Annals of Hepatology 28 (2023) 100873

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Special Issue on Genomic Medicine in Obesity and Chronic Liver Damage

Diagnostic accuracy of blood biomarkers and non-invasive scores for the diagnosis of NAFLD and NASH: Systematic review and meta-analysis

Daniela Contreras[a], Alejandra González-Rocha[b], Patricia Clark[a,c], Simón Barquera[b], Edgar Denova-Gutiérrez[b,*]

[a] Faculty of Medicine, National Autonomous University of Mexico, Mexico City, Mexico
[b] Nutrition, and Health Research Center, National Institute of Public Health, Cuernavaca, Mexico
[c] Clinical Epidemiology Research Unit, Children Hospital of Mexico "Federico Gómez", Mexico City, Mexico

ARTICLE INFO

Article History:
Received 25 July 2022
Accepted 13 October 2022
Available online 10 November 2022

Keywords:
Non-invasive risk scores
Meta-analysis
Systematic review
Fatty liver disease

ABSTRACT

Introduction and objectives: Fatty liver disease is an important public health problem. Early diagnosis is critical to lower its rate of progression to irreversible/terminal stages. This study aimed to evaluate the accuracy of non-invasive prediction scores for fatty liver disease (NAFLD and NASH) diagnosis in adults.
Materials and methods: A search was conducted in 10 databases, a qualitative synthesis of 45 studies, and quantitative analysis of the six most common scores. There were 23 risk scores found for NAFLD diagnosis and 32 for NASH diagnosis. The most used were Fatty Liver Index (FLI), aspartate aminotransferase (AST) to Platelet Ratio Index, Fibrosis-4 Index (FIB-4), AST/alanine aminotransferase (ALT) ratio, BARD score, and NAFLD fibrosis score (NFS).
Results: The results from the meta-analysis for FLI: Area under the curve (AUC) of 0.76 (95% Confidence Interval [CI] 0.73, 0.80), sensitivity 0.67 (CI 95% 0.62, 0.72) and specificity 0.78 (CI 95% 0.74, 0.83). The AST to Platelet Ratio Index: AUC 0.83 (CI 95% 0.80, 0.86), sensitivity 0.45 (95% CI 0.29, 0.62), and specificity of 0.89 (95% CI 0.83, 0.92). The NFS: AUC of 0.82 (CI 95% 0.78, 0.85), sensitivity 0.30 (CI 95% 0.27, 0.33) and specificity 0.96 (CI 95% 0.95,0.96).
Conclusions: The FLI for NAFLD and AST to Platelet Ratio Index for NASH were the risk scores with the highest prognostic value in the included studies. Further research is needed for the application of new diagnostic risk scores for NAFLD and NASH.

1. Introduction

Fatty liver disease (FLD) is defined as the accumulation of liver fat (hepatic steatosis) in >5% of hepatocytes with or without inflammation and fibrosis [1]. The spectrum of FLD has been evolving; for example, NAFLD encompasses two subtypes, simple fatty liver and NASH, both with an absence of a coexisting etiology of chronic liver disease or secondary cause of steatosis, including drug use, significant alcohol consumption (>20g daily in females or >30 g in males), viral hepatitis, inherited or acquired metabolic states [2–4]. Recently, the term metabolic associated fatty liver disease (MAFLD) has emerged, which includes hepatic steatosis in combination with one criterion for metabolic dysfunction (i.e., overweight or obesity, type 2 diabetes (T2D) or evidence of metabolic dysregulation) [5]. Metabolic syndrome continues to be one of the strongest risk factors for NAFLD [6]. Patients with NAFLD have a disease progression that could include liver fibrosis, cirrhosis, and hepatocellular carcinoma [7].

NAFLD is a significant public health problem, as it is prevalent in about a quarter of the world's adult population [2,5]. According to the Global Burden of Disease Study 2019, NAFLD is accountable for 4.36 million Years of Life Lost (95% uncertainty interval [UI]: 3.30, 5.59) and 4.42 million Global Disability-Adjusted Life-Years (95% UI: 3.35, 5.67) [8]. Early diagnosis of individuals with a high risk for developing NAFLD is critical to diminish its rate of progression to irreversible and terminal stages; and to allow effective management of its comorbidities to address its poor health-related quality of life and the economic burden to the patients and their families [9].

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; FLD, fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; T2D, type 2 diabetes; UI, uncertainty interval; BMI, body mass index; EASL, European association for the study of the liver; EASD, European association for the study of diabetes; EASO, European association for the study of obesity; DTA, diagnostic test accuracy; AUC, area under the curve; MeSH, medical subject headings; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis 4 index; NFS, NAFLD fibrosis score; APRI, AST-to-platelet ratio index; AAR, AST/ALT ratio; FLI, fatty liver index Se, sensitivity; Sp, specificity; HSI, hepatic steatosis index; LFS, liver fat score.

* Corresponding author.
E-mail address: edgar.denova@insp.mx (E. Denova-Gutiérrez).

https://doi.org/10.1016/j.aohep.2022.100873

Currently, the assessment of NAFLD can either be done by liver histology, imaging techniques, blood biomarkers, or non-invasive prediction scores [4]. Liver histology is the gold standard to diagnose and stage its severity; however, its use has been associated with potential complications and interobserver variability of individual pathological features. In addition, imaging techniques, such as ultrasound or magnetic resonance imaging, are costly and usually unavailable in primary care settings [2,10]. Blood biomarkers or non-invasive prediction scores using biochemical and clinical parameters offer a cost-effective approach for NAFLD or NASH diagnosis [10]. Also, the uneven distribution of steatosis, inflammation, or fibrosis throughout the liver indicates that scoring systems could accurately reflect the risk for liver disease; highlighting the need to evaluate their efficacy in the affected population [11]. Previous studies described well known predictive scores; for example: Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS) developed in a cohort of patients with NAFLD and could be used to predict the presence of advanced fibrosis [10], and the Fatty Liver index (FLI) to detect the presence of steatosis. The European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) recommend the use of non-invasive scores whenever imaging tools are not available or feasible [12]. Nevertheless, new models have been introduced and the validation of other models has progressed.

Therefore, the purpose of this paper is to identify and evaluate the diagnostic accuracy of blood biomarkers and non-invasive scores, for the diagnosis of NAFLD or NASH in adults, compared to image studies or liver biopsy, by performing a systematic review and meta-analysis.

2. Methods

The present study was performed following the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (DTA) methodology [13] and Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy (PRISMA-DTA) statement [14]. PROSPERO:CRD42021254842 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021254842).

2.1. Inclusion criteria

2.1.1. Types of studies and participants

Cohort and cross-sectional studies published between January 2010 and January 2022 were included. A range of 11 years was established considering previous reviews to provide new evidence. The population included were apparently healthy adults (>18 years) and adults diagnosed with NAFLD, without any prior diagnosis of any other acute or chronic disease or intervention.

2.1.2. Risk scores

Studies with risk scores suggested by previous guidelines [12] as FLI and NFS, were included. Also, every study that reported the development or the validation of a non-invasive risk score for NAFLD or NASH. Risk scores may consist of one or more variables; all of those developed or analyzed in each article were included.

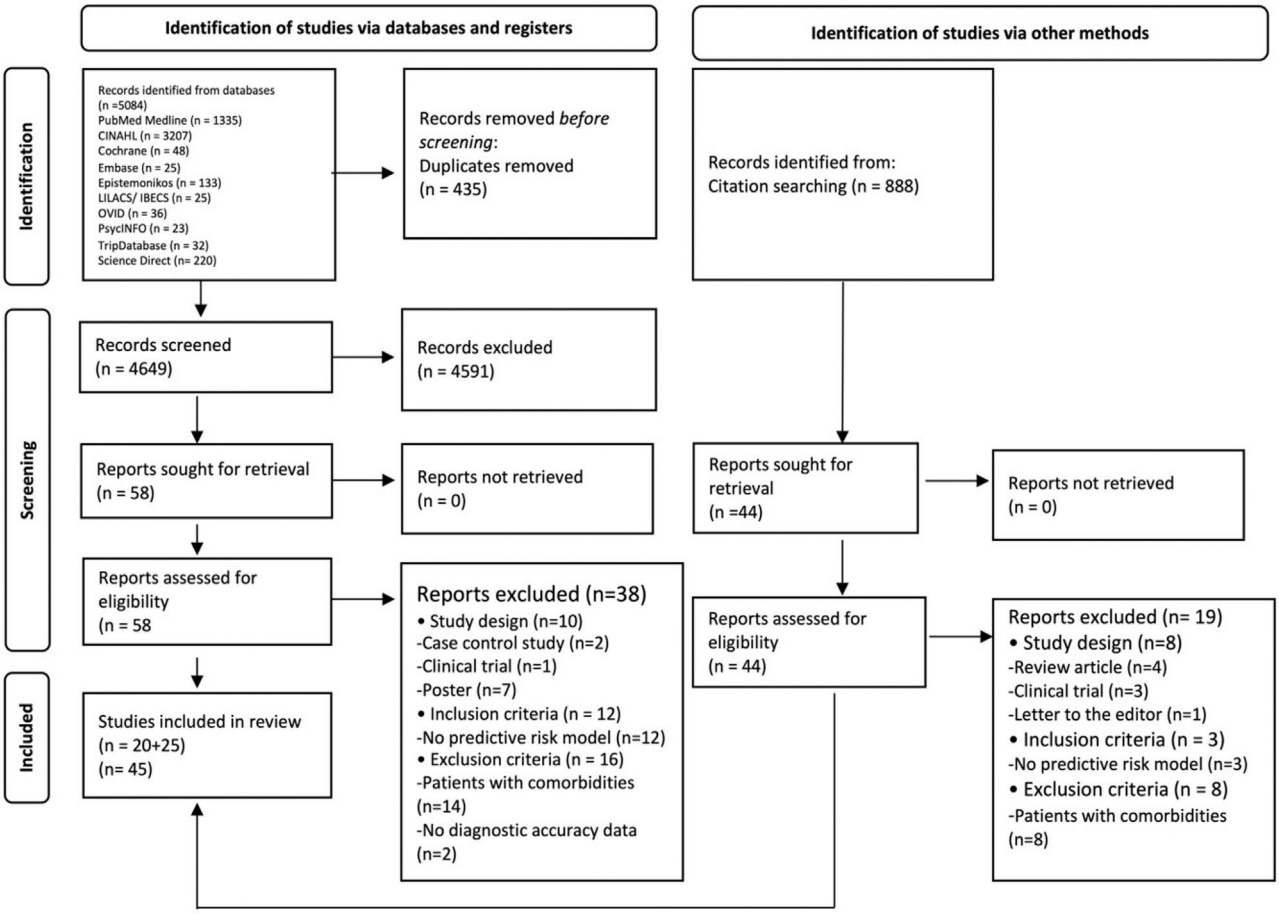

Fig. 1. Flow diagram of the identification, screening and studies selection.

Table 1
Analysis of sensitivity, specificity, statistic-c or AUC of models.

Author & Year	Model Name		AUC (95% CI)	Sensitivity	Specificity
Non-Alcoholic Fatty Liver Disease (NAFLD)[a]					
Lee et al., 2010 [22]	Hepatic Steatosis Index		0.82 (0.81-0.83)	0.45	0.93
Park et al., 2011 [23]	Index System for NAFLD		0.80 (0.75-0.84)	0.72	0.76
Miyake et al., 2012 [26]	NAFLD Index	Males	0.87 (0.86-0.89)	0.78	0.81
		Females	0.87 (0.86-0.88)	0.84	0.76
Koehler et al., 2013 [29]	Fatty Liver Index		0.81 (0.80-0.83)	0.60	0.82
	Lipid Accumulation Product		0.79 (0.77−0.80)	(NA)	(NA)
Cheung et al., 2014 [30]	Fatty Liver Index		0.76 (0.74-0.77)	0.68	0.74
	Hepatic Steatosis Index		0.73 (0.71-0.75)	0.66	0.69
	Lipid Accumulation Product		0.74 (0.72-0.76)	(NA)	(NA)
	Liver Fat Score		0.77 (0.75-0.79)	0.26	0.96
Lee et al., 2014 [31]	Comprehensive model	Males	0.85 (NA)	0.67	0.85
		Females	0.89 (NA)	0.71	0.88
Otgonsuren et al., 2014 [32]	New Non-Invasive Model (ION)		0.77 (0.75-0.79)	0.60	0.82
	Fatty Liver Index		0.74 (0.72−0.76)	(NA)	0.80
Lesmana et al., 2015 [33]	NALFD Scoring System		0.83 (0.81-0.86)	0.76	0.70
Ruhl et al., 2015 [35]	Fatty Liver Index		0.78 (0.74-0.81)	0.69	0.77
	US Fatty Liver Index		0.80 (0.77-0.83)	0.62	0.88
Wang et al., 2015 [36]	Zhejiang University Index, ZJU Index		0.83 (0.82-0.84)	0.42	0.93
Yang et al., 2015 [34]	Fatty Liver Index	Males	0.83 (0.82-0.83)	0.63	0.80
		Females		0.62	0.86
De Ledinghen et al., 2016 [37]	Fatty Liver Index		0.66 (0.59-0.74)	(NA)	(NA)
Xia et al., 2016 [38]	Chinese NAFLD Score		0.74 (0.69-0.80)	0.79	0.62
Lin et al., 2017 [39]	Model to Predict Onset of NAFLD in Elderly Adults		0.68 (0.62-0.71)	0.40	0.86
Zhang Q. et al, 2017 [40]	NAFLD Risk Prediction Scoring Model		0.82 (0.78-0.85)	0.77	0.75
Zhang S. et al., 2017 [41]	Triglyceride glucose-body mass index		0.84 (0.82-0.85)	(NA)	(NA)
Zhou et al., 2017 [42]	NAFL Risk Score	Males	0.74 (0.73-0.75)	(NA)	(NA)
		Females	0.82 (0.81-0.84)	(NA)	(NA)
Feng et al., 2019 [43]	New Diagnostic formula of CAP (controlled attenuation parameter)		0.93 (NA)	0.88	0.90
Abd et al., 2020 [24]	NAFLD Screening Tool		0.81 (0.75-0.87)	0.87	0.62
Cai et al., 2020 [25]	NAFLD Prediction Model		0.86 (0.84-0.88)	(NA)	(NA)
Pan et al., 2020 [27]	Nomogram model for predicting the risk of NAFLD		0.84 (0.82-0.87)	0.55	0.89
Perazzo et al., 2020 [28]	Steato-ELSA		0.83 (0.81-0.85)	0.84	0.69
	Fatty Liver Index		0.82 (0.80-0.84)	0.77	0.74
	Hepatic Steatosis Index		0.80 (0.78-0.82)	0.94	0.45
	NAFLD-Liver Fat Score		0.77 (0.75-0.79)	0.79	0.67
Non-Alcoholic Steatohepatitis (NASH)					
Author & Year	**Model Name**	**Measurement**	**AUC (95% CI)**	**Sensitivity**	**Specificity**
Cales et al., 2010 [44]	NASH-CRN	Fibrosis	0.87 (NA)	(NA)	(NA)
	Metavir F>2	Fibrosis	0.94 (NA)	(NA)	(NA)
McPherson et al., 2010 [45]	AST/ALT ratio	Fibrosis	0.83 (0.74-0.91)	0.74	0.78
	APRI	Fibrosis	0.67 (0.54-0.80)	0.27	0.89
	BARD Score	Fibrosis	0.77 (0.68-0.87)	0.89	0.44
	FIB-4	Fibrosis	0.86 (0.78-0.94)	0.26	0.98
	NAFLD Fibrosis Score	Fibrosis	0.81 (0.71-0.91)	0.33	0.98
Raszeja et al., 2010 [56]	BARD Score	Fibrosis	0.82 (NA)	0.87	0.73
Adams et al., 2011 [60]	APRI	Fibrosis	0.79 (0.71−0.86)	0.72	0.77
	BARD Score	Fibrosis	0.70 (0.62−0.78)	0.60	0.72
	Hepascore	Fibrosis	0.81 (0.73−0.90)	0.76	0.84
	Fibrotest	Fibrosis	0.80 (0.73−0.88)	0.61	0.90
	FIB-4	Fibrosis	0.86 (0.80−0.92)	0.74	0.87
Kruger et al., 2011 [61]	APRI	Fibrosis	0.85 (NA)	0.75	0.86
	AST/ALT ratio	Fibrosis	0.61 (NA)	0.58	0.62
	NASH fibrosis score	Fibrosis	0.77 (NA)	0.76	0.69
Sumida et al., 2011 [62]	NAFIC Score	Fibrosis	0.80 (NA)	0.84	0.82
	NAFLD fibrosis score	Fibrosis	0.69 (NA)	0.33	0.95
Younossi et al., 2011 [63]	Model for NASH	Steatohepatitis	0.81 (0.70-0.89)	(NA)	(NA)
	Model for NASH-Related Fibrosis	Fibrosis	0.80 (0.68-0.88)	(NA)	(NA)
	Model for NASH-Related Advanced Fibrosis	Fibrosis	0.81 (0.70-0.89)	NA	(NA)
Sumida et al., 2012 [64]	FIB-4	Fibrosis	0.87 (NA)	0.48	0.95
	AST/ALT ratio	Fibrosis	0.79 (NA)	0.66	0.76
	APRI	Fibrosis	0.82 (NA)	0.67	0.81
	Age-platelet index	Fibrosis	0.81 (NA)	0.66	0.78
	NAFLD Fibrosis Score	Fibrosis	0.86 (NA)	0.33	0.96
	BARD Score	Fibrosis	0.77 (NA)	0.80	0.65
	N (Nippon) score	Fibrosis	0.72 (NA)	0.80	0.58
Cao et al., 2013 [65]	Non-invasive scoring system	Steatohepatitis	0.92 (0.87-0.97)	0.89	0.86
Demir et al., 2013 [66]	NIKEI	Fibrosis	0.97 (0.94-1.00)	0.67	0.96
	FIB-4	Fibrosis	0.93 (0.87-0.99)	(NA)	(NA)
	AST/ALT Ratio	Fibrosis	0.81 (0.72-0.90)	0.64	0.84
	NAFLD Fibrosis Score	Fibrosis	0.96 (0.92-0.99)	0.19	1.00
	BARD Score	Fibrosis	0.67 (0.55-0.78)	0.67	0.54
Alkhouri et al., 2014 [46]	OxNASH Score	Fibrosis	0.67 (0.58-0.77)	0.75	0.61
Cui et al., 2015 [47]	AST/ALT Ratio	Fibrosis	0.83 (0.73-0.92)	0.87	0.61
	APRI	Fibrosis	0.81 (0.70-0.91)	0.25	0.96
	BARD Score	Fibrosis	0.82 (0.72-0.91)	0.87	0.64
	FIB-4	Fibrosis	0.86 (0.78-0.95)	0.84	0.72
	NAFLD Fibrosis Score	Fibrosis	0.82 (0.70-0.93)	0.21	0.96
	Bonacini Cirrhosis Discriminant Score	Fibrosis	0.83 (0.73-0.93)	0.05	1.00
	Lok Index	Fibrosis	0.84 (0.73-0.94)	0.27	0.96
	NASH CRN Model	Fibrosis	0.80 (0.68-0.92)	(NA)	(NA)

(*continued*)

Table 1 (*Continued*)

Author & Year	Model Name		AUC (95% CI)	Sensitivity	Specificity
McPherson et al, 2015 [48]	FIB-4	Fibrosis	0.72 (0.62-0.82)	(NA)	(NA)
	NAFLD Fibrosis Score	Fibrosis	0.83 (0.74-0.92)	0.28	0.98
Boursier et al., 2016 [49]	APRI	Fibrosis	0.75 (NA)	0.61	0.76
	BARD Score	Fibrosis	0.70 (NA)	0.79	0.51
	FIB-4	Fibrosis	0.78 (NA)	0.76	0.67
	FibroMeter NAFLD	Fibrosis	0.76 (NA)	0.80	0.62
	FibroMeter V2G	Fibrosis	0.82 (NA)	0.77	0.72
	Fibrotest	Fibrosis	0.74 (NA)	0.81	0.57
	Hepascore	Fibrosis	0.78 (NA)	0.67	0.76
	NAFLD Fibrosis Score (NFS)	Fibrosis	0.73 (NA)	0.77	0.60
Loong et al., 2017 [50]	FM VCTE	Fibrosis	0.90 (NA)	0.18	0.99
	FibroMeter NAFLD	Fibrosis	0.77 (NA)	0.21	0.97
	APRI	Fibrosis	0.72 (NA)	(NA)	(NA)
	FIB-4	Fibrosis	0.70 (NA)	(NA)	(NA)
	NAFLD Fibrosis Score (NFS)	Fibrosis	0.65 (NA)	(NA)	(NA)
	BARD Score	Fibrosis	0.61 (NA)	(NA)	(NA)
	AST/ALT ratio	Fibrosis	0.56 (NA)	(NA)	(NA)
Tada et al., 2018 [51]	FIC-22	Steatohepatitis	0.82 (0.75-0.89)	0.89	0.63
	FIB-4	Steatohepatitis	0.76 (0.68-0.84)	(NA)	(NA)
Tasneem et al., 2018 [52]	GULAB Score	Steatohepatitis	0.76 (NA)	0.82	0.56
Chuah et al., 2019 [53]	MACK-3	Steatohepatitis	0.81 (0.74-0.87)	0.84	0.81
	Cytokeratin 18	Steatohepatitis	0.72 (0.65-0.80)	(NA)	(NA)
	BARD Score	Steatohepatitis	0.63 (0.55-0.72)	(NA)	(NA)
	NAFLD Fibrosis Score	Steatohepatitis	0.70 (0.63-0.78)	(NA)	(NA)
	FIB-4	Steatohepatitis	0.72 (0.65-0.79)	(NA)	(NA)
Siddiqui et al, 2019 [54]	FIB-4	Fibrosis	0.80 (0.78-0.82) [b]	0.28	0.97
	NAFLD Fibrosis Score	Fibrosis	0.78 (0.76-0.80) [b]	0.30	0.95
	APRI	Fibrosis	0.76 (0.74- 0.79) [b]	0.40	0.90
	AST/ALT ratio	Fibrosis	0.68 (0.66-0.71) [b]	0.26	0.90
Zhou et al., 2019 [55]	Novel Nomogram	Fibrosis	0.83 (0.76-0.90)	0.69	0.82
	APRI	Fibrosis	0.67 (0.56-0.78)	0.62	0.68
	NAFLD Fibrosis Score	Fibrosis	0.60 (0.48-0.72)	0.76	0.46
	FIB-4	Fibrosis	0.62 (0.51-0.74)	0.66	0.58
	BARD Score	Fibrosis	0.58 (0.46-0.70)	0.31	0.84
Gao et al., 2020 [57]	Novel diagnostic algorithm	Fibrosis	0.81 (0.74-0.87)	(NA)	(NA)
	MACK-3	Fibrosis	0.75 (0.68−0.82)	(NA)	(NA)
	FIB-4	Fibrosis	0.70 (0.62−0.76)	(NA)	(NA)
	NAFLD Fibrosis Score	Fibrosis	0.63 (0.55−0.70)	(NA)	(NA)
Ogawa et al., 2020 [58]	AAT-A3F	Steatohepatitis	0.70 (NA)	0.79	0.58
	APRI	Steatohepatitis	0.65 (NA)	0.51	0.81
	Cytokeratin 18	Steatohepatitis	0.67 (NA)	0.49	0.86
	FIB-4	Steatohepatitis	0.62 (NA)	0.64	0.67
	M2BPGi	Steatohepatitis	0.67 (NA)	0.55	0.80
Zheng et al., 2020 [59]	G-NASH model	Steatohepatitis	0.85 (0.76-0.93)	0.82	0.81

AST/ALT ratio, aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio; AAT-A3F, Tri-antennary trisialylated mono-fucosylated glycan of alpha-1 anti-trypsin; APRI, AST to Platelet Ratio Index; AUC, area under the curve; CRN, Clinical research network; FIB-4, Fibrosis 4 Score; M2BPGi, Mac-2 binding protein glycosylation isomer; NA, not available; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; T2D, type 2 diabetes; VCTE, Vibration-controlled transient elastography.

[a] Objective of diagnose: Steatosis.

[b] c-statistic.

2.1.3. Reference standard

Studies reporting abdominal ultrasound and/or liver biopsy to diagnose NAFLD or NASH were included.

2.1.4. Types of outcomes

Studies that include the area under the receiver operating characteristic curve (AUC) or C-Statistic, sensitivity (Se) and specificity (Sp) were included.

2.2. Exclusion criteria

Studies in which the participants had a known coexisting chronic condition, such as liver disease or cirrhosis, without enough data about diagnostic accuracy estimates and letters, posters, reviews, commentaries, predictive scores for mortality and machine learning were also excluded.

2.3. Electronic search

The search was conducted in 10 databases: Pubmed/Medline, CINAHL, Cochrane central library, Embase, Epistemonikos, LILACS/ IBECS, OVID, PsycINFO, TripDatabase, and ScienceDirect on October 2021 and updated on January 2022, with a search strategy previously designed, and adjusted per database using MeSH terms and others determined by consensus between the authors (Supplementary Table 1).

2.3.1. Other sources

The reference list of previous reviews and of the included studies were screened to identify additional studies.

2.4. Data collection and analysis

2.4.1. Selection of studies

All the duplicated studies were removed. Titles, abstracts, and full text studies were independently screened by duplicate (AGR/DC). A third reviewer (ED-G) was reached for disagreement (Fig. 1).

2.4.2. Data extraction

Data were extracted and organized by the characteristics of the risk scores. The data set included country, population, mean age, score and reference tests features, accuracy values, and study design.

2.4.3. Assessment of methodological quality

Two reviewers (AGR/DC) independently assessed the methodological quality using the QUADAS-2 tool [15] with RevMan 5.4 [16]. The QUADAS-2 tool analyzes four domains in terms of their risk of bias: (1) Patient Selection, (2) Index test, (3) Reference Standard, and 4) Flow and timing. Regarding applicability concerns, it evaluates three domains: (1) Patient selection, (2) Index test, and (3) Reference Standard. Each potential bias and concern were graded as high, low or unclear risk.

2.5. Statistical analysis and data synthesis

The meta-analysis included scores validated in four or more populations and provided complete data for sensitivity, specificity, and AUC with their respective 95% confidence intervals (95% CI), also identified with similar cut-off points for the outcomes and similar diagnostic objective. The cut-off values used for the classification and data synthesis for advanced fibrosis were aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) ≥1, AST/ALT ratio (AAR) ≥0.8, NAFLD Fibrosis Score (NFS) ≥0.676, BARD score ≥2, and Fibrosis-4 Index (FIB-4) ≥3.25 [17]. Studies with high applicability concerns or risk of bias were not included in the meta-analysis. Then, the two-by-two table to identify the True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN), was calculated using the formula proposed by Kim et al. [18], where P was defined as the number of patients, and S as the number of all subjects (TP= Se * P, TN=Sp * (S-P), FP= (S-P)-TN, FN=P-TP). The sensitivity, specificity, and AUC summary were carried out by bivariate mixed-effects binary regression modeling framework. The publication bias was evaluated by a funnel plot asymmetry, and a linear regression of log odds ratios on the inverse root of effective sample sizes was performed.

All the analyses were carried out with Stata 17.0 and the forest plots with RevMan 5.4.

2.5.1. Certainty of the evidence

The certainty of the evidence from the meta-analysis was performed according to the guidelines of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) Working group [19]. For the imprecision domain, it was classified using the standards published by Okeh and Okoro [20] to identify the relationship between AUC and diagnostic accuracy. Heterogeneity was calculated with Galbraith (radial) plots of standardized logit transformed proportion. The GRADE system classifies the evidence into four categories, from high to very low. All the analyses were carried out with the online software GRADEpro GDT Version 3.67 [21].

3. Results

3.1. Search results

A total of 5,972 studies were identified: 5,084 from databases and 888 from citation searching. After removing duplicates, 4,649 titles and abstracts were screened. Then, 4,591 studies were eliminated, 102 studies were analyzed in full-text, and 57 excluded. Finally, 45 studies were included [22–66]; 22 studies that evaluated diagnostic risk scores for NAFLD [22–43] and 23 that evaluated NASH [44–66]. Of those, 55 different diagnostic risk scores were extracted; their main characteristics are summarized in Supplementary Table 2.

3.2. Target population

The data included participants from 19 countries (China [25,27,36,39–43,56,57,59,65], the United States [32,35,46,45,54,63], and Japan [26,51,58,62,64]). Participants in the included studies had a mean age of 49 years which ranged from 35 to 76 years. For NAFLD, 19 of the studies included enrolled individuals who apparently were healthy [20–31,33–36,38–42], and three studies included patients with a previous NAFLD diagnosis [32,37,43]. Of the included studies for NAFLD diagnosis, 18 used as reference standard abdominal ultrasounds [22–31,33–36,38–42], four used liver biopsy [32,36,37,43], and for NASH diagnosis, all the studies included liver biopsy.

3.3. Risk scores for non-alcoholic fatty liver disease prediction

In the 22 studies for NAFLD diagnosis [22–43], 23 different risk scores were found (Supplementary Table 2). The most common were Fatty Liver Index (FLI) [28–30,32,34,35,37] and Hepatic Steatosis Index (HSI) [22,28,40]. The most common variables were body mass index (BMI) found in 17, triglycerides in 15, ALT in 14; and AST and fasting glucose in eight.

The AUCs ranged from 0.66 to 0.93. The highest AUC was for the New Diagnostic formula of controlled attenuation parameter by Feng et al. [43] and the lowest by de Lédinghen et al. [37]. The risk score with the highest sensitivity was HSI by Perazzo et al. [28], with 0.94 and a specificity of 0.45. The highest specificity was Liver Fat Score (LFS) by Cheung et al. [30], with 0.96 and a sensitivity of 0.26 (Table 1).

Table 2
Summary of the meta-analysis and certainty of the evidence.

Outcome	Number of studies (Number of patients)	GRADE classification
FLI test to screen NAFLD in healthy population Se: 0.67 (95% CI 0.61, 0.72) Sp: 0.77 (95% CI 0.69, 0.83)		
True positives	6 studies	⊕⊕⊕◯
False negatives	22146 patients	Moderate
True negatives	6 studies	⊕⊕⊕◯
False positives	29278 patients	Moderate
AST/ALT ratio test to screen NASH Se: 0.63 (95% CI 0.44, 0.79) Sp: 0.77 (95% CI 0.68, 0.84)		
True positives	6 studies	⊕⊕◯◯ [a,b,c]
False negatives	688 patients	Low
True negatives	6 studies	⊕⊕◯◯ [a,b,c]
False positives	2416 patients	Low
APRI test to screen NASH Se: 0.45 (95% CI 0.29, 0.62) Sp: 0.89 (95% CI 0.83, 0.92)		
True positives	5 studies	⊕⊕◯◯ [b,c]
False negatives	665 patients	Low
True negatives	5 studies	⊕⊕⊕◯
False positives	2172 patients	Moderate
BARD score to screen NASH Se: 0.72 (95% CI 0.58, 0.83) Sp: 0.65 (95% CI 0.55, 0.75)		
True positives	7 studies	⊕⊕⊕◯
False negatives	952 patients	Moderate
True negatives	7 studies	⊕⊕⊕◯
False positives	2736 patients	Moderate
FIB -4 score to screen NASH Se: 0.57 (95% CI 0.39, 0.74) Sp: 0.89 (95% CI 0.77, 0.95)		
True positives	6 studies	⊕⊕◯◯ [b,c]
False negatives	927 patients	Low
True negatives	6 studies	⊕⊕⊕◯
False positives	2630 patients	Moderate
NFS score to screen NASH Se: 0.30 (95% CI 0.27, 0.33) Sp: 0.96 (95% CI 0.95,0.96)		
True positives	7 studies	⊕◯◯◯ [a, b]
False negatives	795 patients	Very low
True negatives	7 studies	⊕⊕⊕⊕
False positives	2749 patients	High

APRI, AST to platelet ratio index; AST/ALT ratio, aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio; FLI, fatty liver index; FIB-4, fibrosis 4 score; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NFS, NAFLD fibrosis score; Se, sensitivity; Sp, specificity.
[a] Downgraded because very serious imprecision presented.
[b] Downgraded because serious inconsistency.
[c] Downgraded because serious imprecision presented.

3.4. Risk scores for non-alcoholic steatohepatitis prediction

In the 23 studies for NASH diagnosis, there were 32 different risk scores found. The most common were FIB-4 [45,47–51,53–55,57,58,60,64,66] NFS [45,44–50,53–55,57,61,62,64,66], BARD score

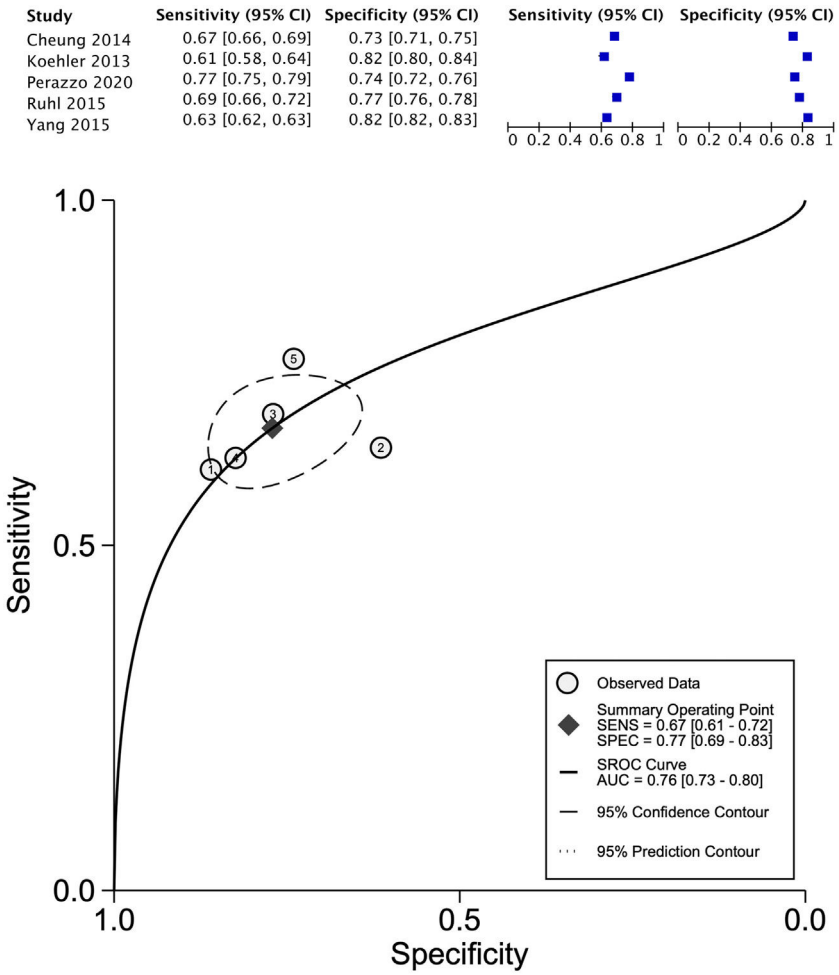

Fig. 2. Meta-analysis of NAFLD using predictive FLI model validated in healthy population.

[45,47,49,50,53,55,56,60,65,66], and APRI [45,47,49,50,54,55,58,60,61,64]. The most common variables were AST in 21, ALT in 17, fasting glucose in 14, and age in 11 risk scores (Supplementary Table 2). For the score outcomes, a range of AUC was observed from 0.56 to 0.97. The highest AUC was NIKEI by Demir et al. [66], and the lowest AST/ALT ratio by Loong et al. [50]. The highest sensitivity was identified for the FIC-22 model by Tada et al. [51], with 0.89 and a specificity of 0.62. The risk score with the highest specificity was NFS by Demir et al. [66], with a specificity of 1.00 and a sensitivity of 0.19 (Table 1). For the diagnostic objective, 16 risk scores were developed for steatohepatitis and 71 for fibrosis.

3.5. Risk of bias and applicability concerns

The graph and summary of the risk of bias are presented in the Supplementary Fig. 1.

3.5.1. Risk of bias and applicability concerns for non-alcoholic fatty liver disease

Two studies had a high risk for "patient selection" bias. These studies did not state whether the authors used a consecutive or random sample of the enrolled patients; also, case-control design within the cohorts was not avoided [21,41]. One study had a high risk for "reference standard" bias since it did not provide a precise NAFLD diagnosis [21]. Two studies had a high risk for "flow and timing" bias since they did not indicate an appropriate timing between the index and the reference test and because not all patients were included in the analysis [38,43]. However, high applicability concerns were not found.

3.5.2. Risk of bias and applicability concerns for non-alcoholic steatohepatitis

Three studies had a high risk of "patient selection" bias and high concern for applicability since cohorts associated with clinical trials were used [43,53,54]. Two studies were found with high-risk of "index test" bias; one did not define NASH [62], and another did not specify if the index test results were interpreted without knowledge of the results of the reference standard, this is also a high applicability concern [48]. In addition, two studies had a high risk for "reference test" bias and a high concern of applicability since they did not provide a NASH classification [56,63]. Finally, three studies had a high risk for "flow and timing" bias since it was unclear if there was an appropriate time interval between the index test and reference standard. Also, not all the participants were included in the analysis [51,57,66].

3.6. Meta-analysis and certainty of the evidence

Six risk scores met the criteria to be included; FLI [28–30,34,35] for the analysis of the diagnosis of NAFLD and AST/ALT [45,47,54,61,64,66], FIB-4 [45,47,49,54,61,64], NFS [44,47,48,54,62,64,66], APRI [45,47,54,61,64], and BARD [45,47,49,55,56,60,64] score for NASH. The details are presented in Table 2.

The data for FLI was analyzed in five studies which provided a summary point AUC of 0.76 (95% CI: 0.73, 0.80) with a sensitivity of 0.67 (95% CI: 0.62, 0.72) and low certainty; a specificity of 0.78 (95% CI: 0.74, 0.83) and moderate certainty, this risk score was validated in a total of 49,468 subjects (Fig. 2). The data for APRI was obtained

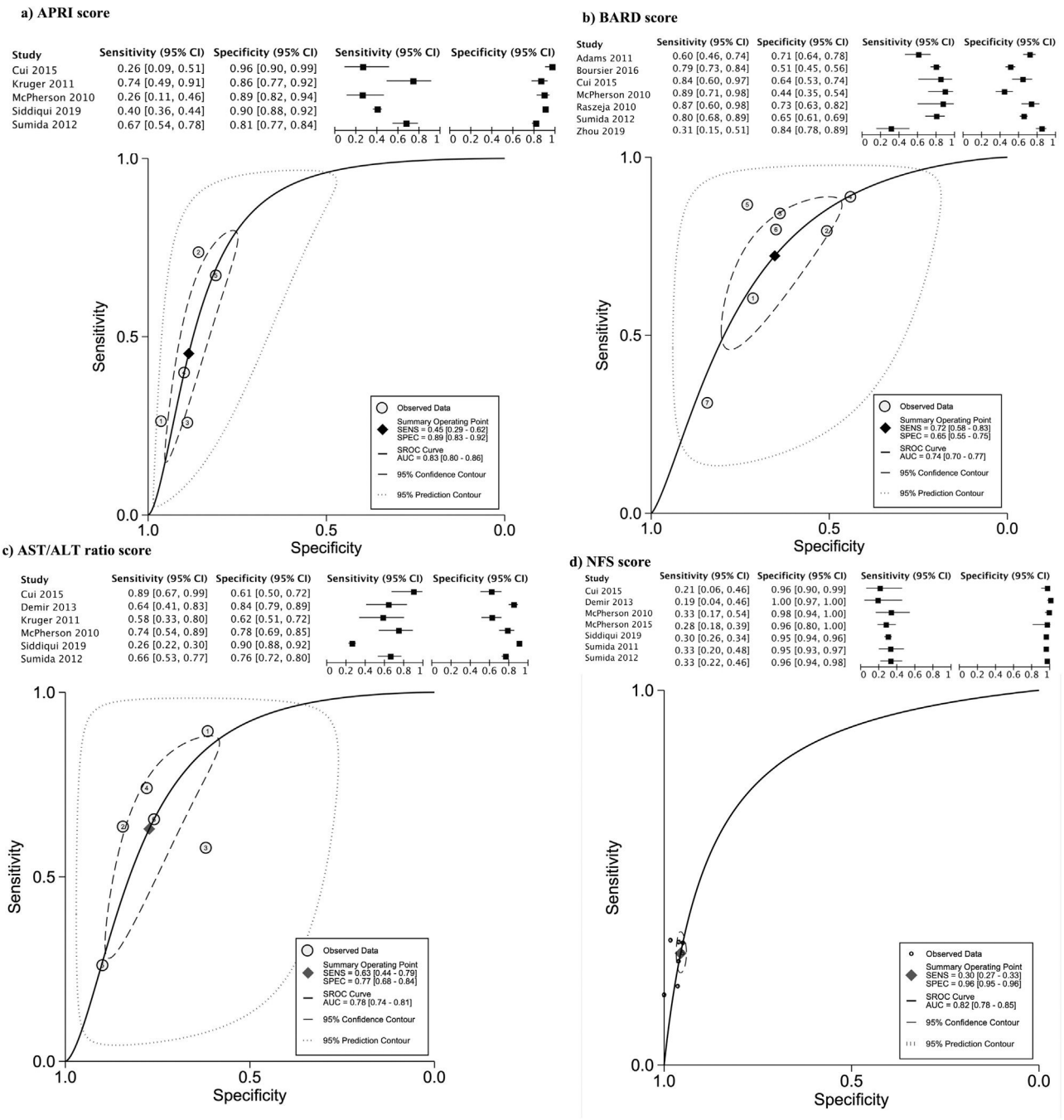

Fig. 3. Forest plots and graphs for the meta-analysis of five predictive models for non-alcoholic steatohepatitis (NASH), classified for advance fibrosis: (a) AST to platelet ratio index (APRI); (b) BARD score; (c)aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio; (d) NAFLD Fibrosis score (NFS).

from five studies with a summary point AUC of 0.83 (95% CI: 0.80, 0.86), a sensitivity of 0.45 (95% CI: 0.29, 0.62) with low certainty, and specificity of 0.89 (95% CI: 0.83, 0.92) with moderate certainty, in a total of 2,837 subjects (Fig. 3a). The BARD score was analyzed in seven studies with a total of 1,964 subjects with a summary point AUC of 0.74 (95% CI: 0.70, 0.77), sensitivity of 0.72 (95% CI: 0.58, 0.83), and specificity of 0.65 (95% CI: 0.55, 0.75) both with moderate certainty (Fig. 3b). The analysis conducted for AST/ALT ratio in six studies with a total of 3,104 subjects had a summary point AUC of 0.78 (95% CI: 0.74, 0.81) with a sensitivity of 0.63 (95% CI: 0.44, 0.79) and moderate certainty, also, specificity of 0.77 (95% CI: 0.68, 0.84) and low certainty (Fig. 3c). The NFS presented a summary point AUC of 0.82 (95% CI: 0.78, 0.85) in seven studies with a sensitivity of 0.30 (95% CI: 0.27, 0.33) in 795 patients and low certainty, and specificity of 0.96 (95% CI: 0.95, 0.96) in 2,749 patients with high certainty (Fig. 3d). The FIB-4 meta-analysis of six studies for the risk of fibrosis, with a total of 3,557 subjects, reported a summary point AUC of 0.81 (95% CI: 0.77, 0.84), sensitivity of 0.57 (95% CI: 0.39, 0.74) classified as low certainty because of reduced discriminatory performance and high inconsistency, and specificity of 0.89 (95% CI: 0.77, 0.95) with moderate certainty (Fig. 4).

3.7. *Publication bias*

There was no publication bias identified in the meta-analysis, with exception of the AST/ALT analysis that suggested a small publication bias (Supplementary Fig. 2).

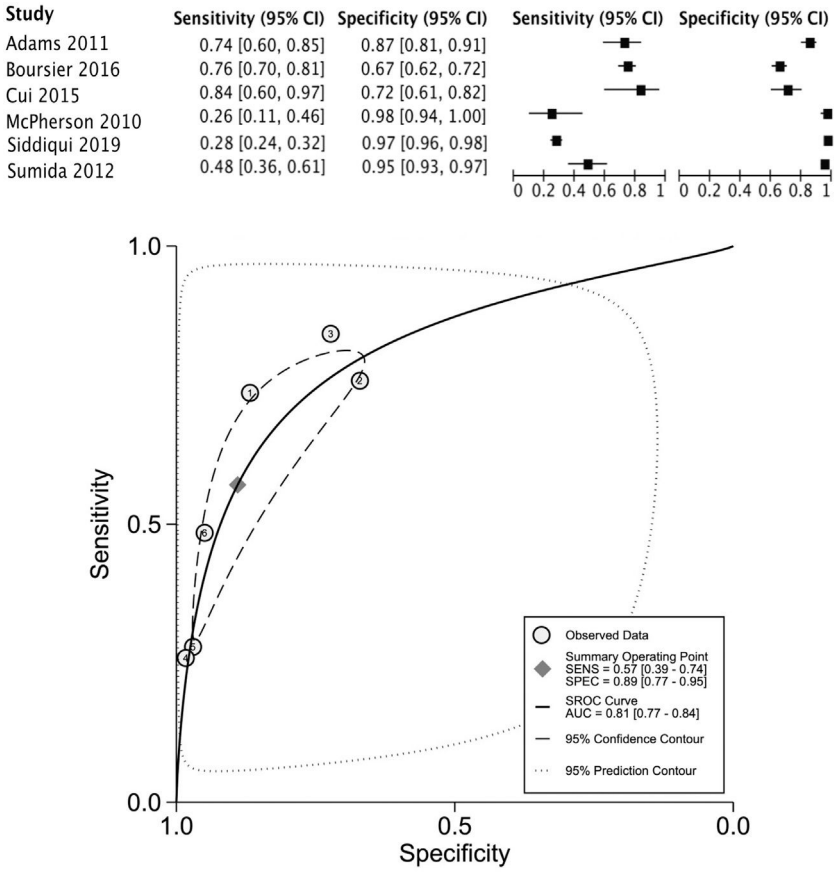

Fig. 4. Forest plot and graph for the meta-analysis of FIB-4 score.

4. Discussion

This study performed a comprehensive search strategy to minimize selection bias. It reviewed a total of 45 publications, from January 2010 to January 2022, in 19 countries, and assessed the spectrum of FLD using non-invasive risk scores; 23 scores for NAFLD diagnosis and 32 scores for NASH diagnosis were summarized. The most commonly risk scores identified were FLI [28–30,32,34,35,37] for NAFLD, and FIB-4 [45,47–51,53–58,61,64,66], NFS [45,47–50,53–55,57,61,62,64,66], APRI [45,47,49,50,54,55,58,60,61,64], and BARD Score [45,47,49,50,53,55,56,60,64,66] for NASH. The risk scores with the highest diagnostic accuracy were FLI (AUC 0.76) for NAFLD, classified as a good accuracy diagnostic and APRI (AUC 0.83) for NASH, classified as a very good diagnostic accuracy. Along with a moderate-moderate and low-moderate certainty of the evidence, respectively.

Previous studies performed systematic reviews of established NAFLD and NASH diagnosis [11,67–70]. Similarities with these studies are that there are a lot of different risk scores with limited performance, also the need for further research to validate the existing scores in similar worldwide populations to reduce heterogeneity and produce better analysis for a solid recommendation. In this review, the outcomes were organized to reduce heterogeneity excluding population with comorbidities, and studies that focused on mortality and complications. This review is analyzing only observational studies and focuses on the diagnostic accuracy of risk scores, intending to study which have a higher sensibility and specificity in the general population, to help in primary care attention to a first prediction of the diagnostic. Previous studies do not validated tools that evaluate the risk of bias or publication bias, which is a cornerstone in clinical decision making.

Our study agrees that further research is needed to apply new diagnostic risk scores for NAFLD, which can eventually validate serum biomarkers of steatosis and advanced stages of FLD and effectively replace imaging methods. Providing aid for timely treatment and referral to specialists [5,69].

Lee *et al*. synthesized the ability of only three risk scores (FLI, APRI, and NFS) in prognosticating NAFLD-related events and divided them into three main categories, fibrosis, liver-related events, and mortality. The review included 13 studies with the limitations of not having a standard population, cut-off values, and follow-up periods; reasons why this study did not provide a meta-analysis [70].

Limitations of this study include a wide age range with no stratification of the age of the population (35-76 years) since older age is a significant risk factor for FLD and its progression [3]. However, this data was not standardized in all the studies and therefore, we could not stratify age groups. A comprehensive search was conducted for studies with risk scores for NAFLD and NASH; though studies without a clear report of the risk score, target population, or outcome could have been omitted. However, a systematic process was followed for the search, reporting results, and interpreting the evidence. A suggested small publication bias was identified in the AST/ ALT meta-analysis, due to small sample size. Additionally, this study has some strengths. First, it compiles updated information about the different risk prediction scores for FLD (NAFLD and NASH), which provide current data to improve the diagnosis and treatment of patients with FLD and at risk of fibrosis [3]. Reviewing observational studies lets us analyze how these risk scores behave in a general population providing policymakers a public health perspective. Also, this study provides data display so that primary care centers can identify the diagnostic risk scores appropriate with their preventive measures and provide an early referral to specialists, such as FLI, to diagnose liver steatosis.

5. Conclusions

The present study adds a detailed synthesis of the existing risk prediction scores, the data synthetized in the meta-analysis bring a

pool measure of the most validated scores and by the certainty of the evidence, it is useful to recognize the scores that fit with good diagnostic accuracy and met good methodology criteria.

The FLI for NAFLD and APRI for NASH were the risk scores with the highest prognostic value in the included studies. Although there are different development models in 19 countries (Mainly USA, China and Japan), future research may consider validating existing scores in different populations to improve homogeneous comparison and a robust pool analysis. The need of the health systems to absorb the global burden of disease of NAFLD and the absence of widely accepted diagnostic scores make it challenging for health care decision-makers to recommend FLD screening in the community. Including the limitations that image and histology studies have in primary health care settings.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary Fig. 1. Risk of bias and applicability concerns graph and summary for a)NAFLD and b)NASH studies

Supplementary Fig. 2. Funnel plot for the meta-analysis of non-alcoholic steatohepatitis (NASH) using five predictive models: (a) AST to platelet ratio index (APRI); (b) Fibrosis-4 score (FIB-4); (c) aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio; (d) BARD score; (e) NAFLD Fibrosis score (NFS) and NAFLD (f) FIL.

Conflicts of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Daniela Contreras: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Alejandra González-Rocha:** Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Patricia Clark:** Conceptualization, Writing – review & editing. **Simón Barquera:** Conceptualization, Writing – review & editing. **Edgar Denova-Gutiérrez:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Acknowledgments

This work was carried out during the period 2021 to 2022. DC received a scholarship from CONACyT to obtain a Ph.D. degree (CVU 392126). Raquel Temesvari, DNP, for language and writing assistance for this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2022.100873.

References

[1] Lindenmeyer CC, McCullough AJ. The natural history of nonalcoholic fatty liver disease-an evolving view. Clin Liver Dis 2018;22(1):11–21. https://doi.org/10.1016/j.cld.2017.08.003.
[2] Younossi ZM. Non-alcoholic fatty liver disease – a global public health perspective. J Hepatol 2019;70(3):531–44. https://doi.org/10.1016/j.jhep.2018.10.033.
[3] van Kleef LA, Ayada I, Alferink LJM, Pan Q, de Knegt RJ. Metabolic dysfunction-associated fatty liver disease improves detection of high liver stiffness: the rotterdam study. Hepatology 2022;75(2):419–29. https://doi.org/10.1002/hep.32131.
[4] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology 2018;67(1):328–57. https://doi.org/10.1002/hep.29367.
[5] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73(1):202–9. https://doi.org/10.1016/j.jhep.2020.03.039.
[6] Mundi MS, Velapati S, Patel J, Kellogg TA, Abu Dayyeh BK, Hurt RT. Evolution of NAFLD and its management. Nutr Clin Pract 2020;35(1):72–84. https://doi.org/10.1002/ncp.10449.
[7] Bernal-Reyes R, Castro-Narro G, Malé-Velázquez R, Carmona-Sánchez R, González-Huezo MS, García-Juárez I, et al. Mexican consensus on nonalcoholic fatty liver disease. Rev Gastroenterol México 2019;84(1):69–99. https://doi.org/10.1016/j.rgmx.2018.11.007.
[8] Global Burden or Disease Collaborative Network. Total burden related to NAFLD. Institute for Healthcare Metrics and Evaluation (IHME). Seattle, WA: IHME, University of Washington; 2019. Available from: http://www.healthdata.org/results/gbd_summaries/2019/total-burden-related-to-nafld-level-3-cause. Published Abril 13, 2019. Accessed Aug 1, 2021.
[9] Denova-Gutiérrez E, Lara-Castor L, Hernández-Alcaraz C, Hernández-Ávila M, Aguilar-Salinas C, Kershenobich D, et al. Prevalence and predictors of elevated liver enzyme levels in Mexico: the Mexican National Health and Nutrition Survey, 2016. Ann Hepatol 2021;26:100562. https://doi.org/10.1016/j.aohep.2021.100562.
[10] Lind L, Johansson L, Ahlström H, Eriksson JW, Larsson A, Risérus U, et al. Comparison of four non-alcoholic fatty liver disease detection scores in a Caucasian population. World J Hepatol 2020;12(4):149–59. https://doi.org/10.4254/wjh.v12.i4.149.
[11] Dowman J.K., Tomlinson J.W., Newsome P.N. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 201;33(5):525–40. https://doi.org/10.1111/j.1365-2036.2010.04556.x.
[12] European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.
[13] Deeks JJ, Bossuyt PMM. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy eds. Cochrane; 2021. Available from: https://training.cochrane.org/handbook-diagnostic-test-accuracy/PDF/v2. Published 2021. Accessed September 28, 2021.
[14] Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ 2020;370:m2632. https://doi.org/10.1136/bmj.m2632.
[15] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(8):529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.
[16] Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
[17] Pérez-Gutiérrez OZ, Hernández-Rocha C, Candia-Balboa RA, Arrese MA, Benítez C, Brizuela-Alcántara DC, et al. Validation study of systems for non-invasive diagnosis of fibrosis in nonalcoholic fatty liver disease in Latin population. Ann Hepatol 2013;12(3):416–24. https://doi.org/10.1016/S1665-2681(19)31004-X.
[18] Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part I. General guidance and tips. Korean J Radiol 2015;16(6):1175–87. https://doi.org/10.3348/kjr.2015.16.6.1175.
[19] Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations editors. The GRADE Working Group; 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html. Published Accessed February 2, 2022.
[20] Okeh UM, Okoro CN. Evaluating measures of indicators of diagnostic test performance: fundamental meanings and formulars. J Biom Biostat 2012;3(1):10. https://doi.org/10.4172/2155-6180.1000132.
[21] GRADEpro G.D.T. GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime; 2021. Available from: www.gradepro.org.
[22] Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42(7):503–8. https://doi.org/10.1016/j.dld.2009.08.002.
[23] Park YJ, Lim JH, Kwon ER, Kim HK, Jung MC, Seol KH, et al. Development and validation of a simple index system to predict nonalcoholic fatty liver disease. Korean J Hepatol 2011;17(1):19–26. https://doi.org/10.3350/kjhep.2011.17.1.19.
[24] Abd El-Wahab EW, Zein El-Abedin RA, Ahmed WM, Shatat HZ. Validation of a non-laboratory based screening tool for predicting non-alcoholic fatty liver disease in an egyptian setting. Am J Med Sci 2020;360(6):662–77. https://doi.org/10.1016/j.amjms.2020.06.020.
[25] Cai X, Aierken X, Ahmat A, Cao Y, Zhu Q, Wu T, et al. A nomogram model based on noninvasive bioindicators to predict 3-year risk of nonalcoholic fatty liver in non-obese mainland Chinese: a prospective cohort study. Biomed Res Int 2020;2020:8852198. https://doi.org/10.1155/2020/8852198.
[26] Miyake T, Kumagi T, Hirooka M, Koizumi M, Furukawa S, Ueda T, et al. Metabolic markers and ALT cutoff level for diagnosing nonalcoholic fatty liver disease: a community-based cross-sectional study. J Gastroenterol 2012;47(6):696–703. https://doi.org/10.1007/s00535-012-0534-y.
[27] Pan X, Xie X, Peng H, Cai X, Li H, Hong Q, et al. Risk prediction for non-alcoholic fatty liver disease based on biochemical and dietary variables in a Chinese Han population. Front Public Health 2020;8(220). https://doi.org/10.3389/fpubh.2020.00220.
[28] Perazzo H, Benseñor I, Mill JG, Pacheco AG, da Fonseca MJM, Griep RH, et al. Prediction of liver steatosis applying a new score in subjects from the Brazilian

longitudinal study of adult health. J Clin Gastroenterol 2020;54(1):e1–10. https://doi.org/10.1097/MCG.0000000000001007.
[29] Koehler EM, Schouten JNL, Hansen BE, Hofman A, Stricker BH, Janssen HLA. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. Clin Gastroenterol Hepatol 2013;11(9):1201–4. https://doi.org/10.1016/j.cgh.2012.12.031.
[30] Cheung CL, Lam KS, Wong IC, Cheung BM. Non-invasive score identifies ultrasonography-diagnosed non-alcoholic fatty liver disease and predicts mortality in the USA. BMC Med 2014;12:154. https://doi.org/10.1186/s12916-014-0154-x.
[31] Lee YH, Bang H, Park YM, Bae JC, Lee BW, Kang ES, et al. Non−laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. PLoS One 2014;9(9):e107584. https://doi.org/10.1371/journal.pone.0107584.
[32] Otgonsuren M, Estep MJ, Hossain N, Younossi E, Frost S, Henry L, et al. Single non-invasive model to diagnose non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). J Gastroenterol Hepatol 2014;29(12):2006–13. https://doi.org/10.1111/jgh.12665.
[33] Lesmana CRA, Pakasi LS, Inggriani S, Aidawati ML, Lesmana LA. Development of non-alcoholic fatty liver disease scoring system among adult medical check-up patients: a large cross-sectional and prospective validation study. Diabetes Metab Syndr Obes 2015;8:213–8. https://doi.org/10.2147/DMSO.S80364.
[34] Yang BL, Wu WC, Fang KC, Wang YC, Huo TI, Huang YH, et al. External validation of fatty liver index for identifying ultrasonographic fatty liver in a large-scale cross-sectional study in Taiwan. PLoS One 2015;10(3):e0120443. https://doi.org/10.1371/journal.pone.0120443.
[35] Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 2015;41(1):65–76. https://doi.org/10.1111/apt.13012.
[36] Wang J, Xu C, Xun Y, Lu Z, Shi J, Yu C, et al. ZJU index: a novel model for predicting nonalcoholic fatty liver disease in a Chinese population. Sci Rep 2015;5:16494. https://doi.org/10.1038/srep16494.
[37] de Lédinghen V, Wong GL, Vergniol J, Chan HL, Hiriart JB, Chan AW, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2016;31(4):848–55. https://doi.org/10.1111/jgh.13219.
[38] Xia MF, Yki-Järvinen H, Bian H, Lin HD, Yan HM, Chang XX, et al. Influence of ethnicity on the accuracy of non-invasive scores predicting non-alcoholic fatty liver disease. PLoS One 2016;11(8):e0160526. https://doi.org/10.1371/journal.pone.0160526.
[39] Lin YJ, Gao XM, Pan WW, Gao S, Yu ZZ, Xu P, et al. A model to predict the onset of non-alcoholic fatty liver disease within 2 years in elderly adults. J Gastroenterol Hepatol 2017;32(10):1739–45. https://doi.org/10.1111/jgh.13760.
[40] Zhang Q, Wong CKH, Kung K, Chan JCY, Sy BTW, Lam M, et al. Development and validation study of a non-alcoholic fatty liver disease risk scoring model among adults in China. Fam Pract 2017;34(6):667–72. https://doi.org/10.1093/fampra/cmx049.
[41] Zhang S, Du T, Li M, Jia J, Lu H, Lin X, et al. Triglyceride glucose-body mass index is effective in identifying nonalcoholic fatty liver disease in nonobese subjects. Medicine 2017;96(22):e7041. (Baltimore). https://doi.org/10.1097/MD.0000000000007041.
[42] Zhou YJ, Zheng JN, Liu WY, Miele L, Vitale A, Van Poucke S, et al. The NAFL Risk Score: A simple scoring model to predict 4-y risk for non-alcoholic fatty liver. Clin Chim Acta 2017;468:17–24. https://doi.org/10.1016/j.cca.2017.01.021.
[43] Feng G, He N, Zhou YF, Li XP, Niu C, Liu ML, et al. A simpler diagnostic formula for screening nonalcoholic fatty liver disease. Clin Biochem 2019;64:18–23. https://doi.org/10.1016/j.clinbiochem.2018.11.011.
[44] Calès P, Boursier J, Chaigneau J, Lainé F, Sandrini J, Michalak S, et al. Diagnosis of different liver fibrosis characteristics by blood tests in non-alcoholic fatty liver disease. Liver Int 2010;30(9):1346–54. https://doi.org/10.1111/j.1478-3231.2010.02314.x.
[45] McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59(9):1265–9. https://doi.org/10.1136/gut.2010.216077.
[46] Alkhouri N, Berk M, Yerian L, Lopez R, Chung YM, Zhang R, et al. OxNASH score correlates with histologic features and severity of nonalcoholic fatty liver disease. Dig Dis Sci 2014;59(7):1617–24. https://doi.org/10.1007/s10620-014-3031-8.
[47] Cui J, Ang B, Haufe W, Hernandez C, Verna EC, Sirlin CB, et al. Comparative diagnostic accuracy of magnetic resonance elastography vs. eight clinical prediction rules for non-invasive diagnosis of advanced fibrosis in biopsy-proven non-alcoholic fatty liver disease: a prospective study. Aliment Pharmacol Ther 2015;41(12):1271–80. https://doi.org/10.1111/apt.13196.
[48] McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62(5):1148–55. https://doi.org/10.1016/j.jhep.2014.11.034.
[49] Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65(3):570–8. https://doi.org/10.1016/j.jhep.2016.04.023.
[50] Loong TC, Wei JL, Leung JC, Wong GL, Shu SS, Chim AM, et al. Application of the combined FibroMeter vibration-controlled transient elastography algorithm in Chinese patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2017;32(7):1363–9. https://doi.org/10.1111/jgh.13671.
[51] Tada T, Kumada T, Toyoda H, Saibara T, Ono M, Kage M. New scoring system combining the FIB-4 index and cytokeratin-18 fragments for predicting steatohepatitis and liver fibrosis in patients with nonalcoholic fatty liver disease. Biomarkers 2018;23(4):328–34. https://doi.org/10.1080/1354750X.2018.1425915.
[52] Tasneem AA, Luck NH, Majid Z. Factors predicting non-alcoholic steatohepatitis (NASH) and advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). Trop Dr 2018;48(2):107–12. https://doi.org/10.1177/0049475517742261.
[53] Chuah KH, Wan Yusoff WNI, Sthaneshwar P, Nik Mustapha NR, Mahadeva S, Chan WK. MACK-3 (combination of hoMa, Ast and CK18): A promising novel biomarker for fibrotic non-alcoholic steatohepatitis. Liver Int 2019;39(7):1315–24. https://doi.org/10.1111/liv.14084.
[54] Siddiqui MS, Yamada G, Vuppalanchi R, Van Natta M, Loomba R, Guy C, et al. Diagnostic accuracy of non-invasive fibrosis models to detect change in fibrosis stage. Clin Gastroenterol Hepatol 2019;17(9):1877–85. https://doi.org/10.1016/j.cgh.2018.12.031.
[55] Zhou YJ, Ye FZ, Li YY, Pan XY, Chen YX, Wu XX, et al. Individualized risk prediction of significant fibrosis in non-alcoholic fatty liver disease using a novel nomogram. United Eur Gastroenterol J 2019;7(8):1124–34. https://doi.org/10.1177/2050640619868352.
[56] Raszeja-Wyszomirska J, Szymanik B, Ławniczak M, Kajor M, Chwist A, Milkiewicz P, et al. Validation of the BARD scoring system in Polish patients with nonalcoholic fatty liver disease (NAFLD). BMC Gastroenterol 2010;10:67. https://doi.org/10.1186/1471-230X-10-67.
[57] Gao F, Huang JF, Zheng KI, Pan XY, Ma HL, Liu WY, et al. Development and validation of a novel non-invasive test for diagnosing fibrotic non-alcoholic steatohepatitis in patients with biopsy-proven non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2020;35(10):1804–12. https://doi.org/10.1111/jgh.15055.
[58] Ogawa K, Kobayashi T, Furukawa JI, Hanamatsu H, Nakamura A, Suzuki K, et al. Tri-antennary tri-sialylated mono-fucosylated glycan of alpha-1 antitrypsin as a non-invasive biomarker for non-alcoholic steatohepatitis: a novel glycobiomarker for non-alcoholic steatohepatitis. Sci Rep 2020;10(1):321. https://doi.org/10.1038/s41598-019-56947-1.
[59] Zheng KI, Liu WY, Pan XY, Ma HL, Zhu PW, Wu XX, et al. Combined and sequential non-invasive approach to diagnosing non-alcoholic steatohepatitis in patients with non-alcoholic fatty liver disease and persistently normal alanine aminotransferase levels. BMJ Open Diabetes Res Care 2020;8(1):e001174. https://doi.org/10.1136/bmjdrc-2020-001174.
[60] Adams LA, George J, Bugianesi E, Rossi E, De Boer WB, van der Poorten D, et al. Complex non-invasive fibrosis models are more accurate than simple models in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2011;26(10):1536–43. https://doi.org/10.1111/j.1440-1746.2011.06774.x.
[61] Kruger FC, Daniels CR, Kidd M, Swart G, Brundyn K, van Rensburg C, et al. APRI: a simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J 2011;101(7):477–80.
[62] Sumida Y, Yoneda M, Hyogo H, Yamaguchi K, Ono M, Fujii H, et al. A simple clinical scoring system using ferritin, fasting insulin, and type IV collagen 7S for predicting steatohepatitis in nonalcoholic fatty liver disease. J Gastroenterol 2011;46(2):257–68. https://doi.org/10.1007/s00535-010-0305-6.
[63] Younossi ZM, Page S, Rafiq N, Birerdinc A, Stepanova M, Hossain N, et al. A biomarker panel for non-alcoholic steatohepatitis (NASH) and NASH-related fibrosis. Obes Surg 2011;21(4):431–9. https://doi.org/10.1007/s11695-010-0204-1.
[64] Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol 2012;12(1):2. https://doi.org/10.1186/1471-230X-12-2.
[65] Cao W, Zhao C, Shen C, Wang Y. Cytokeratin 18, alanine aminotransferase, platelets and triglycerides predict the presence of nonalcoholic steatohepatitis. PLoS One 2013;8(12):e82092. https://doi.org/10.1371/journal.pone.0082092.
[66] Demir M, Lang S, Schlattjan M, Drebber U, Wedemeyer I, Nierhoff D, et al. NIKEI: a new inexpensive and non-invasive scoring system to exclude advanced fibrosis in patients with NAFLD. PLoS One 2013;8(3):e58360. https://doi.org/10.1371/journal.pone.0058360.
[67] Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011;43(8):617–49. https://doi.org/10.3109/07853890.2010.518623.
[68] Festi D, Schiumerini R, Marzi L, Di Biase AR, Mandolesi D, Montrone L, et al. Review article: the diagnosis of non-alcoholic fatty liver disease – availability and accuracy of non-invasive methods. Aliment Pharmacol Ther 2013;37(4):392–400. https://doi.org/10.1111/apt.12186.
[69] Lazarus JV, Mark HE, Anstee QM, Arab JP, Batterham RL, Castera L, et al. Advancing the global public health agenda for NAFLD: a consensus statement. Nat Rev Gastroenterol Hepatol 2022;19(1):60–78 Jan. https://doi.org/10.1038/s41575-021-00523-4.
[70] Lee J, Vali Y, Boursier J, Spijker R, Anstee QM, Bossuyt PM, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: a systematic review. Liver Int 2021;41(2):261–70. https://doi.org/10.1111/liv.14669.