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Research Article

Are non-invasive scores reliable for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis diagnostic?

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Abstract. Objective: the aim of this study was to evaluate the value of four biological markers (fatty liver index - FLI, Steatotest - ST, AST to platelet ratio - APRI, hepatic steatosis index - HSI) for the diagnosis and staging of NAFLD and for the diagnosis of NASH. Material and Methods: We prospectively included 112 patients with biopsy-proven NAFLD in our study. The histological features were evaluated using the Kleiner score. Four biological markers (FLI, ST, APRI and HIS) were used for the non-invasive assessment of steatosis and steatohepatitis. Results: Three biological scores proved to have a good discriminative ability in differentiating between various stages of steatosis (p=0.05 for FLI, 0.04 for ST and 0.005 for HIS). All these scores proved reliable in the diagnosis of moderate steatosis (p=0.01 for FLI and ST and <0.001 for HSI). We did not find a significant statistical difference between most scores when used for the diagnosis of NASH, except for the APRI score (p=0.04). Conclusion: ST, FLI and HIS are reliable tests for the diagnosis and staging of NAFLD, besides being precise, non-expensive and easy to use. APRI, a score for fibrosis, was correlated with NASH and should draw attention to the presence of NASH in patients with hepatic steatosis.

Key Words: nonalcoholic fatty liver disease, steatosis, fatty liver index, APRI, non-invasive.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in developed countries. NAFLD consists of a wide spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC) (Amarapurkar et al 2007). It is now widely believed that only patients with histologic NASH can progress towards cirrhosis and liver-related mortality (Teli et al 1995, Adams et al 2006, Rafiq et al 2010, Musso et al 2011).

Clinically, the diagnosis of NAFLD requires exclusion of other causes of liver disease, such as viral hepatitis, alcohol consumption, Wilson disease and hemochromatosis. NAFLD and NASH have been proven to be strongly associated with the presence of obesity and lifestyle-related diseases, especially type 2 diabetes mellitus.

Liver biopsy remains the "old gold standard" for the diagnosis of NASH (Matteoni et al 2009, Younossi et al 2011). Up to 10–20% of individuals with NAFLD have NASH (Amarapurkar et al 2007). In the absence of accurate non-invasive diagnostic methods for NASH, such as biochemical markers or imaging techniques, liver biopsy is needed to make a definite diagnosis. Because liver biopsy is an invasive and expensive method, the research of the last decade focused on finding non-invasive alternatives for the diagnostic of NAFLD and NASH.

Several predictive scores can be used to evaluate the stage of steatosis and fibrosis in patients with chronic hepatitis. Of these, the most promising are Steatotest (ST), developed by BioPredictive, Fatty Liver Index (FLI) (Bedogni et al 2006), the homeostatic model assessment (HOMA) (Zein et al 2007), Fibrotest (Ratziu et al 2006), Hepascore (Adams et al 2005), FibroMeter (Cales et al 2009), APRI (AST to platelet ratio index) (Wai et al 2003) and HSI (hepatic steatosis index) (Lee et al 2010).

The fatty liver index (FLI) is an algorithm for the prediction of steatosis based on 4 anthropometrical and biochemical factors (body mass index, waist circumference, triglyceride and gamma-glutamyl transpeptidase (GGT) levels) (Bedogni et al 2006) elaborated for the assessment of steatosis severity.

SteatoTest (ST) (Biopredictive, Paris, France) is a simple test that combines the values of 10 blood components. It was developed in order to provide a quantitative estimate of steatosis in NAFLD (Poynard et al 2005).

APRI (AST to platelet ratio), a score using 2 readily-available laboratory results (AST level and platelet count) can predict significant fibrosis and cirrhosis (Wai et al 2003).

The hepatic steatosis index is the result of a formula that incorporates BMI, ALT/AST ratio, triglyceride level and the presence of DM (type 2 diabetes mellitus) (Lee et al 2010).
The aim of this study was to establish the diagnostic performance of four biological markers (FLI, ST APRI, HSI) in the diagnosis and staging of NAFLD and in the diagnosis of NASH.

Patients and method

We prospectively included in our study 112 patients with biopsy-proven NAFLD. The study was performed in the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania, between 2014-2017. The exclusion criteria were: other etiologies of chronic liver disease: chronic hepatitis B or C, autoimmune hepatitis, Wilson's disease, history of hepatotoxic or steatosis-inducing drug use, alcohol consumption (>20 g/day for women, >30 g/day for men) and diabetes mellitus type 2.
Blood samples were obtained in order to assess the metabolic profile (fasting blood sugar, total cholesterol, LDL and HDL cholesterol, triglycerides) and liver function (AST, ALT). All assessments were made on an automatic analyzer (Konelab 30 I – Thermo Electron Corp Finland). For the calculation of SteatoTest, haptoglobin, apolipoprotein and alpha 2-macroglobulin were assessed by nephelometry and the values were inserted together with anthropometric measurements and other common tests in a patented formula on the dedicated site (Biopredictive, Paris). The results provided a classification of steatosis severity.
An abdominal ultrasound examination was performed in each study patient using a GE Logiq 7 device with a 5.5 MHz convex probe, the day prior to the liver biopsy.
Liver biopsies were performed in our department, the samples were obtained under ultrasonographic guidance and stained with hematoxylin-eosin and Masson's trichrome, and were assessed blindly by an expert pathologist.
The pathological features in NAFLD patients were evaluated according to Kleiner's criteria. The NAS score was calculated in each patient, taking into account: steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2). The score values allowed to identify and classify NASH as follows: 0-2 - no NASH, 3-4 probable NASH, 5-8 – definite NASH) (Kleiner et al 2005).
FLI is a composite index combining 4 parameters: body mass index (BMI), waist circumference (WC), triglyceride and gamma-glutamyl transpeptidase (GGT) levels in a mathematical algorithm, developed for the detection of steatosis.
FLI = [e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (GGT) + 0.053*WC - 15.745] / [1 + e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (GGT) + 0.053*WC- 15.745] * 100
The score ranges from 0 and 100. A FLI score < 30 rules out NAFLD, while a FLI score ≥ 60 indicates fatty liver disease (Bedogni et al 2005).
SteatoTest combines the results of 10 blood tests: alpha 2 macroglobulin (g/L), haptoglobin (g/L), apolipoprotein A (g/L), total bilirubin (μmol/L), GGT (IU/L), ALT (IU/L), AST (IU/L), total cholesterol (mmol/L), triglycerides (mmol/L), fasting glucose (mmol/L) with age, gender and BMI. SteatoTest uses numerical values that are then inserted in the Biopredictive website. The scores range from 0 to 1.00 with higher scores indicating a greater probability of significant lesions.
SteatoTest is part of the more complex FibroMax test; all these tests are patented algorithms (Biopredictive, France) and are provided with instructions for use, ensuring a reliable interpretation (Poynard et al 2005; Munteanu et al 2008).
APRI (AST to platelet ratio index) can predict significant fibrosis and cirrhosis.
APRI= AST level (/ULN) / Platelet counts (109/L) x 100
An APRI value ≤ 0.50 signifies the absence and APRI >1.5 the presence of significant fibrosis. Similarly, APRI ≤ 1.00 predicts the absence and APRI>2.00 the presence of cirrhosis.
The hepatic steatosis index (HSI) depends on BMI, ALT/AST ratio, triglyceride levels and the presence of DM (type 2 diabetes mellitus).
Hepatic steatosis index (HSI) = 8 × ALT/AST ratio + BMI (+2, if DM; +2, if female)
At a value <30.0, HSI can rule out NAFLD with a sensitivity of 92.5% (95% CI, 91.4–93.5) and a negative likelihood ratio of 0.186 (95% CI, 0.163–0.213), and at a value of >36.0, HSI can detect NAFLD with a specificity of 92.4% (95% CI, 91.3–93.4) and a positive likelihood ratio of 6.069 (95% CI, 5.284–6.970) (Lee et al 2010).
Statistical analysis. Comparisons between groups were made using the Student's t-test (ANOVA) for continuous variables with normal distribution, for multiple comparisons and the $\chi 2$ test for categorical variables. Values were expressed as mean ± SD. Continuous variables with non normal distribution were expressed as median and 95% confidence interval (CI). A p value < 0.05 was considered statistically significant. Binary analysis was performed using receiver operator characteristic (ROC) curves, separating patients into 2 groups based on the presence of NASH. The diagnostic value of each test was assessed through the area under the ROC (AUROC), and it was also expressed as a percentage for diagnostic accuracy. We used MedCalc® 17.2. and SPSS version 15.0 (SPSS Inc. Chicago, IL, USA) for the statistical analysis.
The study was performed in full accordance with the Declaration of Human Rights (Helsinki, 1975) and with its further revisions. A complete, comprehensive and clear informed consent was provided for patients. The study protocol excluded vulnerable persons, prisoners, mentally impaired persons, severely injured patients, with no legal representatives to sign the consent in their place.
The study was approved by the local ethical committee of the "Prof. Dr. Octavian Fodor" Clinical Emergency Hospital, Cluj-Napoca. All patients gave informed consent prior to being included in the study.

Results

We included 112 patients in the study, 78 (69.64%) of which were male. The median age at start was 47.33 ±12.08 years. The mean weight was 89.05±14.81 kg with a mean BMI at the limit between overweight and grade I obesity (30.14± 4.22). Regarding the lipid profile, the patients had slightly increased values of cholesterol and triglycerides, with normal HDL–cholesterol values. The fasting blood sugar was normal with normal insulin levels. In what concerns liver function, we found alterations of ALT levels (60.00 (47.00—68.75)) but with a normal AST and bilirubin levels. In terms of liver morphology, we had 42.85 % of patients with moderate steatosis, 11.5 % with severe steatosis and 55.3% with NASH (NAS score > 5points). The main characteristics of the patients are presented in Table 1.

Table 1. The main demographic and biological characteristics of the patients included in the study

Variable	Mean/ median (95% CI), %
Age (years)	47.33±12.08
Gender (m/f)	78/34
Weight (kg)	89.05±14.81
BMI (kg/m^2)	30.14± 4.22
Abdominal circumference (cm)	101.24 ± 11.83
Cholesterol (mg/dl)	231.00 (291.20-246.58)
Triglycerides (mg/dl)	174.50 (152.00-206.94)
HDL-cholesterol (mg/dl)	45.00 (39.00-48.00)
Fasting blood sugar (mg/dl)	101.00 (97.35-106.00)
Insulin (U/l)	13.19 (10.02-15.83)
ALT (UI/L)	60.00 (47.00—68.75)
AST (UI/l)	36.00 (31.00-42.75)
Bilirubin (mg/dl)	0.71 (0.65-0.80)
GGT (UI/l)	57 (50-70.66)
Iron (mg/dl)	79.00 (62.35-90.48)
Platelets (x10^3)	237.00 (224.51-257.48)
INR	1.01 (0.98-1.04)
Spleen diameter (mm)	108.29 (104.91-112.69)
Steatosis (grade) (no/(%))	21/44/34/13 (18.9/38.7/30.6/11.7%)
NASH (NAS score) (no/(%))	12/38/62 (10.7/33.9/55.3%)

Table 2. The assessment of steatosis severity using fatty liver index (FLI), SteatoTest (ST) and hepatic steatosis index (HSI)

	S0	S1	S2	S3	p
Score					
FLI	75.13±23.16	54.70±10.20	89.41±15.43	91.19±2.21	0.05
ST	0.70±0.18	0.72±0.19	0.84±0.28	0.96±0.72	0.04
HSI	35.17±19.51	33.76±18.4	41.64±10.53	47.50±7.86	0.005

Table 3. The assessment of moderate steatosis using biological scores: FLI, ST and HSI

Steatosis grade	S01	S23	p
Score			
FLI	60.99±36.27	89.34±12.57	0.01
ST	0.70±0.18	0.88±0.45	0.01
HSI	33.76±18.27	43.28±7.86	<0.001

The next step was to assess the diagnostic capacity of biological scores (FLI, ST and HIS) for the detection of steatosis. The biological scores proved to have a good discriminative capacity in differentiating various stages of steatosis (p=0.05 for FLI, 0.04 for ST and 0.005 for HIS) (table 2). We divided the study group into two subgroups depending on the grade of steatosis (S01 vs S23), in order to test the discriminative capacity for moderate steatosis. All three scores proved reliable in the diagnosis of moderate steatosis (p=0.01 for FLI and ST and <0.001 for HSI) (table 3).

Table 4. The assessment of NASH using biological scores: FLI, ST and HSI

	No NASH	Probable NASH	Definite NASH	p
Score				
FLI	78.77±23.67	75.96±86.95	89.92±2.13	0.71
ST	0.69±0.21	0.76±0.15	0.79±0.42	0.01
HSI	37.84±16.37	40.45±13.87	41.44±5.74	0.56
APRI	0.09±0.03	1.6±0.12	3.7±0.61	0.04

The non-invasive diagnosis of NASH is a permanent challenge. We tested the performance of biological steatosis scores in the assessment of NASH. The study group was divided depending on the NAS score into the "no NASH", "probable NASH" and "definite NASH" categories. We added the APRI score, which was elaborated for the assessment of fibrosis in different liver diseases, to the scores used in the assessment of steatosis. The scores, except for the APRI score (p=0.04), did not find a significant statistical difference between the three subgroups (table 4). In order to minimize the importance of the probable NASH group during the analysis, we merged the "no NASH" and "probable NASH" groups, and the APRI score was again found reliable in the discrimination of patients with definite NASH. Using AUROCs, we obtained a 0.733 diagnostic accuracy for APRI. Secondly, we tested the ability of biological scores to exclude the NASH status but none of the tests proved reliable in this respect (table 5). The AUROCs for FLI, ST and HSI were 0.612, 0.585 and 0.515, respectively (Fig 1).

Discussions

The prevalence of NAFLD is rising alongside that of obesity, dyslipidemia, cardiovascular disease, type 2 diabetes mellitus. The urge to find non-invasive, fast and cheap methods for the diagnosis and staging of NAFLD lead to research studies in this direction.

Ultrasonography is a widely spread, accessible, fast method with good diagnostic performance: 67% sensibility, 77% specificity and 67% positive predictive value (Graif et al 2000), but it is used only for diagnosis, not for staging. In addition, it cannot discriminate between NASH and NAFLD.

The stage of fatty infiltration of hepatocytes is very important when assessing the progression of NAFLD, due to the pathophysiological link between fatty infiltration (lipotoxicity) and the progression towards fibrosis, with insulin resistance (IR) as the initiating factor (Ekstedt et al 2006).

The progression of IR is the "first hit" and leads to simple liver steatosis; the "second hit" factors (reactive oxygen species, mitochondrial dysfunction, endotoxemia) lead to the establishment of NASH, fibrogenetic response and potential progression towards cirrhosis (Day 2002; Browning & Horton 2004). Most of the researchers concluded that NASH alone (not NAFLD) can progress towards cirrhosis and its complications (Soderberg et al 2010, Ekstedt et al 2006). In this context, it is important to differentiate NAFLD from NASH and to assess the stage of fibrosis. Furthermore, the severity of steatosis may change within weeks of the therapeutic intervention and, therefore, cannot be repeatedly monitored using invasive procedures (Aldoheyan et al

Table 5. The discriminative capacity of biological scores in the assessment of NASH (NAS>5points) and for NASH exclusion

	No NASH + Probable NASH	NASH	p	No NASH (NASH excluded)	Probable NASH + NASH	p
Score						
FLI	78.77±23.54	79.08±25.13	0.98	77.39±23.67	89.92±2.13	0.43
ST	0.74 ±0.17	0.79±0.41	0.45	0.69±0.21	0.78±0.32	0.33
HSI	37.89±16.25	40.66±12.51	0.3	38.85±15.43	41.44±5.74	0.55
APRI	1.5±0.12	3.6±0.12	0.01	0.9±0.03	2.9±0.19	0.17

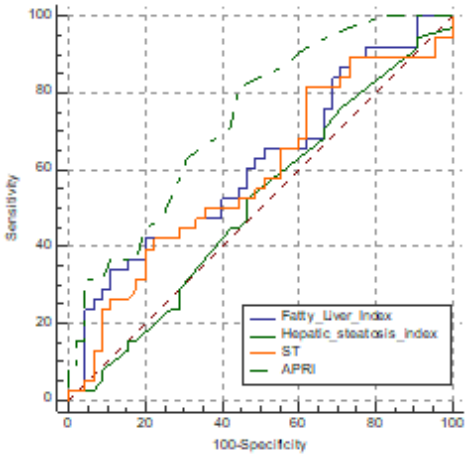

Fig 1. The diagnostic accuracy of biological scores in patients with proven NASH

2016). Therefore, there is a significant need for non-invasive procedures and tests to follow up the progression of NAFLD.

In the present study, we evaluated the role of four non-invasive scores in the assessment of liver steatosis and their efficiency in the diagnosis of NASH. The FLI, ST and HIS biological scores discriminated accurately between moderate or severe steatosis but also helped in evaluating the different stages of steatosis, as suggested in the original articles that first described the scores. (Poynard et al 2005; Munteanu et al 2008, Bedogni et al 2006, Lee et al 2010).

It is important to mention that the scores include anthropometric measurements such as waist circumference and BMI, since steatosis is known to be correlated with these features (Dixon et al 2001, Preuss et al 2018). In addition, biological scores are based on biological markers such as triglycerides and blood sugar level, which are clearly involved in the accumulation of lipids in the liver (Preuss et al 2018, Golabi et al 2018). FLI and HSI can be used in clinical practice for the assessment of steatosis severity. Potential clinical uses of FLI include the identification of subjects to be referred for ultrasonography and the selection of patients for intensified lifestyle counseling (Bayard et al 2006, Marchesini et al 2005).

Difficulties arise when trying to diagnose NASH. Apart from liver biopsy, there is no reliable test to ensure a valid diagnosis. Some researchers suggested that biological tests including markers of apoptosis such as cytokeratin-18 are correlated with the presence of NASH. (Grigorescu et al 2012). Others proved that direct biological markers such as matrix metalloproteinases can be included in diagnostic scores for NASH (Ando et al 2018). We aimed to use simple, non-expensive tests including biological routine markers for the diagnosis of NASH. We did not find any significant association between FLI, HSI or ST and the presence of NASH. However, APRI was the only score we tested which proved efficient in the discrimination of patients with NASH (p=0.01, AUROC= 0.733). The APRI score was elaborated for the assessment of fibrosis in different liver diseases. The correlation between NASH and APRI highlights the importance of inflammation in the development of fibrosis in NAFLD.

Our study has several unique features. Firstly, we recruited consecutive patients who underwent percutaneous liver biopsies and were interpreted by only one pathologist. Secondly, we proved that the APRI score has a good reliability in the diagnosis of NASH. To our knowledge, this association has not been reported in literature before.

The limitations of these tests may be overcome by the controlled attenuation parameter (CAP) feature, which has been recently developed to quantify the attenuation of ultrasound during the measurement of liver stiffness (transient elastography; FibroScan) (Wong et al 2015). Further studies comparing these non-invasive scores and CAP will clarify these limitations.

Conclusion

We proved that ST, FLI and HIS are reliable tests for the diagnosis and staging of NAFLD, besides being precise, non-expensive and easy to use. On the other hand, we identified a correlation between APRI – a fibrosis score – and the presence of NASH; this correlation is a warning of the importance of NASH in the development of fibrosis. These tests are affordable and fast, and alongside liver ultrasound, they can identify patients requiring lifestyle modifications and medical treatment.

References

Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem 2005; 51(10): 1867-1873

Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol 2005;42:132–138.

Aldoheyan T, Hassanain M, Al-Mulhim A, Al-Sabhan A, Al-Amro S, Bamehriz F, et al. The effects of bariatric surgeries on nonalcoholic fatty liver disease. Surg Endosc 2017;31(3):1142-1147.

Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gas- troenterol Hepatol 2007;22:788–93.

Ando W, Yokomori H, Tsutsui N, Yamanouchi E, Suzuki Y, Oda M, Inagaki Y, Otori K, Okazaki I. Serum matrix metalloproteinase-1 level represents disease activity as opposed to fibrosis in patients with histologically proven nonalcoholic steatohepatitis. Clin Mol Hepatol 2018;24(1):61-76

Bayard M, Holt J, Boroughs E: Nonalcoholic fatty liver disease. Am Fam Physician 2006;73:1961-1968.

Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.

Cales P, Laine F, Boursier J, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J Hepatol 2009;50(1):165-173.

Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121(1):91-100.

Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow- up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873.

Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). Medicine (Baltimore). 2018;97(13):e0214.

Grigorescu M, Crisan D, Radu C, Grigorescu MD, Sparchez Z, Serban A. A novel pathophysiological-based panel of biomarkers for the diagnosis of nonalcoholic steatohepatitis. J Physiol Pharmacol 2012;63(4):347-53.

Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al, Nonalcoholic Steatohepatitis Clinical Research Network, 2005 Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41(6):1313-1321

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.

Marchesini G, Natale S, Manini R, Agostini F. Review article: the treatment of fatty liver disease associated with the meta- bolic syndrome. Aliment Pharmacol Ther 2005;22(Suppl 2):37-39.

Wong GL, Wong VW. Fat and fiber: how the controlled attenuation parameter complements non-invasive assessment of liver fibrosis. Dig Dis Sci 2015;60:9–12.

Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–1419.

Munteanu M, Ratziu V, Morra R. Non-invasive biomarkers for the screening of fibrosis, steatosis and steatohepatitis in patients with metabolic risk factors: FibroTest-FibroMax experience. J Gastrointestin Liver Dis 2008;17(2):187-191.

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;43:617–49.

Poynard T, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, et al, The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Comp Hepatol 2005;4:10.

Preuss HG, Kaats GR, Mrvichin N, Swaroop A, Bagchi D, Clouatre D, Preuss JM. Examining the Relationship Between Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome in Nondiabetic Subjects. J Am Coll Nutr 2018;13:1-9.

Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7(2):234–238.

Rafiq N, Younossi ZM. Nonalcoholic fatty liver disease: a practical approach to evaluation and management. Clin Liver Dis 2009;13:249–266.

Ratziu V, Massard J, Charlotte F, et al. Diagnostic value of biochemicalmarkers (FibroTest-FibroSURE) forthe prediction of liver fibrosis inpatients with non-alcoholic fatty liver disease. BMC Gastroenterol 2006;6:6.

Soderberg C, Stal P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010;51:595–602.

Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. Hepatology 1995;22:1714–1719.

Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518-26.

Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis (NASH): inter-protocol agreement and ability to predict liver-related mortality. Hepatology 2011;53(6):1874–1882.

Zein CO, Edmison JM, Schluchter M, Feldstein AE, Zein NN, McCullough A. A NASH predictive index (NPI) for use in patients with nonalcoholic fatty liver disease. Hepatology 2007;46(4):747A.

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