ORIGINAL ARTICLE

HEPATOLOGY

doi.org/10.1590/S0004-2803.24612023-050

Diagnostic accuracy of the non-invasive markers NFLS, NI-NASH-DS, and FIB-4 for assessment of different aspects of non-alcoholic fatty liver disease in individuals with obesity: cross-sectional study

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HIGHLIGHTS

- In a bariatric population, more than 90% of the patients presented with histopathological steatosis and some degree of fibrosis, whereas over 20% had active NASH.
- FIB-4 score had high overall accuracy in assessing the presence of advanced liver fibrosis in individuals with obesity.
- NFLS score was moderately accurate for the assessment of hepatic steatosis in individuals with obesity.
- NI-NASH-DS was moderately accurate for the assessment of NASH in individuals with obesity.

Received: 29 March 2023
Accepted: 13 June 2023

Declared conflict of interest of all authors: none
Disclosure of funding: none
Declaration of use of artificial intelligence: none
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ABSTRACT – Background – Non-invasive markers have been developed to assess the presence and severity of liver abnormalities related to non-alcoholic fatty liver disease (NAFLD). **Objective –** To analyze the diagnostic accuracy of non-invasive NAFLD markers (NAFLD liver fat score [NLFS], non-invasive non-alcoholic steatohepatitis detection score [NI-NASH-DS] and fibrosis score based on four variables [FIB-4]) in individuals with obesity undergoing bariatric surgery. **Methods –** A descriptive retrospective cross-sectional study was carried out enrolling 91 individuals who underwent bariatric surgery at a tertiary-level public university hospital. Non-invasive NAFLD markers were calculated using laboratory tests, clinical and anthropometric variables and diagnostic accuracy tests were calculated comparing them in relation to the gold-standard test for this analysis (histopathological evaluation). **Results –** A total of 85.7% of the participants were female and mean age was 39.1±9.8 years. The average body mass index was 38.4±3.6 kg/m^2. At histopathological examination, 84 (92.3%) patients presented with steatosis, 82 (90.1%) with some type of fibrosis; 21 (23.1%) patients were diagnosed with NASH according to the NAFLD activity score criteria. The overall accuracy of NLFS score was 58.2% for general hepatic steatosis and 61.5% for moderate to severe steatosis. The overall accuracy of FIB-4 was 95.4% for advanced fibrosis. NI-NASH-DS had a 74.7% overall accuracy for NASH. **Conclusion –** In a population of individuals with obesity, the FIB-4 score had high overall accuracy in assessing the presence of advanced liver fibrosis, whereas the NFLS and NI-NASH-DS had moderate accuracies for the assessment of steatosis and NASH, respectively.

Keywords – Non-alcoholic fatty liver disease; obesity; liver function tests; fatty liver; biomarkers.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical-pathological condition in which abnormal fat deposition occurs in the liver without significant alcohol consumption or other secondary causes. The term encompasses a spectrum of liver histopathological abnormalities, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFLD occurs when the hepatic triglyceride content exceeds 5% of liver weight. Currently, NAFLD is the most common form of liver disease, with an approximate worldwide prevalence of 20%. It should be noted that, in individuals with obesity, this prevalence is usually greater than 70%, which emphasizes a strong association between NAFLD and excess weight[1-4].

The visceral accumulation of fat and increased insulin resistance associate with a multifactorial condition known as metabolic syndrome. This condition, characterized by a set of cardiovascular risk factors, diabetes, hypertension, and dyslipidemia, has a direct relationship with steatohepatitis itself[5,6]. Its pathophysiology encompasses insulin resistance, increased levels of pro-inflammatory cytokines, and oxidative stress, which leads to hepatic steatosis and inflammation, with hepatocyte injury, which may progress to fibrosis, cirrhosis, and even hepatocellular carcinoma. Therefore, the association between metabolic syndrome and NAFLD is frequent, with a joint diagnosis of both being described in about 33% of patients, which suggests NAFLD as a possible hepatic phenotype of metabolic syndrome[7-9].

The histopathological spectrum of NAFLD involves a wide range of alterations with different meanings, both clinical and pathological. Steatosis occurs by fat vacuoles within the hepatocytes, both large (macrovesicular) and small (microvesicular) droplets, predominantly composed of triglycerides. There are no typical features to separate alcoholic steatosis from non-alcoholic steatosis, based on purely histological findings. The presence of an inflammatory infiltrate predominantly composed of polymorphonuclear cells associated with steatosis characterizes the hepatic inflammation of NAFLD, which can manifest itself in a predominantly lobular and/or portal location. Hepatocyte degeneration through a specific form of hydrops characterizes hepatocellular ballooning. The abnormal scarring process underlying the disease progression leads to fibrosis, initially perisinusoidal or pericellular, until progressing to the formation of complete fibrous septa (bridging fibrosis) and, mostly in severe cases, the diffuse formation of nodules (cirrhosis)[10-13].

Among the various methods for diagnosing NAFLD, the one that stands out is liver biopsy, which is undoubtedly considered the gold-standard for an ultimate diagnosis, with the necessary histological differentiations. However, because it is an expensive, invasive, and risky procedure, biopsy ends up being inaccessible to a large part of the population at risk[14,15]. Thus, there is the possibility of using imaging tests such as abdominal ultrasound scan, computed tomography, and magnetic resonance imaging. Of these, ultrasound scan is the most cost-effective method for screening, since it has low cost and appropriate sensitivity. Despite this, none of the imaging methods is aptly capable of properly differentiating steatohepatitis and to provide a nuanced definition of the severity of liver abnormalities. It should be noted that there are already other methods, such as elastography through ultrasound or magnetic resonance, which can detect the occurrence of liver fibrosis, even in early stages; however, these tools are not yet available for most public services in our country[16-19].

In view of the aforementioned facts, non-invasive markers have been developed to assess the presence and severity of liver abnormalities related to NAFLD. These surrogate markers were designed to estimate and predict the risk of occurrence of specific histopathological aspects based on highly available and easily accessible variables[20]. The NAFLD liver fat score (NLFS) was developed for detection of simple steatosis, the fibrosis score based on four variables (FIB-4) for detection of advanced liver fibrosis, and the non-invasive score for detection of NASH (NI-NASH-DS) for diagnosis of NASH[21-23].

The current study sought to analyze the diagnostic accuracy of non-invasive NAFLD markers (NLFS, NI-NASH-DS and FIB-4) in individuals with obesity undergoing bariatric surgery.

METHODS

Study design

A descriptive cross-sectional study was carried out enrolling individuals who underwent bariatric surgery at a public tertiary-level university hospital. Non-invasive NAFLD markers were calculated using laboratory tests, clinical and anthropometric variables and compared in relation to the gold-standard test for this analysis (histopathological evaluation through liver biopsy). The study protocol was analyzed and approved in May 10th, 2022 by the Research Ethics Committee of our institution under opinion number 5.398.996/FCM-UNICAMP.

Study population

Individuals aged over 18 years, who underwent bariatric surgery at this facility between January and October/2018, who agreed to participate in this protocol by signing an informed consent form, were included. Individuals considered vulnerable (underage, disabled or mentally ill), patients with liver diseases of other natures, users of alcohol or hepatotoxic drugs were excluded. All participants underwent preoperative weight loss; surgery was performed when they had lost around 10% of their initial weight.

Of 102 individuals who underwent surgery within the specified time-period, 91 were selected for the study. The reasons for exclusion were alcohol use (n=3), incomplete or non-standard histopathological data in medical records (n=7), and other liver diseases (n=1).

Liver biopsy technique

Liver biopsies are routinely performed as part of the healthcare protocol for individuals undergoing bariatric surgery at this facility due to the high risk of severe forms of NAFLD in this population. Biopsy is performed by extracting a 2-cm fragment from the left lobe of the liver during surgical procedures.

Study variables

Demographic (age and gender), clinical (presence of comorbidities), anthropometric (body mass index – BMI), NAFLD-related histopathological variables, and non-invasive scores for NAFLD assessment were analyzed.

Histopathological variables

Histological analysis was performed by the same pathology team on all samples. All slides were routinely stained with hematoxylin-eosin. NAFLD was stratified according to the Brunt Classification: steatosis (absent, mild, moderate and severe); fibrosis (0 – absent, 1 – isolated periportal or perisinusoidal, 2 – periportal and perisinusoidal; 3 – presence of septal fibrosis; 4 – cirrhosis), lobular inflammation (grade 0 – absent, 1+, 2+, 3+), and hepatocellular ballooning (0 – absent; grade 1 or grade 2)[24].

The diagnosis of NASH was made through the analysis of the NAFLD Activity Score (NAS), defined by the sum of the degrees of intensity of macrovesicular steatosis, lobular inflammation, and hepatocellular ballooning. According to the Pathology Committee of the NASH Clinical Research Network (NCRN), a definite NASH diagnosis is obtained by a score greater than or equal to 5[25].

Non-invasive markers

• NAFLD fatty liver score (NLFS)

Kotronen et al.[21] described this score for detection of simple hepatic steatosis. It aims to quantify the degree of fat in the liver by assigning scores to different parameters: metabolic syndrome, fasting insulin level, type 2 diabetes, aspartate aminotransferase (AST) and AST/ALT ratio. Using a cutoff of -0.640, NFLS predicts increased liver fat content with a sensitivity of 86% and a specificity of 71% according to its validation study.

It is calculated using the following formula:

NFLS = 1.18 × metabolic syndrome (1, if yes; 0, if no) + 0.45 × diabetes (2, if yes; 0, if no) + 0.15× insulin (mU/L) + 0, 04 × AST (U/L) − 0.94 × (AST/ALT) − 2.89.

• Fibrosis score based on four variables (FIB-4)

This was described by Sterling et al. in 2006 to detect advanced fibrosis. In its original validation study, a FIB-4 score <1.45 had a 90% negative predictive value for advanced fibrosis; in contrast, a FIB-4 >3.25 would have a specificity of 97% for advanced fibrosis[22].

It is calculated using the formula:

$$\text{FIB-4} = (\text{Age} \times \text{AST}) / (\text{Platelets} \times \sqrt{\text{ALT}}).$$

Non-invasive score for NASH detection (NI-NASH-DS)

It was described by Billeter et al.[23] in 2021, with the intention of predicting the risk of NASH, and uses the variables BMI, ALT, albumin, and triglycerides.

Based on a logistic regression, the formula below was determined:

NI-NASH-DS = −32.771 + 0.227 × BMI (kg/m²) + 0.062 × ALT (U/L) + 0.024 × TG (mg/dL) + 3.881 × albumin (g/dL).

The cutoff value of 0.649 was able to predict the occurrence of NASH with a sensitivity of 77% and specificity of 88%, according to the original validation cohort[23].

Statistical analysis

To analyze the scores' accuracies, calculations of diagnostic accuracy tests were performed: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. The gold-standard method was the histopathological study of liver biopsies. The significance level adopted for the statistical tests was 5% (P<0.05). The software SAS Release 8.2 (SAS Institute Inc., Cary, NC) was used to carry out the analysis.

RESULTS

Out of 91 participants, 78 (85.7%) were female. The mean age at surgery was 39.1±9.8 years. The average BMI value of the patients was 38.4±3.6 kg/m². As for the comorbidities of the patients, 38 (41.8%) had hypertension and 19 (20.9%) had type 2 diabetes.

At histopathological examination, 84 (92.3%) patients presented with steatosis, 57 (62.6%) of whom having mild forms and 22 (24.2%), moderate forms. In addition, 82 (90.1%) of the patients were diagnosed with some type of fibrosis: 42 (46.1%) with mild forms and 36 (39.6%) with moderate forms; 4 (4.4%) presented with bridging fibrosis. Regarding NASH, 21 (23.1%) patients were diagnosed according to the NAS activity score criteria.

TABLE 1 presents a detailed description of the general characteristics of the study population.

The overall accuracy of NLFS score was 58.2% for general hepatic steatosis, alongside 60.7% sensitivity and 28.6% specificity. Using the same cutoff but determining the outcome as only moderate to severe steatosis, its accuracy rose to 61.5%, alongside 92% sensitivity and 50% specificity. The overall accuracy of FIB-4 was 95.4% for advanced fibrosis, alongside nil sensitivity and 100% specificity. As for NI-NASH-DS, it presented with a 74.7% accuracy for NASH as defined by a NAS histological score equal or above 5, alongside 28.6% sensitivity and 88.6% specificity.

TABLE 2 presents the complete analysis of each score.

TABLE 1. General characteristics of the study population.

N	91
Age (years)	39.1 ± 9.8
Gender	Female: 85.7% Male: 14.3%
BMI (kg/m²)	38.4 ± 3.6
Comorbidity profile	Hypertension: 38 (41.8%) Type 2 Diabetes: 19 (20.9%) Dyslipidemia: 18 (19.7%) Metabolic Syndrome: 41 (45.1%)
NAFLD-related histopathological aspects	
Steatosis	Absent: 7 (7.7%) Mild (1+): 57 (62.6%) Moderate (2+): 22 (24.2%) Severe (3+): 3 (3.3%)
Fibrosis	F0: 9 (9.9%) F1: 42 (46.1%) F2: 36 (39.6%) F3: 4 (4.4%) F4: 0
Lobular inflammation	Absent: 4 (4.4%) Mild (1+): 48 (52.7%) Moderate (2+): 32 (35.2%) Severe (3+): 7 (7.7%)
Hepatocellular ballooning	Absent: 10 (11%) Grade 1: 61 (67%) Grade 2: 20 (22%)
Histopathological presence of NASH	Definite NASH (NAS ≥5): 21 (23.1%)

N: number of individuals; BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NAS: NAFLD activity score.

DISCUSSION

Given the rising importance of NAFLD in recent years, with increasingly concerning rates of occurrence in different regions of the world, and its significant risk of progression to severe forms, early detection assumes a role of great importance within this context. Usually, most of the studies that estimate NAFLD-related data are based on imaging tests and/or levels transaminases. The gold-standard method,

TABLE 2. Analysis of diagnostic accuracy of the scores non-alcoholic fatty liver disease fat liver score, non-invasive non-alcoholic steatohepatitis detection score, and 4-variable fibrosis score.

	NLFS	NLFS (moderate to severe steatosis)	NI-NASH-DS	FIB-4
Sensitivity	60.7%	92%	28.6%	0
Specificity	28.6%	50%	88.6%	100%
Positive likelihood ratio	0.9	1.8	2.5	NA
Negative likelihood ratio	1.4	0.2	0.8	1.0
Positive predictive value	91.1%	41.1%	42.9%	NA
Negative predictive value	5.7%	94.2%	80.5%	95.4%
Overall accuracy	58.2%	61.5%	74.7%	95.4%

NFLS: NAFLD fat liver score; NI-NASH-DS: non-invasive non-alcoholic steatohepatitis detection score; FIB-4: 4-variable fibrosis score; NAFLD: non-alcoholic fatty liver disease; NA: not applicable.

however, is histopathologic examination of liver biopsy specimens. However, it is an invasive, costly, and risky method. The use of surrogate scores whose calculation is based on widely available demographic, anthropometric, and laboratory variables has become increasingly frequent and relevant, since these scores can be widely applied to large populations and are intended to predict the probability of occurrence of different histopathological aspects of the disease, each of them with different prognostic significance. These scores do not substitute histopathological exams by any means, but their combined use allows risk stratification with specific nuances that no imaging or laboratory exam alone can provide[26,27].

The present study analyzed the diagnostic accuracy of three different non-invasive scores, each one focused on a specific aspect of NAFLD, in a population entirely comprised of individuals with obesity undergoing bariatric surgery, i.e., a high-risk group for NAFLD, including its severe forms. This is a population in which a general prevalence of NAFLD above 90% was observed, with approximately 90% of the individuals also presenting hepatic fibrosis, although in incipient stages in most cases. The high prevalence of NAFLD and its advanced forms in bariatric populations had previously been reported[28-31]. Studies enrolling individuals with obesity undergoing bariatric surgery have reported a 6–94% frequency of fibrosis and a 26–55% frequency of NASH. When histological criteria are applied, rates of fibrosis tend to be over 80%, with most of these cases comprising mild to moderate degrees[32-35].

The accuracies of the NFLS for assessment of steatosis, NI-NASH-DS for assessment of steatohepatitis, and FIB-4 for assessment of advanced fibrosis were analyzed in the current study. The NAFLD Fatty Liver Score (NLFS) had moderate sensitivity and a high positive predictive value. These findings indicate a reasonable ability to detect the disease in the general population; additionally, a positive test has a high chance of being correct. Thus, its application may be of great relevance, since although isolated steatosis is relatively benign, it has some potential to evolve into fibrosing inflammatory forms, especially liver cirrhosis, and even hepatocellular carcinoma[36]. Specificity and negative predictive value for this score were relatively low, which would indicate a poor ability to rule out disease even with a negative result. Thus, its overall accuracy was only moderate and even lower than that of its validation cohort[21]. On the other hand, when the same cutoff value was used to detect only more severe forms of steatosis (grades 2 and 3 in the histological examination), increases in both sensitivity and negative predictive value were observed, with moderate specificity and positive predictive value, revealing a better discretionary ability of the test to detect this more severe form of disease in high-risk populations like that of the present study. Based on these results, the use of this score to detect moderate or severe steatosis with satisfactory results can be recommended. Melania et al. also demonstrated a high degree of agreement between NFLS findings and another indirect score, the fatty liver index (FLI)[37].

The NI-NASH-DS demonstrated high specificity values and positive predictive value, but associated with low sensitivity and moderate negative predictive value. Thus, a positive test has a high probability of being correct, but with a low ability to detect the disease among those affected and a reasonable probability of a negative test being correct, leading to a con-

siderable global accuracy (74%). Similarly, the validation cohort of this marker has already shown that the test has better reliability when used in patients with morbid obesity[23]. Nonetheless, the overall accuracy is moderate and the ability to detect the disease in the general study population remains low. Therefore, it is a method that has its value for use on a large scale, but whose results must be analyzed with caution. It is also noteworthy that even the histological diagnosis of NASH through the NAS histological system has important limitations as well, such as the high frequency of indeterminate results. However, all individuals classified as definite NASH according to this system obligatorily present with steatosis with lobular inflammation and/or ballooning, i.e., no individual classified as NASH presented without both the latter conditions at the same time. It should be noted that, to the best of our knowledge and to date, the current study is only the second to analyze the accuracy of this score, and it is recommended that its reproducibility in different populations be evaluated as soon as possible.

The FIB-4 score demonstrated excellent results, with an overall accuracy greater than 90%, alongside very high specificity and negative predictive value. However, the prevalence of advanced fibrosis (Kleiner-Brunt stages 3 or 4) in the study population was very low (below 5%), which suggests that such a performance would be justified more by the low prevalence than by the discretionary power of the test itself in this population. It should be noted that other studies on the same marker show a limited performance in predicting changes in the type of fibrosis, but reveal good consistency of the marker in predicting long-term morbidity and mortality[22,38]. This score was also previously analyzed for the detection of severe steatosis in a bariatric population in the same country as this study, but it showed low accuracy for this purpose, which is not its original objective for which he was designed[39]. Markers that could assess incipient stages of fibrosis would likely be of more interest for similar populations.

The current study has some limitations that must be taken into consideration. Its retrospective data collection leads to poorer data quality and the cross-sectional design precludes establishing causal links. In addition, a relatively small and very homogeneous sample was analyzed, with a very large predominance of female individuals and with low amplitude in anthropometric terms, since they were bariatric patients. Thus, the results cannot be extrapolated to populations with other characteristics. Histological analysis would be better assessed using special stains, such as Masson's trichrome; however, they were not available at this facility for routine use. The pre-operative weight loss through which the study population underwent may also have somewhat influenced our findings. For example, a considerable number of individuals presented with fibrosis and without NASH. Since the evaluations were performed around the time of surgery, it is likely that some NASH features could have been mitigated by the initial weight loss; however, as fibrosis is usually more refractory to weight loss than inflammation, ballooning, and steatosis, the rate of fibrosis currently observed is seemingly disproportionate[40-42]. Nevertheless, the presented results are consistent and give rise to the expansion of the use of these scores in clinical and epidemiological practice, given their ease of application, low cost, and the possibility of predicting the risk of progression of a common disease through simple and highly available assessments.

CONCLUSION

The findings of the present study allow us to conclude that, in a population of individuals with obesity undergoing bariatric surgery, the FIB-4 score had high overall accuracy in assessing the presence of advanced liver fibrosis, limited by its low sensitivity, whereas the NFLS and NI-NASH-DS had moderate accuracies for the assessment of steatosis and NASH, respectively.

Authors' contribution

Haddad GM: data curation (lead), investigation (lead), visualization (equal), writing – original draft (lead); Gestic MA: data curation (supporting), formal analysis (supporting), investigation (supporting), methodology (supporting); Utrini MP: data curation (supporting), investigation (supporting), resources (supporting), software (supporting); Chaim FDM: data curation (supporting), investigation (supporting), resources (supporting), software (supporting); Chaim EA: conceptualization (supporting), data

curation (supporting), resources (lead), supervision (supporting); Cazzo E: conceptualization (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), supervision (lead), validation (lead), visualization (lead), writing – review and editing (lead). All authors reviewed and approved the final version submitted for publication.

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Haddad GM, Gestic MA, Utrini MP, Chaim FDM, Chaim EA, Cazzo E. Acurácia diagnóstica dos marcadores não-invasivos NFLS, NI-NASH-DS e FIB-4 para avaliação de diferentes aspectos da doença hepática gordurosa não-alcoólica em indivíduos com obesidade: estudo transversal. Arq Gastroenterol. 2024;61:e23050.

RESUMO – Contexto – Marcadores não-invasivos foram desenvolvidos para avaliar a presença e a gravidade de anormalidades hepáticas relacionadas à doença hepática gordurosa não-alcoólica (DHGNA). **Objetivo –** Analisar a acurácia diagnóstica de marcadores não-invasivos de DHGNA (escore de gordura hepática da DHGNA [NLFS], escore não-invasivo de detecção de esteato-hepatite não-alcoólica [NI-NASH-DS] e escore de fibrose de 4 variáveis [FIB-4]) em indivíduos obesos submetidos à cirurgia bariátrica. **Métodos –** Foi realizado um estudo descritivo retrospectivo transversal com 91 indivíduos submetidos à cirurgia bariátrica em um hospital universitário público de nível terciário. Marcadores não-invasivos de DHGNA foram calculados por meio de exames laboratoriais, variáveis clínicas e antropométricas; testes de acurácia diagnóstica foram calculados comparando-os em relação ao exame padrão-ouro para essa análise (avaliação histopatológica). **Resultados –** Um total de 85,7% dos participantes eram do sexo feminino e a média de idade foi de 39,1±9,8 anos. O índice de massa corporal médio foi de 38,4±3,6 kg/m². Ao exame histopatológico, 84 (92,3%) pacientes apresentavam esteatose, 82 (90,1%) com algum grau de fibrose; 21 (23,1%) pacientes foram diagnosticados com esteato-hepatite não-alcoólica (EHNA) de acordo com os critérios do escore de atividade da DHGNA. A acurácia global do escore NLFS foi de 58,2% para esteatose hepática e 61,5% para esteatose moderada a grave. A acurácia global do FIB-4 foi de 95,4% para fibrose avançada. NI-NASH-DS apresentou uma acurácia global de 74,7% para EHNA. **Conclusão –** Em uma população de indivíduos com obesidade, o escore FIB-4 teve alta acurácia global para avaliar a presença de fibrose hepática avançada, enquanto o NFLS e o NI-NASH-DS tiveram acurácias moderadas para avaliar a esteatose e EHNA, respectivamente.

Palavras-chave – Doença hepática gordurosa não alcoólica; obesidade; testes de função hepática; fígado gorduroso; biomarcadores.

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