VI.

Discussion

The development of NASH, together with their elevated probability of acquiring progressively increasing degrees of liver fibrosis, makes assessing patients with NAFLD a critical priority. Additionally, individuals with advanced liver disease are more prone to complications like liver failure and even cancer. Therefore, accurately identifying the stage of fibrosis in these patients is essential for subsequent treatment decisions as well as assessing risks.

Incorporating noninvasive tests (NITs), including the FIB-4 index, NAFLD Fibrosis Score (NFS), and AST/platelet ratio index (APRI) into the diagnostic algorithms for NAFLD becomes

Table III. General characteristics of the population.

Characteristic variable		Count (n)	Percentage (%)
Gender	Female	67	51.9%
	Male	62	48.1%
Diabetes mellitus diagnosis	No	90	69.8%
	Yes	39	30.2%
Hypertension diagnosis	No	97	75.2%
	Yes	32	24.8%
Ischemic heart disease diagnosis	No	114	88.4%
	Yes	15	11.6%
Smoking status	No	104	80.6%
	Yes	25	19.4%
Family history of hepatic diseases	No	126	97.7%
	Yes	3	2.3%
Drug intake	No	30	23.3%
	Yes	99	76.7%
Cancer diagnosis	No	119	92.2%
	Yes	10	7.8%
Fibrosis stages	F0	40	31.2%
	F1/F2	39	30.5%
	F3/F4	49	38.3%
FIB-4	<1.45	54	42.2%
	1.45-3.25	35	27.3%
	>3.25	39	30.5%

Fibrosis index based on 4 factors (FIB-4).

Table IV. Correlation between FIB-4 score and liver biopsy results.

FIB-4 score (n and %)	Scheuer system			Total	p
	F0	F1, F2	F3, F4		
<1.45	23 (42.6%)	25 (46.3%)	6 (11.1%)	54	0.000
1.45-3.25	12 (34.3%)	9 (25.7%)	14 (40.0%)	35	
>3.25	5 (12.8%)	5 (12.8%)	29 (74.4%)	39	

Fibrosis index based on 4 factors (FIB-4).

Table V. Performance of FIB-4 in detecting mild and advanced fibrosis.

	Cutoff	Sensitivity	Specificity	PPV	NPV
Mild fibrosis (≥F1)	1.45	64%	57.5%	77%	42.5%
Advanced fibrosis (≥F3)	1.45	87%	60%	58%	88.8%
	3.25	59%	87%	74.4%	77%

Positive predictive value (PPV), negative predictive value (NPV).

Table VI. Variables associated with discordant liver biopsy and FIB-4 results.

	25.6% of those with FIB-4 score >3.25 had no/minimal fibrosis (F0) or mild/moderate (F1/F2)	57.4% of those with FIB-4 score <1.45 had mild/moderate (F1/F2) or advanced (F3/F4)
Diabetes mellitus	40%	29%
Hypertension	40%	22.5%
Ischemic heart disease	20%	6.5%
Smoking status	20%	19%
Cancer diagnosis	10%	6.5%

necessary and clinically beneficial as its stage can often predict long-term clinical outcomes. These models possess exceptional predictive capabilities when it comes to discerning potential diseases or fatalities related specifically to the liver's functioning. Indeed, it has been demonstrated that these results sometimes even surpass those obtained through traditional methods such as liver biopsy when it comes down to accuracy levels attained by medical practitioners, thereby proving invaluable in clinical settings. By employing non-invasive methods, a wealth of valuable, actionable data regarding the fibrosis stage becomes readily accessible, bypassing the need for painful, invasive procedures. Consequently, this expedites the process of risk stratification, facilitating prompt decision-making regarding preventative treatments aimed at enhancing patient outcomes and halting disease progression[14,16-19].

The utility of the FIB-4 index as a screening tool has primarily been studied[20] in patients with hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV) infection, amongst other high-prevalence populations at secondary centers. However, its comparative effectiveness to liver stiffness measurement (LSM) using Fibroscan remains uncertain. Although encouraging results[20,21] have emerged regarding the potential of FIB-4 for non-invasive liver fibrosis scoring amongst certain patient groups, further evaluation is needed before definitive conclusions can be drawn.

This investigation aimed to examine whether utilizing the FIB-4 index could successfully identify levels of liver fibrosis in those afflicted by NAFLD. The study consisted of a group comprising 128 subjects who were assessed by taking a sample of a biopsy. Our analysis indicates that utilizing the Scheuer system effectively distinguishes between different severity levels in cases of non-alcoholic fatty liver disease, where methods like the Fibro Test or APRI test may not be effective for non-invasive detection of hepatic conditions.

The distribution of liver fibrosis stages resulted in findings indicating that approximately thirty-one percent (31%) presented minimal fibrosis (F0), while roughly thirty-point five (30.5%) indicated milder forms of fibrosis (F1+F2); advanced fibrosis (F3+F4) was observed in the majority of cases which accounted for thirty-eight-point three (38.3%) percent of those assessed.

In analysis, the FIB-4 index underwent groupings based on cutoff points indicating less than 1.45, between 1.45 and 3.25, and greater than values denoting >3.25.

In NAFLD patients with liver fibrosis, results were compared using the FIB-4 index and the Schueuer scoring system. Of the 54 cases with a FIB-4 score <1.45, 48 (88.9%) agreed with the liver biopsy results (Scheuer F0-F1-F2). To exclude severe fibrosis (F3-F4), 39 cases had a FIB-4 score >3.25; 29 (74%) of them were concordant with the liver biopsy findings (Scheuer F3-F4), and 10 (26%) had disagreeing results (F0-F1-F2).

The FIB-4 test is an effective, noninvasive tool that can help healthcare professionals identify individuals with metabolic co-factors who are at risk of developing liver disease. In recognition of its utility, the European Association for the Study of the Liver (EASL) has included it in its clinical practice guideline (CPG)[22] on noninvasive tests (NITs). According to the EASL CPG, patients with a FIB-4 score lower than 1.3 have a low-risk profile and do not need a referral to specialist liver clinics, provided they complete follow-up testing after one or three years – depending on their risk category – for monitoring purposes. However, patients with a FIB-4 score equal to or greater than 1.3 should be considered for additional assessment through another noninvasive diagnostic test called Fibroscan followed by re-stratification accordingly[22].

NPV and sensitivity of the test were 88.8% and 87%, respectively, at an advanced fibrosis cutoff point of 1.45, which allowed to exclude nearly 89% of patients suffering from advanced fibrosis. Using the upper cutoff value of 3.25, 74.4% of patients with advanced fibrosis were correctly classified.

The findings of various studies[23-26] showed that FIB-4 had an NPV of 94.7%, 74.3% sensitivity, and 80% specificity for advanced fibrosis at cutoff point 1.45; however, the upper cutoff value of 3.25 to diagnose significant fibrosis had a sensitivity of 59% and a specificity of 74%.

The primary goal of further analysis was to determine why some patients' liver biopsy results varied from their corresponding FIB-4 scores. After reviewing patient records closely, researchers identified that individuals with mild to moderate fibrosis levels (F0, F2) registering a score higher than 3.25 on the FIB-4 test showed an elevated incidence of co-existing conditions such as diabetes mellitus or hypertension - around 40% for both variables, respectively. In contrast, patients displaying mild to severe damage levels (F1, F4) but scoring below 1.45 on the test had considerably lower percentages for both comorbidities.

These findings are consistent with previous studies[27,28]. Therefore, this suggests that if someone has preexisting conditions like hypertension or diabetes mellitus, this can significantly influence their corresponding FIB-4 test results, leading to discordance with liver biopsy results. Consequently, it's essential to consider such factors while interpreting FIB-4 scores in a clinical setting.

When it comes to advanced fibrosis, the FIB-4 index can be used similarly to magnetic resonance elastography. Thus, it may be possible to predict the risk of HCC using the FIB-4 index. In previous studies[29], chronic hepatitis B (CHB) and NAFLD patients with a high FIB-4 index were more likely to develop HCC. Hepatic fibrosis is still diagnosed through liver biopsy, which remains the gold standard. It is, however, unlikely that invasive biopsies can be performed on all patients with NAFLD-CHB, so the FIB-4 index might be a more appropriate tool to evaluate hepatic fibrosis. In developing nations, the constitutive FIB-4 parameters (age, AST, ALT, platelet count) are already included in the standard liver disease workup[14].

Our research results have many limitations. As a first concern, its retrospective design may impact the sensitivity and specificity of the evaluated tests. Second, the study setting (specialty care hospitals for NAFLD patients) may explain the high prevalence of cirrhosis and advanced fibrosis since many cases of cirrhosis go untreated and neglected. Thirdly, the comparison is very challenging. The FIB-4 tool's results are compared with those of the gold-standard fibrosis evaluation tool. However, the degree of fibrosis may also be overestimated or underestimated by liver biopsy (LB). Finally, the technical difficulties involved in examining liver biopsy samples would make them unreliable.

Additional studies are required to confirm that FIB-4 is as accurate as liver biopsy in risk stratification for liver-related morbidity and mortality. Using more sophisticated models to prognosticate NAFLD events may improve the performance and clinical utility of non-invasive markers.

Conclusions

The FIB-4 index may be used as a screening tool in the primary care setting. To raise awareness of liver diseases, this non-invasive marker, which is inexpensive, simple, and quick, could identify people in need of further liver fibrosis evaluation.

Conflict of Interest
The authors declare that they have no conflict of interest.

Funding
This work was supported by An-Najah National University.

Authors' Contributions
All authors contributed considerably to this work. J.A, Q.A, M.A, M.A, D.N, and N.A. were responsible for designing the study and drafting the manuscript. J.A, Y.A, and M.A analyzed the data, M.A, M.S, A.D, A.K, A.D, and N.A were responsible for the data collection and interpretation. All authors had reviewed, edited and approved the final version of the manuscript.

Ethics Approval
Ethical approval was taken from the Institutional Review Board (IRB) of An-Najah National University (No.: Med. August, 2022/34).

Informed Consent
Informed consent was obtained from all individual participants included in the study, which was conducted according to the Helsinki Declaration of Human Rights.

Acknowledgments
The authors acknowledge all participants in this study for their cooperation and contribution. As well as thank NNUH and its staff.

Availability of Data and Materials
The data sets supporting the results of the current research are available from the corresponding authors upon request.

ORCID ID
Mohammad Alnees: 0000-0002-5577-8499
Abdalaziz Darwish: 0000-0002-3231-3672
Duha Najajra: 0009-0007-3561-2380
Qusay Abdoh: 0009-0001-4356-8240

References

1) Zambrano-Huailla R, Guedes L, Stefano JT, de Souza AAA, Marciano S, Yvamoto E, et al. Diagnostic performance of three non-invasive fibrosis scores (Hepamet, FIB-4, NAFLD fibrosis score) in NAFLD patients from a mixed Latin American population. Ann Hepatol 2020; 19: 622-626.
2) Mitsala A, Tsalikidis C, Romanidis K, Pitiakoudis M. Non-Alcoholic Fatty Liver Disease and Extrahepatic Cancers: A Wolf in Sheep's Clothing? Current Oncology 2022; 29: 4478-4510.

3) Pinyopornpanish K, Khoudari G, Saleh MA, Angkurawaranon C, Pinyopornpanish K, Mansoor E, Dasarathy S, McCullough A. Hepatocellular carcinoma in nonalcoholic fatty liver disease with or without cirrhosis: a population-based study. BMC Gastroenterol 2021; 21: 394.
4) Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, Eguchi Y, Wong VW, Negro F, Yilmaz Y, Romero-Gomez M, George J, Ahmed A, Wong R, Younossi I, Ziayee M, Afendy A; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol 2019; 17: 748-755.e3.
5) Gangopadhyay A, Ibrahim R, Theberge K, May M, Houseknecht KL. Non-alcoholic fatty liver disease (NAFLD) and mental illness: Mechanisms linking mood, metabolism and medicines. Front Neurosci 2022; 16: 1926.
6) Campos-Murguía A, Ruiz-Margáin A, González-Regueiro JA, Macías-Rodríguez RU. Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease. World J Gastroenterol 2020; 26: 5919.
7) Sanai FM, Abaalkhail F, Hasan F, Farooqi MH, Nahdi NA, Younossi ZM. Management of nonalcoholic fatty liver disease in the Middle East. World J Gastroenterol 2020; 26: 3528-3541.
8) Younossi ZM, Yilmaz Y, Yu ML, Wai-Sun Wong V, Fernandez MC, Isakov VA, Duseja AK, Mendez-Sanchez N, Eguchi Y, Bugianesi E, Burra P, George J, Fan JG, Papatheodoridis GV, Chan WK, Alswat K, Saeed HS, Singal AK, Romero-Gomez M, Gordon SC, Roberts SK, El Kassas M, Kugelmas M, Ong JP, Alqahtani S, Ziayee M, Lam B, Younossi I, Racila A, Henry L, Stepanova M; Global NASH Council. Clinical and Patient-Reported Outcomes From Patients With Nonalcoholic Fatty Liver Disease Across the World: Data From the Global Non-Alcoholic Steatohepatitis (NASH)/ Non-Alcoholic Fatty Liver Disease (NAFLD) Registry. Clin Gastroenterol Hepatol 2022; 20: 2296-2306.e6.
9) Ando Y, Jou JH. Nonalcoholic Fatty Liver Disease and Recent Guideline Updates. Clin Liver Dis (Hoboken) 2021; 17: 23-28.
10) Ajmera V, Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis. Mol Metab 2021; 50: 101167.
11) Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019; 156: 1264-1281.e4.
12) Xu XL, Jiang LS, Wu CS, Pan LY, Lou ZQ, Peng CT, Dong Y, Ruan B. The role of fibrosis index FIB-4 in predicting liver fibrosis stage and clinical prognosis: A diagnostic or screening tool? J Formos Med Assoc 2022; 121: 454-466.
13) Alexander M, Loomis AK, Fairburn-Beech J, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Avillach P, Egger P, Kendrick S, Waterworth DM, Sattar N, Alazawi W. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med 2018; 16: 131.
14) Lee J, Vali Y, Boursier J, Spijker R, Anstee QM, Bossuyt PM, Zafarmand MH. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. Liver Int 2021; 41: 261-270.
15) IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.
16) Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. Gastroenterology 2005; 129: 113-121.
17) Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015; 149: 389-397.e10.
18) Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers. J Hepatol 2018; 68: 305-315.
19) Viganò M, Pugliese N, Cerini F, Turati F, Cimino V, Ridolfo S, Rocchetto S, Foglio F, Terrin M, La Vecchia C, Rumi MG, Aghemo A. Accuracy of FIB-4 to Detect Elevated Liver Stiffness Measurements in Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in Referral Centers. Int J Mol Sci 2022; 23: 12489.
20) Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; 43: 1317-1325.
21) Bril F, McPhaul MJ, Caulfield MP, Clark VC, Soldevilla-Pico C, Firpi-Morell RJ, et al. Performance of Plasma Biomarkers and Diagnostic Panels for Nonalcoholic Steatohepatitis and Advanced Fibrosis in Patients With Type 2 Diabetes. Diabetes Care 2020; 43: 290-297.
22) Bril F, McPhaul MJ, Caulfield MP, Clark VC, Soldevilla-Pico C, Firpi-Morell RJ, Lai J, Shiffman D, Rowland CM, Cusi K. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. J Hepatol 2021; 75: 659-689.
23) Boursier J, Hagström H, Ekstedt M, Moreau C, Bonacci M, Cure S, Ampuero J, Nasr P, Tallab L, Canivet CM, Kechagias S, Sánchez Y, Dincuff E, Lucena A, Roux M, Riou J, Trylesinski A, Romero-Gomez M. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol 2022; 76: 1013-1020.

24) Boursier J, Guillaume M, Leroy V, Irlès M, Roux M, Lannes A, Foucher J, Zuberbuhler F, Delabaudière C, Barthelon J, Michalak S, Hiriart JB, Peron JM, Gerster T, Le Bail B, Riou J, Hunault G, Merrouche W, Oberti F, Pelade L, Fouchard I, Bureau C, Calès P, de Ledinghen V. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. J Hepatol 2019; 71: 389-396.

25) Patel YA, Gifford EJ, Glass LM, Turner MJ, Han B, Moylan CA, Choi S, Suzuki A, Provenzale D, Hunt CM. Identifying Nonalcoholic Fatty Liver Disease Advanced Fibrosis in the Veterans Health Administration. Dig Dis Sci 2018; 63: 2259-2266.

26) Rigor J, Diegues A, Presa J, Barata P, Martins-Mendes D. Noninvasive fibrosis tools in NAFLD: validation of APRI, BARD, FIB-4, NAFLD fibrosis score, and Hepamet fibrosis score in a Portuguese population. Postgrad Med 2022; 134: 435-440.

27) Boursier J, Canivet CM, Costentin C, Lannes A, Delamarre A, Sturm N, Le Bail B, Michalak S, Oberti F, Hilleret MN, Irles-Depé M, Fouchard I, Hermabessiere P, Barthelon J, Calès P, Cariou B, de Ledinghen V, Roux M. Impact of Type 2 Diabetes on the Accuracy of Noninvasive Tests of Liver Fibrosis With Resulting Clinical Implications. Clin Gastroenterol Hepatol 2023; 21: e325.

28) Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009; 7: 1104-1112.

29) Kim M, Lee Y, Yoon JS, Lee M, Kye SS, Kim SW, Cho Y. The fib-4 index is a useful predictor for the development of hepatocellular carcinoma in patients with coexisting nonalcoholic fatty liver disease and chronic hepatitis b. Cancers (Basel) 2021; 13: 2301.