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ORIGINAL ARTICLE

The practical utility of non-invasive indices in metabolic hepatic steatosis☆

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KEYWORDS
Steatosis;
Fibrosis;
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Abstract
Background: Metabolic hepatic steatosis (metHS) is the most frequent cause of chronic liver disease in our environment. The ''gold standard'' for its diagnosis continues to be liver biopsy, but this is an invasive technique, is not risk-free, and has great interobserver variability, so noninvasive diagnostic methods are necessary.
Objective: To determine the diagnostic accuracy of non-invasive methods based on clinical and analytical data compared to liver biopsy, and to analyse their concordance with each other in the overall cohort and in subpopulations at risk of metHS.
Methods: Prospective observational study of 245 patients aged 19–80 years diagnosed with metHS by liver biopsy. Steatosis indices were calculated: FLI (Fatty Liver Index), LAP (Liver Accumulation Product), HSI-(Hepatitis Score Index) and fibrosis indices: Non-alcoholic fatty liver disease fibrosis score (NFS), fibrosis-4 index (FIB-4) and Hepamet Fibrosis Score (HFS).
Results: The non-invasive steatosis indices showed high sensitivity, and those of fibrosis, high specificity. To assess steatosis, FLI was the most sensitive index in all subpopulations (89–97%), except in women. To assess fibrosis, HFS offers maximum sensitivity in diabetics (86.7%) and is

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the index with the highest negative predictive value overall. The COR curves for non-invasive indices in steatosis and fibrosis compared to liver biopsy showed greater areas under the curve for the fibrosis indices, with NFS and HFS offering greater diagnostic accuracy (area > 0.8, p < 0.05). HFS also offers high diagnostic sensitivity in the diabetic population.
Conclusions: Non-invasive indices of steatosis are more sensitive and those of fibrosis more specific than liver biopsy. NFS and HFS offer the highest diagnostic accuracy, with HFS having the highest negative predictive value.

PALABRAS CLAVE
Esteatosis;
Fibrosis;
Índices no invasivos

Utilidad práctica de los índices no invasivos en la esteatosis hepática metabólica

Resumen
Antecedentes: La esteatosis hepática metabólica (EHmet) es la causa más frecuente de hepatopatía crónica en nuestro medio. El «gold standard» para su diagnóstico sigue siendo la biopsia hepática, pero es una técnica invasiva, no exenta de riesgos, con gran variabilidad interobservador por lo que son necesarios métodos no invasivos de diagnóstico.
Objetivo: Determinar la exactitud diagnóstica de índices no invasivos basados en datos clínicos y analíticos comparada con la biopsia hepática, y analizar la concordancia de éstos entre sí en la cohorte global y en subpoblaciones de riesgo de EHmet.
Métodos: Estudio observacional prospectivo de 245 pacientes entre 19 y 80 años diagnosticados de EHmet mediante biopsia hepática. Se calcularon índices de esteatosis: FLI (Fatty Liver Index), LAP (Liver Accumulation Product), HSI-(Hepatitis Score Index) y de fibrosis: Non alcoholic fatty liver disease fibrosis score (NFS), índice fibrosis-4 (FIB-4)y Hepamet Fibrosis Score (HFS).
Resultados: Los índices no invasivos de esteatosis demostraron alta sensibilidad y los de fibrosis alta especificidad. Para valorar esteatosis el FLI fue el índice más sensible en todas las subpoblaciones (89-97%) excepto en mujeres. Para valorar fibrosis el HFS ofrece máxima sensibilidad en diabéticos (86,7%) y es el índice con mayor valor predictivo negativo en global. las curvas COR para índices no invasivos en esteatosis y fibrosis comparado con biopsia hepática mostraron mayores áreas bajo la curva para los índices de fibrosis, siendo el NFS y HFS los que ofrecen mayor exactitud diagnóstica (área > 0,8, p < 0,05). Además en población diabética el HFS ofrece alta sensibilidad diagnóstica.
Conclusiones: Los índices no invasivos de esteatosis son más sensibles y los de fibrosis más específicos comparados con la biopsia hepática. El NFS y HFS los que ofrecen mayor exactitud diagnóstica, siendo el HFS el que presenta mayor valor predictivo negativo.

Introduction

Metabolic hepatic steatosis (metHS) is a clinical pathology term that comprises a range of diseases, from simple steatosis to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma in the absence of significant alcohol intake (<20 g per day in women and <30 g per day in men).[1,2] The prevalence of metHS is rising alongside the prevalence of obesity in our setting; its prevalence in Spain is 25%–30%[3] and could increase exponentially in a few years to 49%.[4]

The natural history of metHS starts with simple hepatic steatosis, which usually follows a benign, stable course, whereas steatohepatitis tends to progress to fibrosis and, in advanced cases, degenerate into cirrhosis or hepatocellular carcinoma.[5] All this leads to higher mortality rates in patients: 18% in patients with steatohepatitis versus 3% in patients with simple steatosis after 18.5 years of follow-up.[6] The most significant causes of death in these patients are cardiovascular diseases, which are associated with the main risk factors that influence metHS progression, such as obesity and metabolic syndrome (MetS).[7,8] However, in advanced stages of the disease, complications of cirrhosis are the leading causes of death.

Ultrasound is usually the initial method of diagnosing steatosis (93% sensitivity if >33% steatosis). However, sensitivity decreases when steatosis affects <30% of hepatocytes. Furthermore, it neither measures nor offers information on hepatic fibrosis, which is the primary prognostic factor for survival.[9,10]

Liver biopsy is the gold standard for diagnosing metHS,[2,11] but this is an invasive technique, is not risk-free and has great interobserver variability. Given these reasons and the importance of identifying patients with early-grade fibrosis, indices combining clinical and laboratory parameters have

been developed to determine the severity of both steatosis and hepatic fibrosis in metHS in quick, simple, low-cost ways.

The diagnostic accuracy of these indices or a combination thereof has not yet been firmly established or characterised in the different risk populations. The most commonly used are as follows: Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI) and Liver Accumulation Product (LAP) for steatosis; and Non-alcoholic fatty liver disease Fibrosis Score (NFS), Fibrosis-4 index (FIB-4) and Hepamet Fibrosis Score (HFS) for fibrosis.

Taking all the above into account, the objective of this study was to determine the diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) of non-invasive indices compared to liver biopsy, as well as to analyse their diagnostic accuracy in certain risk populations such as patients with hypertension, patients with type 2 diabetes mellitus (T2DM), patients with MetS and patients with obesity.

Patients and methods

This was an observational study in a *prospective* cohort of patients diagnosed with metHS by liver biopsy between 2005 and 2019.

Study population

A total of 245 patients who visited the gastroenterology clinic at Hospital Clínico Universitario de Valladolid [Valladolid University Clinical Hospital], referred for elevated transaminases after other causes of liver disease had been ruled out or with a diagnosis on ultrasound of steatosis, with subsequent liver biopsy diagnostic of metHS, were included.

The exclusion criteria were: significant alcohol intake (>20 g alcohol per day in women; >30 g in men); hepatotoxic drugs; hepatitis B virus surface antigen positivity; hepatitis C antibody positivity; elevated transferrin saturation (>45% in men and >40% in women) and ferritin >1,000 ng/ml; a diagnosis of type 1 diabetes mellitus, autoimmune hepatitis or alpha-1 antitrypsin deficiency; ceruloplasmin levels below the lower limit of normal; and uncontrolled thyroid disease.

Informed consent was obtained from each patient included in the study according to the current ethical principles. The study protocol fulfilled the ethical directives of the 1975 Declaration of Helsinki (1983 revision) and was approved by the hospital's ethics committee.

General, anthropometric and clinical-chemistry characteristics

The following were analysed: demographic, epidemiological and clinical variables; anthropometric measurements such as height (cm), weight (kg), body mass index (BMI) (kg/m^2) and waist (cm)-to-hip (cm) ratio; and blood pressure (BP), both systolic (SBP) and diastolic (DBP). Body weight was measured with the subjects wearing neither clothes nor shoes, using scales (Omrom, Los Angeles, California, United States). Height was measured with metric tape (Omrom, Los Angeles, California, United States) while patients stood shoeless with their shoulders in normal alignment. BMI was calculated using the following equation: (body weight [kg] divided by height [m^2]). Patients with a BMI > 30 kg/m^2 were considered obese. Waist circumference (WC) was measured at the navel using extended metric tape (Omrom, Los Angeles, California, United States) with subjects standing after normal expiration. BP was recorded as the average of two consecutive measurements (Omrom, Los Angeles, California, United States).

The following clinical chemistry variables were also analysed: glucose, albumin and platelets; lipid profile (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol and triglycerides), liver profile (total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ART], gamma-glutamyl transpeptidase [GGT] and alkaline phosphatase), uric acid, fasting insulin and insulin resistance calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). All parameters were determined on a single day using a COBAS INTEGRA 400 automated clinical chemistry analyser (Roche Diagnostic, Montreal, Canada).

Cardiovascular risk factors

To assess potential cardiovascular risk factors (CVRFs), the criteria proposed by the International Diabetes Federation (IDF) were used. These criteria include[12]: central obesity (waist circumference: >94 cm in men, >80 cm in women), BP (SBP $\geq$ 130 mmHg; DBP $\geq$ 85 mmHg), baseline blood glucose $\geq$100 mg/dl, triglyceridaemia $\geq$150 mg/dl, serum HDL-C levels (<40 mg/dl in men; <50 mg/dl in women). MetS was diagnosed when a single individual had central obesity plus at least two of the following four factors[12]: hypertension (HTN), hypertriglyceridaemia, hyperglycaemia or low serum HDL-C levels. Tobacco use was also recorded as a CVRF.

Diagnosis using non-invasive indices

In the study, the FLI, LAP, HSI, NFS, FIB-4 and HFS indices, as well as a combination thereof, listed with their corresponding formulas below, were analysed in a period not exceeding three months from liver biopsy.

- *FLI*[13] = ($e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{WC} - 15{,}745}$)/1 + $e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{WC} - 15{,}745}$) $\times$100).
- (<30 not steatosis, $\geq$30 and <60 indeterminate, $\geq$60 steatosis).
- *LAP*[14]:
- Men: LAP = (WC [cm] − 65) $\times$ triglycerides [mol/l]).
- Women: LAP = (WC [cm] − 58) $\times$ triglycerides [mol/l]).
- (<4 not steatosis and $\geq$4 steatosis in men and for women <4.4 not steatosis, $\geq$4.4 steatosis).
- *HSI*[15] = 8 $\times$ (ALT/AST) + BMI (+2 female; +2 T2DM). If <30 not steatosis, $\geq$30 and <36 indeterminate, and $\geq$36 steatosis.
- *NFS*[16] = −1,675 + 0.037 $\times$ age (years) + 0.094 $\times$ BMI (kg/m^2) + 1.13 $\times$ T2DM (yes 1; no 0) + 0.99 $\times$ (AST/ALT) − 0.013 $\times$ platelets (U/l) − 0.66 $\times$ albumin (g/dl).

- (<−1,455 mild fibrosis, ≥−1,455 and <0.675 indeterminate, and ≥0.675 advanced fibrosis).
- *FIB-4*[17] = (age × AST)/(platelets [U/ml]) × (sqrt [ALT]).
- (<1.3 mild fibrosis, ≥1.3 and <2.67 indeterminate, and ≥2.67 advanced fibrosis).
- *HFS*[18] = $1/(1 + e^{(5{,}713 - 0.996 \times \text{age [45-64 years]} - 1{,}745 \times \text{age [>65 years]} + 0.907 \times \text{male gender} - 0.771 \times \text{diabetes mellitus} - 0.746 \times \text{AST [35-69 IU/ml]} - 1{,}992 \times \text{AST [>70 IU/ml]} - 0.044 \times \text{albumin [4-40.49 mg/dl]} - 0.944 \times \text{albumin [<4 mg/dl]} - 1{,}028 \times \text{HOMA-IR [2-30.99]} - 2{,}087 \times \text{HOMA-IR [>4]} - 0.876 \times \text{platelets [155.0-219,999]} - 2{,}241 \times \text{platelets [<155,000]})}$.
- (<0.12 mild fibrosis, ≥0.12 and <0.24 indeterminate, and ≥0.24 advanced fibrosis).

Indeterminate results in all indices were discarded.

Combination of fibrosis indices. A score (''combination of indices'') was prepared with the result of the non-invasive fibrosis indices according to the following classification with the intent of evaluating whether a combination thereof offers advantages in terms of greater diagnostic accuracy.

- *FIB-4:* if <1.30 = 0, 1.30–2.67 = 1 and >2.67 = 2.
- *NFS:* if <−1,455 = 0, <−1,455 = 1, and >0.675 = 2.
- *HFS:* if <0.12 = 0, 0.12–0.24 = 1, and >0.24 = 2.

After adding up points: if 0–1 point, fibrosis is ruled out; if 2–3 points, indeterminate result, and if ≥4, advanced fibrosis.

Liver biopsy

All patients underwent percutaneous liver biopsy with preparation according to the guidelines.[19] All biopsies were evaluated by the same pathologist and were routinely processed. For their prospective evaluation, the biopsies were digitised and also evaluated by an external pathologist. Biopsies with at least 11 liver lobules were considered valid.

To histopathologically classify liver biopsies, the SAF diagnostic algorithm was used to evaluate three parameters: steatosis (S) (considering 5%–33% steatosis S1, 33%–66% S2 and >66% S3), hepatic activity (hepatocellular ballooning; lobular inflammation) (A) and fibrosis (F). Steatosis was evaluated by scoring as follows: <5% = 0, 5%–33% = 1, >33%–66% = 2 and >66% = 3. Hepatocellular ballooning was graded from 0 to 2: no ballooned cells = 0, few ballooned cells = 1 and many ballooned cells/prominent ballooning = 2. Lobular inflammation was graded from 0 to 3: no foci = 0, <2 foci of 200 per field = 1, 2–4 foci of 200 per field = 2 and >4 foci of 200 per field = 3.[20,21] Fibrosis was reported as: stage 0 = no fibrosis; 1 = mild perisinusoidal/pericellular fibrosis; 2 = perisinusoidal/pericellular fibrosis with periportal fibrosis; 3 = perisinusoidal/pericellular fibrosis, portal fibrosis and bridging fibrosis; and 4 = cirrhosis.[22]

Statistical analysis

Data were processed using the SPSS statistical software package (IBM Corp. Released 2011. IBM SPSS Statistics Version 25.0., SPSS Inc., Chicago, Illinois, United States). Continuous variables were reported in terms of mean ± SD for a normal distribution or in terms of median and range for a non-normal distribution. Qualitative variables were reported in terms of absolute and relative frequencies (percentages). To study the association between qualitative variables, the chi-squared test was used, with Yates's correction and Fisher's exact test as required. For quantitative variables, the Kolmogorov–Smirnov test was used to determine the normality of the distributions. Agreement between indices was measured using the kappa statistic. Sensitivity, specificity, PPV and NPV were calculated using liver biopsy as a reference. Receiver operating characteristic (ROC) curves were applied to determine the area under the curve of the non-invasive tests compared to liver biopsy. A p value <0.05 was considered significant.

Table 1 Baseline population characteristics.

Characteristics	Mean	SD
Age (years)	45.41	12.30
Alcohol (g per day)	2.15	7.20
Body mass index (kg/m²)	37.31	9.72
Waist-to-hip ratio	0.97	0.06
Laboratory results		
Uric acid (mg/dl)	5.59	1.59
Creatinine (mg/dl)	0.85	0.20
Albumin (g/dl)	4.42	0.44
Glucose (mg/dl)	109.49	32.90
Insulin (mg/dl)	15.64	10.69
HOMA-IR	4.39	3.74
Total cholesterol (mg/dl)	186.44	47.24
HDL (mg/dl)	44.01	16.00
LDL (mg/dl)	112.95	38.55
Triglycerides (mg/dl)	155.97	77.16
Platelets (U/l)	267,783.67	77,843.67
CV risk factors	**n**	**%**
Smoking	34	13.90
Metabolic syndrome	116	47.30
Diabetes mellitus	49	20
Hypertension	180	73.50
Hypertriglyceridaemia	116	47.30
Obesity	171	71.40

CV: cardiovascular; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: low-density lipoprotein.

Results

Table 1 describes the baseline data for the sample. A total of 245 patients, 132 (53.8%) men and 113 (46.2%) women, were studied. The mean age was 45.4 ± 12.3 years. CVRFs showed the following distribution: 49 (20%) were T2DM, 180 (73.5%) hypertension, 171 (71.4%) obesity, 116 (47.3%) MetS and 34 (13.9%) smoking. Out of all patients, 26 (10.6%) had simple steatosis, 155 (63.3%) ballooning, 191 (78%) lobular inflammation, 133 (54.3%) inflammation and ballooning (steatohepatitis) and 43 (17.6%) had significant fibrosis (F ≥ 2) on liver biopsy; of the latter, 27 had advanced fibrosis (F3–F4) and 10 had cirrhosis (F4).

Regarding the diagnostic accuracy of the non-invasive indices compared to liver biopsy, it can be seen that, overall, the steatosis indices show greater sensitivity for moderate to

Table 2 Diagnostic accuracy of non-invasive indices compared to biopsy.

Steatosis indices				
	Sensitivity	Specificity	PPV	NPV
FLI	89.7%	11.8%	69.8%	33.3%
LAP	58.3%	51%	72.8%	35.1%
HSI	73.1%	36.3%	69.6%	40.3%
Fibrosis indices				
	Sensitivity	Specificity	PPV	NPV
NFS	30.2%	99%	86.7%	86.6%
FIB-4	18.6%	99.5%	88.9%	84.8%
HFS	57.1%	88.2%	52.2%	90.2%
Combination of all three	61.6%	84.7%	55.3%	87.9%

FIB-4: Fibrosis-4; FLI: Fatty Liver Index; HFS: Hepamet Fibrosis Score; HSI: Hepatic Steatosis Index; LAP: Liver Accumulation Product; NFS: Non-alcoholic fatty liver disease Fibrosis Score; NPV: negative predictive value; PPV: positive predictive value.

severe steatosis ($S \geq 2$) and the fibrosis indices show greater specificity for advanced fibrosis (Table 2).

Rates of agreement between *steatosis* indices were 64.2% (FLI versus LAP), 68.9% (FLI versus HSI) and 69.1% (LAP versus HSI), with kappa coefficients between 0.2 and 0.3.

Rates of agreement between *fibrosis* indices were 95% (NFS versus FIB-4), 81.2% (NFS versus HFS) and 82.1% (FIB-4 versus HFS), with kappa coefficients between 0.2 and 0.4. Fig. 1 shows the agreement between the steatosis and fibrosis indices.

Analysis of non-invasive indices by risk population

Analysis of the results of the non-invasive indices in different subpopulations (Table 3) revealed that, in relation to indices assessing *steatosis*, in most subgroups, the FLI index is the most sensitive index, as seen in the overall population, and that the specificity of the steatosis indices for detecting advanced steatosis is generally low, except for the HSI in the obese population.

Regarding the *fibrosis* indices, the HFS and a combination of indices offer maximum sensitivity, especially in people with diabetes, and both the FIB-4 and the NFS offer maximum specificity in the main populations at risk of metHS (people with diabetes, people with hypertension and people with MetS), while the HFS offers the greatest NPV.

Fig. 2 shows the ROC curves for non-invasive indices in steatosis and fibrosis compared to liver biopsy, yielding greater areas under the curve for the fibrosis indices, with the NFS and HFS offering the greatest diagnostic accuracy (area > 0.8, $p < 0.05$).

Discussion

The main outcomes of our study were that it identified non-invasive indices both for steatosis and for fibrosis with great diagnostic accuracy in our population of patients with metHS diagnosed by liver biopsy, and that it analysed these results in the different risk subpopulations. Non-invasive steatosis indices are more sensitive, and non-invasive fibrosis indices more specific than liver biopsy. The NFS and HFS offer the greatest diagnostic accuracy.

The search for non-invasive diagnostic tests represents an active area of research in recent years, and these tests are being incorporated into consensus documents and clinical practice guidelines.[23,24] The three types of non-invasive tests – non-invasive indices based on clinical and laboratory data, biomarkers and imaging data – are complementary; the latter also have high specificity and sensitivity[25] but carry the disadvantages of being more costly and less available for use in large populations or as initial screening. Our study found that, among the non-invasive steatosis indices, the FLI proved the most sensitive for diagnosing advanced steatosis, especially in the subpopulations with diabetes and obesity. A study by Bedogni et al. similarly found BMI and abdominal circumference to be the most powerful predictors of metHS, followed by insulin resistance.[13] Therefore, the FLI index could be used as a method of screening for steatosis in diabetic patients, in whom the prevalence is as high as 70%.

According to prior studies, liver fibrosis is considered the main prognostic factor for survival among patients with metHS.[26] The European guidelines (European Association for the Study of the Liver [EASL]) suggest using the NFS and FIB-4 as non-invasive indices to identify patients at risk of advanced fibrosis.[1,27] Our study showed the FIB-4 to be highly specific for the diagnosis of liver fibrosis in the different risk subpopulations. In other studies, these non-invasive fibrosis indices have also shown an association with metHS prognosis assessed by hepatic and cardiovascular mortality[28] and have even determined changes in fibrosis grade over time.[29] Moreover, as seen in other studies, the NFS has a greater NPV for advanced fibrosis than the corresponding PPV,[28] which is consistent with our study. Therefore, its greatest utility in clinical practice would be to rule out advanced fibrosis.[1]

To date, there are no published data in the literature on the usefulness of a combination of multiple non-invasive indices in terms of greater diagnostic accuracy. Our study found that the combined score on the three fibrosis indices, FIB-4, NFS and HFS, did not improve the diagnostic performance of the HFS. In addition, as documented by Ampuero

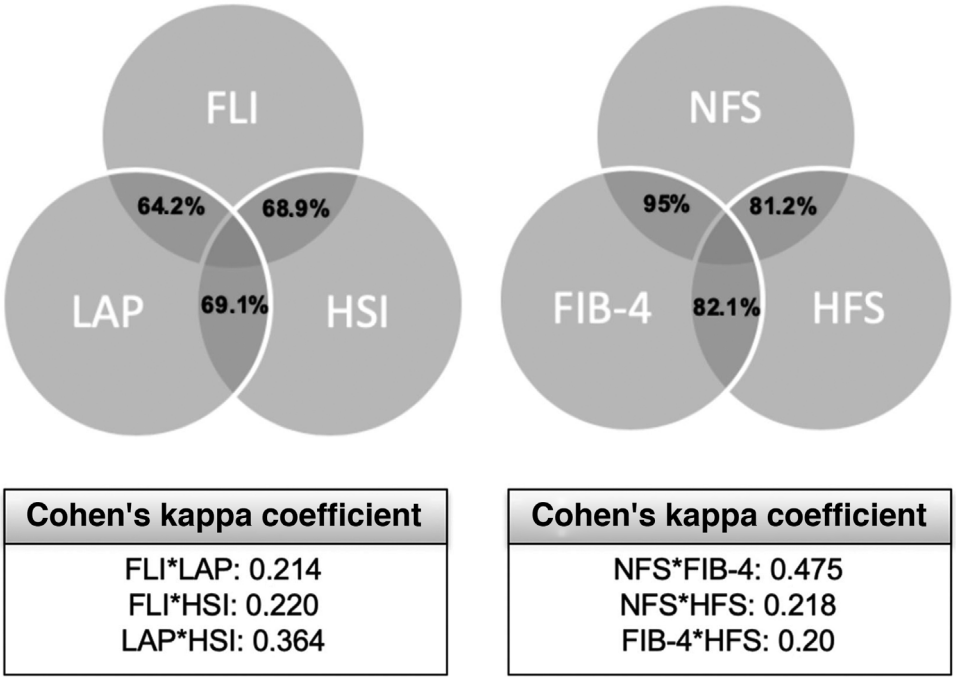


Figure 1 Agreement between steatosis and fibrosis indices with their respective Cohen's kappa coefficients.

Table 3 Analysis of sensitivity and specificity of indices by risk population.

Population (n)	Steatosis		Fibrosis	
	Most sensitive	Most specific	Most sensitive	Most specific
Men (132)	FLI (92.3%)	HSI (58.1%)	HFS/combination (41.2%)	NFS/FIB-4 (100%)
Women (113)	HSI (89%)	LAP (38.9%)	Combination (76%)	FIB-4 (98.8%)
Over 45 years of age (127)	FLI (84.7%)	LAP (51.6%)	Combination (82.1%)	FIB-4 (100%)
Under 45 years of age (118)	FLI (94.7%)	LAP (50%)	HFS/combination (21.4%)	NFS (99.1%)
People with hypertension (180)	FLI (89.9%)	LAP (37%)	Combination (63.4%)	FIB-4 (100%)
People with diabetes (49)	FLI (95.8%)	LAP (50%)	HFS/combination (86.7%)	FIB-4/NFS (100%)
Metabolic syndrome (116)	FLI (91.8%)	LAP (31.3%)	Combination (68%)	FIB-4 (100%)
People with obesity (171)	FLI (97.2%)	HSI (89.9%)	Combination (21.7%)	NFS (98.6%)

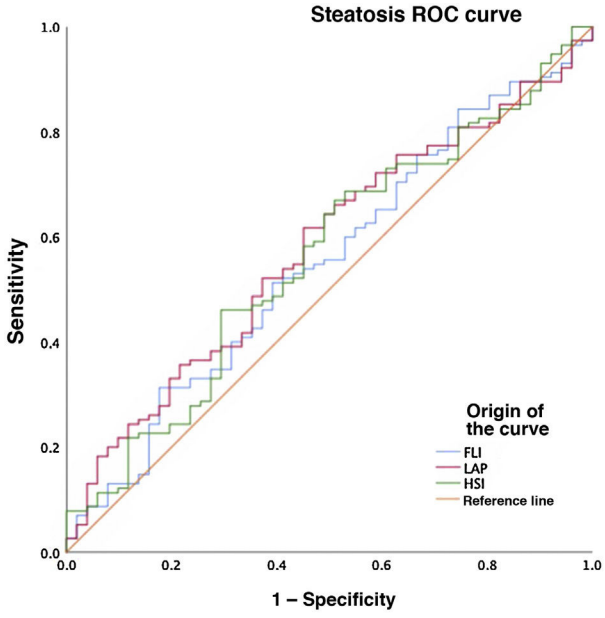
Combination: combination of all three fibrosis indices; FIB-4: Fibrosis-4 index; FLI: Fatty Liver Index; HFS: Hepamet Fibrosis Score; HSI: Hepatic Steatosis Index; LAP: Liver Accumulation Product; NFS: NAFLD Fibrosis Score.

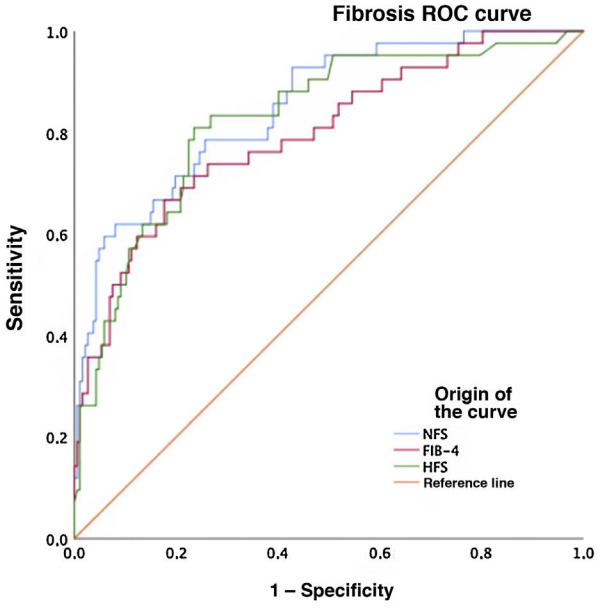
et al.,[18] the HFS offers the advantage of not being affected by the patient's age, BMI, hypertransaminasaemia or diabetes. Furthermore, those authors concluded that the HFS has the greatest net benefit in terms of identifying patients who should undergo liver biopsy and significant improvements in reclassification, thus reducing rates of patients with indeterminate results from 30% to 20% for the FIB-4 and NFS. Our study also found that, in patients with diabetes, the HFS and a combination of fibrosis indices offered similar sensitivity figures. Therefore, the HFS could be the non-invasive index of choice given its sensitivity and high NPV.

The EASL guidelines[1] recommend repeating these indices every two years in patients with metHS and normal liver enzymes at low risk of advanced fibrosis. Patients with suspected fibrosis should be re-evaluated every year, and those with cirrhosis should be re-evaluated every six months for hepatocellular carcinoma monitoring.

Our study had some limitations, including its lack of another non-invasive method for steatosis and for fibrosis such as transient elastography or controlled attenuation parameter (CAP) for comparison to the non-invasive indices. However, using liver biopsy as the gold standard conferred robustness on our results.

In conclusion, in our study, the non-invasive indices assessing *steatosis have greater sensitivity for detecting >33% steatosis*, and those assessing *fibrosis have greater specificity* for detecting significant fibrosis, with the FLI being the most sensitive index and the HSI the most specific index for steatosis, especially in people with diabetes and people with obesity. Regarding the non-invasive *fibrosis* indices, the HFS is the most sensitive and has the greatest NPV, especially in people with diabetes. In light of these results, the non-invasive FLI index, given its high sensitivity, could be used for initial metHS screening (moderate to severe steatosis), and the HFS index would be the most suit-





Test endpoints	Area	Standard error[a]	Asymptotic significance[b]
FLI	.551	.048	.293
LAP	.578	.047	.109
HSI	.562	.048	.202

a. Under nonparametric assumption
b. Null hypothesis: true area = 0.5

Test endpoints	Area	Standard error[a]	Asymptotic significance[b]
NFS	.850	.032	.000
FIB-4	.797	.040	.000
HFS	.827	.036	.000

a. Under nonparametric assumption
b. Null hypothesis: true area = 0.5

Figure 2 ROC curves (non-invasive indices versus liver biopsy).

able for evaluating fibrosis thanks to its high NPV. The FIB-4 and NFS indices would also be useful in the population with diabetes, given their high specificity. Furthermore, the high specificity of the FIB-4 is also maintained in the population with HTN. A combination of indices offers no advantages in terms of diagnostic accuracy over the HFS. The choice of test should be based on each centre's particular characteristics and availability and on each patient's CVRFs.

With this strategy, most patients with metHS could be screened and the referral of patients with advanced grades of fibrosis to hepatology clinics could be optimised. Future prospective studies are needed to validate these indices in patient populations at higher risk of advanced metHS and in certain groups, such as those with immune-mediated diseases, thus avoiding unnecessary biopsies, which would result in lower costs, morbidity and patient discomfort.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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