ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 09, pp. 63793-63796, September, 2023
https://doi.org/10.37118/ijdr.27188.09.2023

RESEARCH ARTICLE OPEN ACCESS

WHAT IS THE PERFORMANCE OF NON-INVASIVE FIBROSIS SCORES IN NON-ALCOHOLIC FATTY LIVER DISEASE IN OBESE PATIENTS?

[*1]Mujgan Tuna, [2]Nazire Aladağ and Dr. Ozlem Cakır Madencı

[1]MD, Dr. Lutfi Kırdar Kartal City Hospital, Obesity Department, Kartal, Istanbul/Turkey
[2]MD, Dr. Lutfi Kırdar Kartal City Hospital, Internal Medicine, Kartal, Istanbul/Turkey
[3]MD, Dr Lutfı Kırdar Kartal Cıty Hospıtal, Biochemistry Department, Istanbul/Turkey

ARTICLE INFO

Article History:
Received 20th June, 2023
Received in revised form
11th July, 2023
Accepted 27th August, 2023
Published online 30th September, 2023

KeyWords:

Non-alcoholic Fatty Liver Disease, Morbid Obesity, Fibrosis.

****Corresponding author: Mujgan Tuna,***

ABSTRACT

Background: Obesity has become a growing health concern and is a major risk factor for nonalcoholicfatty liver disease (NAFLD). The availability of an accurate diagnostictool is Essential to prevent the progression of fibrosis, cirrhosis, and hepatocellularcarcinoma. We aimed to evaluate the clinical and predictiveutility of non invasivescores of fibrosisscore in obeseand morbidly obesepatients with NAFLD. ***Methods:*** A total of 150 patients with BMI>30 kg/m2 andwithout a known liver diseaseare included in this prospective study. NAFLD was diagnosed based on evidence of hepaticsteatosis on ultrasonography by the same radiologist. The following non-in vasiveliverfibrosisscores were calculated according to the laboratory results: As partatetransaminase (AST) to alaninetransaminase (ALT) ratio (AAR), AST-to-plateletratioindex (APRI), BARD score, andfibrosis 4 (FIB- 4). ***Results:*** A total of 150 patients (122 femalesand 28 males) wereincluded in thestudy. The medianage of thesubjectswas 48 years, with a range of 23 to 69 years (2.5-97.5 percentile). Significant differences were observed in HOMA-IR, AAR, APRI, and FIB4 scores between patients with out NAFLD and those with different degrees of hepatosteatosis ($p<0.05$). The APRI score was found to be a predictor of hepatosteatosis, with an oddsratio of 32.9 (95% confidence interval, 0.230-4711). ***Conclusion:*** APRI scoremay be a useful tool for early detection of NAFLD in obeseand morbidly obese patients.

Citation**: *Mujgan Tuna and Nazire Aladağ, 2023.*** *"*What is the performance of non-invasive fibrosis scores in non-alcoholic fatty liver disease in obese patients?". *International Journal of Development Research*, 13, (09), 63793-63796.

INTRODUCTION

Obesity and diabetes mellitus have emerged as global epidemics, affecting a staggering 2.4 billion people worldwide, and their prevalence increases with age. In tandem with the rise in obesity, the incidence of nonalcoholic fatty liver disease (NAFLD) and related liver diseases has increased markedly (Asrani, 2019). In Turkey, obesity has become a growing health concern and is a major risk factor for NAFLD. It is estimated that 48.3% of individuals with a BMI greater than 30 kg/m² develop NAFLD (Değertekin, 2021). The metabolic disturbances caused by obesity affect endothelial function. In particular, hormones such as leptin and resistin stimulate the production of reactive oxygen species (ROS), which trigger an increased release of endothelin-1 (ET-1) from endothelial cells in vivo (Avogaro, 2005). Elevated levels of ET-1 have been associated with cardiovascular disease (CVD) in obesity, and they have also been linked to liver fibrosis in patients with non-alcoholic steatohepatitis (NASH) (Degertekin, 2017). NAFLD refers to the presence of hepatic steatosis, characterized by macrovesicular steatosis in more than 5% of hepatocytes, in individuals without alcohol or drug use, or other causes of hepatic (Puri, 2012). Approximately one-third of the world's population is affected by NAFLD, 30% to 40% of patients with NAFLD progress to NASH, and 10% to 30% of NAFLD cases progress to cirrhosis and hepatocellular carcinoma. Long-term follow-up studies have found an incidence of cirrhosis of 3.1% over an average of 7.6 years (Dam-Larsen, 2009). The progression rate from NASH to hepatocellular carcinoma is 40% in the presence of fibrosis, whereas this rate is 5-18% in the absence of fibrosis (McPherson, 2015). It is worth noting that NAFLD is also associated with extrahepatic complications, including colorectal cancer, chronic kidney disease, and CVD, with CVD being the leading cause of death in NAFLD patients [8]. The availability of an accurate diagnostic tool is essential not only for establishing the diagnosis and severity of the disease but also for monitoring the disease over time and the effectiveness of new therapeutic interventions (Vuppalanchi, 2009). Although liver biopsy is a gold standard for the diagnosis of fibrosis it is an invasive and expensive method thus different noninvasive scores have been developed to stage liver disease. In addition to imaging techniques such as ultrasonography, which offers repeatability but presents some inter- and intra-investigator variability, noninvasive fibrosis scores based on patient characteristics, anthropometric measurements, and laboratory parameters have emerged as useful alternatives, especially for ruling out advanced fibrosis (Hernaez, 2011). Several studies have demonstrated the accuracy of these noninvasive fibrosis scores in predicting advanced fibrosis in NAFLD (Angulo, 2007; Sun, 2016 and Harrison, 2008). Aspartate transaminase (AST) to alanine transaminase (ALT) ratio (AAR), AST-to-platelet ratio index (APRI), BARD score, and fibrosis 4 (FIB- 4) scores are suggested (deCarli, 2020). However, few studies have evaluated the value of these scores specifically in the context of obesity. This study aimed to evaluate the clinical and predictive utility of noninvasive scores of fibrosis; scores AAR, APRI, BARD, and FIB4 in obese and morbidly obese patients with NAFLD.

MATERIAL AND METHODS

Patients: This prospective, single-center study was conducted and received ethical approval from the Ethics Committee (Decision Number: 514/208/10, Date: 08/25/2021). The study included 150 patients diagnosed with obesity and NAFLD who received care at the Obesity Center and Internal Medicine Outpatient Clinic between July and September 2021. Exclusion criteria were individuals below 18 and over 80 years of age, pregnant women, patients with a history of malignancy, severe psychiatric disorders (such as bipolar disorder and psychosis), preexisting liver disease, infectious liver disease (such as viral hepatitis type B, C, or HIV), and excessive alcohol consumption (daily alcohol consumption of more than 30 g/day in men and 20 g/day in women).

Data Collection: Body weight (kg) was measured in lightly clothed subjects using a calibrated balance-beam scale. Body height (cm) was measured with a 2 m vertical wall stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Anthropometric measurements were analyzed using the TanitaMC-580 Body Composition Analyzer (TANITA, MC-580, Japan). Patients with BMI>30 kg/m2 were included in the study. Fasting blood samples were obtained after an 8-10 hour fasting period and used to determine complete blood count, fasting blood glucose level, insulin level, AST, and ALT. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the formula: Fasting blood glucose (mg/dL) × insulin (IU/mL)/405. Noninvasive fibrosis scores were calculated as follows: Aspartate transaminase/alanine transaminase ratio (AAR) = AST/ALT ratio (Angulo, 1999), AST-to-platelet ratio index (APRI) = [AST/upper limit of normal values)/platelet count (10^9/L)] × 100 (Chalasani, 2018), BARD score: calculated based on three variables; BMI, AAR, and diabetes. BMI ≥ 28 kg/m² = 1 point; AST/ALT ≥ 0.8 = 2 points; DM2 = 1 point (Harrison, 2007). FIB-4 Index calculation: based on age, AST, ALT, and platelet count using the following formula: FIB4 = [age (years) × AST (UI/L)] / [platelet count (10^9/L) × ALT (UI/L)] (Shah, 2009). Ultrasonography (General Electric machine model of Versana Premier) was performed by the same experienced radiologist. The features of hepatic steatosis, including echogenicity of the liver, visibility of the diaphragm, intrahepatic vessels, and the posterior part of the right lobe of the liver were evaluated (Ferraioli, 2019). If the liver showed significantly increased echogenicity compared with the renal parenchyma, with attenuated ultrasound transmission, indistinct diaphragm, or less visible echogenic walls of the portal vein, it was classified as hepatosteatosis. Hepatosteatosis was graded as follows: Grade I (mild), Grade II (moderate), and Grade III (severe) (Ferraioli, 2019).

Statistical analysis: Statistical analysis was carried out using MedCalc (Medical Calculation Version 12.4.0; Belgium). The Kolmogorov-Smirnov test assessed the distribution of data and either the Mann-Whitney U test or Kruskal-Wallis test was used for the comparison of non-parametric data. After the Kruskal-Wallis test, a post hoc analysis was conducted using the Mann-Whitney U test. The association between the variables of interest and the presence of fibrosis was tested using a multivariable logistic regression model, estimating odds ratios (ORs) and their 95% confidence intervals.

RESULTS

A total of 150 patients (122 females and 28 males) were included in the study. The median age of the subjects was 48 years, with a range of 23 to 69 years (2.5-97.5 percentile). The summary characteristics of the study population are presented in Table 1.

Table 1. Summary Characteristics of the Study Population

	Median (2.5-97.5 percentile)
Demographics	
Total (n=150)	
Age (years)	48 (23-69)
Gender (females) n (%)	122 (81)
BMI (kg/m^2)	40.8 (30-59)
Laboratory parameters	
Glucose (mg/dl)	99 (77-267)
HOMA-IR	4.3 (1.35-17.15)
ALT (IU/L)	22 (9-112)
AST(IU/L)	19 (11-62)
PLT(10^9/L)	288.5 (182-413)
Non-invasive fibrosis assessment tools	
AAR	0.91 (0.44-1.73)
BARD	3 (1-4)
APRI	0.16 (0.07- 0.63)
FIB 4	0.71 (0.29-1.72)
Concomitant diseases	
Diabetes Mellitus n (%)	68 (45 %)
Metabolic Syndrome n (%)	63 (42%)
Exercise	31(%20,6)
Dietary	36(%24)

Of the participants, 94 patients (62.6%) had morbid obesity with a BMI greater than 40 kg/m². Insulin resistance, indicated by a HOMA-IR value greater than 2.5, was found in 135 (90%) of the patients, and 66 (44%) were diagnosed with diabetes. In addition, 45 (30%) of the subjects had metabolic syndrome. NAFLD was diagnosed based on evidence of hepatic steatosis on ultrasonography in patients without a history of alcohol consumption or chronic liver disease. After ultrasonography, 112 patients (74.6%) were found to have hepatosteatosis, with 31.2% classified as mild and 68.8% as severe. An exercise program consisting of at least 30 minutes of moderate-intensity physical activity was recommended, on average five times per week, consuming approximately 200 kcal per exercise session. However, only 68% of patients adhered to the exercise program, and 37% had poor dietary habits, such as skipping breakfast, snacking between meals, and long breaks between meals followed by binge eating at the last meal. In addition, 26% of subjects had excessive eating habits, including consuming foods of high-energy density, eating large portions, eating at night, and loosing control over eating. Table 2 shows the clinical and laboratory characteristics of patients with and without hepatosteatosis. Significant differences were observed in HOMA-IR, AST, ALT and AAR, APRI, and FIB4 scores between patients without NAFLD and those with different degrees of hepatosteatosis (grade 1, and grades 2 and 3). The results were significantly higher in patients with NAFLD ($p < 0.05$). A multivariate logistic regression model was used to evaluate the predictors of NAFLD and the results are shown in Table 3. The APRI score was found to be a predictor of hepatosteatosis, with an odds ratio of 32.9 (95% confidence interval, 0.230-4711).

DISCUSSION

Our study population consisted of obese adults, among whom NAFLD was diagnosed in 74.6% of the participants using ultrasound examination. This high prevalence highlights the association between obesity and NAFLD. NAFLD is a common condition in obese patients and often progresses to NASH, which is associated with liver inflammation and scarring. In some cases, this can lead to irreversible liver damage and cirrhosis. It is noteworthy that obesity, along with type 2 diabetes mellitus and dyslipidemia, can lead to the development of NAFLD at a younger age. Morbidly obese individuals have an even higher prevalence of NAFLD, ranging from 65% to 90%, with NASH prevalence ranging from 15% to 70% (Mummadi, 2008 and Losekann, 2013).

Table 2. Clinical and laboratory characteristics of the patients with and without hepatosteatosis

	Without hepatosteatosis Median (2.5-97.5)	Grade1 hepatosteatosis Median (2.5-97.5)	Grade2 and 3hepatosteatosis Median (2.5-97.5)	p
TOTAL(n=150)	38	35	77	
Age (years)	47(22-66)	51(21-76)	49(24-70)	0.118
BMI(kg/m^2)	40.7(28.4 - 58.7)	38.9(32.3- 56.6)	41.6(30.0- 59.4)	0.319
HOMA-IR	3.6(0-19.6)	3.8(0-14.4)	4.6(0-15.4)	0.290
ALT (IU/L)	16.5(5.9-61.9)	15.5 (8.7-37.5)	26 (11.4-143)	*0.0001
AST(IU/L)	18.0(10.0-33.4)	16.0(11.0-39.6)	23 (11.8-72.3)	*0.0001
PLT(10^9/L)	279(174-377)	296(215-447)	289 (188-419)	0.449
AAR	1.0 (0.4-2.3	1.0(0.6-1.6)	2 (0-2)	*0.0001
BARD	3(1-4)	3(1-4)	3(1-4)	0.064
APRI	0.1(0-0.3)	0.1(0-0.4)	0.2 (0-0.7)	*0.001
FIB-4 (U/T)	0.7(0.2-1.2)	0.7(0.2-1.7)	0.7(0.3-1.7)	*0.016

Table 3. Multivariate logistic regression model for scores in prediction of fibrosis in NAFLD

Variable	Odds Ratio	95 % CI	p
BARD Score	1.188	0.840-1.677	0.326
FIB 4 Score	1.202	0.299-4.822	0.759
APRI Score	32.930	0.230-4711	0.037

Therefore, it is important to evaluate the risk factors and components of NAFLD and NASH in these patients. According to current NAFLD guidelines, liver biopsy should be considered in patients at high risk for NASH and advanced fibrosis such as those with metabolic syndrome, and when noninvasive methods cannot rule out fatty liver or concomitant chronic liver disease (Ando, 2021). Initially, a simple panel can be used to rule out the presence of advanced fibrosis. If the results are suggestive or inconclusive of advanced fibrosis, a biopsy is required to confirm the findings and determine the need for long-term monitoring for cirrhosis and its complications (Ando, 2021). In our study, significant differences in HOMA-IR, AST, ALT, AAR, APRI, and FIB4 values were found between patients with and without NAFLD at different degrees of steatosis. Patients with NAFLD had higher values, indicating a higher degree of liver injury and fibrosis. These results suggest that insulin resistance, liver enzymes, and fibrosis scores (AAR, APRI, and FIB4) may serve as predictors of NAFLD severity. To further assess the predictors of NAFLD, a multivariate logistic regression model was employed. Our analysis showed that the APRI score was a significant predictor of NAFLD in obese and morbidly obese patients, with an odds ratio of 32.9. This result is consistent with previous studies showing that the APRI score is a reliable predictor of NAFLD in obese and morbidly obese patients (Drolz, 2021). Silva et al. demonstrated that the APRI score has a high specificity of 82% and a low sensitivity of 54% and is a specific noninvasive diagnostic test for NAFLD in severely obese patients (de Brito E Silva, 2022). According to Schmitz's study, APRI was able to discriminate NASH with a sensitivity of 74% and a specificity of 67% with an area under the receiver operating characteristic curve (AUROC) value of 0.76) (Schmitz, 2020).

APRI has advantages such as low cost and repeatability, making it a promising biomarker for the evaluation of liver fibrosis/steatosis compared with liver biopsy and other non-invasive methods (Drolz, 2021). Several studies have investigated other predictors of severe liver fibrosis in patients with NAFLD. Angulo et al. found that older age, obesity, diabetes mellitus, and an AAR score greater than 1 were significant predictors of severe liver fibrosis (Angulo, 1999). Sheth et al. suggested that the AAR score could potentially replace the need for liver biopsy in patients with chronic hepatitis C virus (HCV) infection (Sheth, 1998). Another scoring system, BARD combines three variables and has been associated with advanced fibrosis. Harrison et al. reported that a BARD score greater than 2 was associated with a 17-fold increase in the likelihood of advanced fibrosis (Harrison, 2008). However, several studies have shown lower AUROC values (ranging from 0.65 to 0.7) for the BARD- score (Harrison, 2007 and Shah, 2009). In our study, the BARD score did not prove to be a predictor of hepatosteatosis, and there was no significant difference in scores between patients without NAFLD and those with different degrees of steatosis.

The FIB4 score, a simple and cost-effective method, has been validated for both HCV and NAFLD, two common chronic liver diseases (Angulo, 2007). Drolz et al. found that a FIB4 score greater than 1.0 was associated with advanced fibrosis in morbidly obese NAFLD patients, with an odds ratio of 32.1 (6.7-151.9) (Drolz, 2021). Shah et al. demonstrated that a FIB4 cut-off score greater than 1.3 had a negative predictive value of 83% for advanced fibrosis, suggesting that the FIB4 score could avoid liver biopsy in 54% of cases (Shah, 2009). However, in our study, the FIB4 score did not serve as a predictor of hepatosteatosis, which may be because our study population consisted of obese and morbidly obese individuals. Our study population included mainly women, which can be accepted as a limitation of the study. Besides the diagnosis of NAFLD was performed by ultrasonography, which may have high inter-investigator variability. Nevertheless, this study is important because the clinical utility of different fibrosis scores was evaluated in a specific group of patients with obesity and morbid obesity

CONCLUSION

The availability of an accurate diagnostic tool is essential to preventprogressionof NAFLD to fibrosis, cirrhosis and hepatocellular carcinoma.APRI score may be a useful tool for early detection of NAFLD in obese and morbidly obese patients.Further research iswarranted to validate these findings in larger populations and to assess the utility of the APRI score in a broader context.

REFERENCES

Ando Y, Jou JH. Nonalcoholic Fatty Liver Disease and Recent Guideline Updates. Clin Liver Dis (Hoboken). 2021 Feb 1;17(1):23-28. doi: 10.1002/cld.1045.

Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007 Apr; 45(4):846-54. doi: 10.1002/hep.21496.

Angulo P, Hui JM, Marchesini G, et al. Angulo P, Keach JC, Batts KP, Lindor KD. Independentpredictors of liverfibrosis in patients with nonalcoholicsteatohepatitis. Hepatology 1999; 30:1356–1362.

Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol.* 2019 Jan;70(1):151-171. doi: 10.1016/j.jhep.2018.09.014.

Avogaro A, de Kreutzenberg SV. Mechanisms of endothelial dysfunction in obesity. *Clin Chim Acta.* 2005 Oct;360(1-2):9-26. doi: 10.1016/j.cccn.2005.04.020.

Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018 Jan;67(1):328-357. doi: 10.1002/hep.29367.

Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol*. 2009;44(10):1236-43. doi: 10.1080/00365520903171284.

de Brito E Silva MB, Tustumi F, Dantas AC et al. Obesity and severe steatosis: The Importance of Biochemical Exams and Scores. Arq Bras Cir Dig. 2022 Jan 31;34(4): e1626. doi: 10.1590/0102-672020210002e1626.

de Carli MA, de Carli LA, Correa MB, Junqueira G Jr, Tovo CV, Coral GP. Performance of noninvasive scores for the diagnosis of advanced liver fibrosis in morbidly obese with nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. 2020 Mar;32(3):420-425. doi: 10.1097/MEG.0000000000001519.

Degertekin B, Ozenirler S, Elbeg S, Akyol G. The serum endothelin-1 level in steatosis and NASH, and its relation with severity of liver fibrosis. Dig Dis Sci. 2007 Oct; 52(10):2622-8. doi: 10.1007/s10620-006-9147-8.

Değertekin B, Tozun N, Demir F, Söylemez G, Parkan Ş, Gürtay E, Mutlu D, Toraman M, Seymenoğlu TH. The Changing Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Turkey in the Last Decade. *Turk J Gastroenterol*. 2021 Mar;32(3):302-312. doi: 10.5152/tjg.2021.20062.

Drolz A, Wolter S, Wehmeyer MH, Piecha F, Horvatits T, Schulze Zur Wiesch J, Lohse AW, Mann O, Kluwe J. Performance of non-invasive fibrosis scores in non-alcoholic fatty liver disease with and without morbid obesity. *Int J Obes* (Lond). 2021 Oct;45(10):2197-2204. doi: 10.1038/s41366-021-00881-8.

Ferraioli G, Soares Monteiro LB. Ultrasound-based techniques for the diagnosis of liver steatosis. *World J Gastroenterol*. 2019 Oct 28;25(40):6053-6062. doi: 10.3748/wjg.v25.i40.6053.

Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut. 2008 Oct; 57(10):1441-7. doi: 10.1136/gut.2007.146019.

Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011 Sep 2;54(3):1082-1090. doi: 10.1002/hep.24452.

Losekann A, Weston AC, Carli LA, Espindola MB, Pioner SR, Coral GP. Nonalcoholic fatty liver disease in severe obese patients, subjected to bariatric surgery. ArqGastroenterol 2013 Oct-Dec; https://doi.org/10.1590/S0004-28032013000400009

Mallik M, Singhai A, Khadanga S, Ingle V. The Significant Morbidity and Mortality Indicators in Patients of Cirrhosis. Cureus. 2022 Jan 14;14(1):e21226. doi: 10.7759/cureus.21226.

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 May;62(5):1148-55. doi: 10.1016/j.jhep.2014.11.034.

Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1396-402. doi: 10.1016/j.cgh.2008.08.012.

Puri P, Sanyal AJ. Nonalcoholic fatty liver disease: Definitions, risk factors, and workup. Clin Liver Dis (Hoboken). 2012 Sep 25;1(4):99-103. doi: 10.1002/cld.81

Schmitz SM, Kroh A, Ulmer TF, Andruszkow J, Luedde T, Brozat JF, Neumann UP, Alizai PH. Evaluation of NAFLD and fibrosis in obese patients - a comparison of histological and clinical scoring systems. BMC Gastroenterol. 2020 Aug 5;20(1):254. doi: 10.1186/s12876-020-01400-1.

Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009 Oct;7(10):1104-12. doi: 10.1016/j.cgh.2009.05.033.

Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 1998 Jan;93(1):44-8. doi: 10.1111/j.1572-0241.1998.044.

Sun W, Cui H, Li N, Wei Y, Lai S, Yang Y, Yin X, Chen DF. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. Hepatol Res. 2016 Aug;46(9):862-70. doi: 10.1111/hepr.12647.

Vuppalanchi R, Unalp A, Van Natta ML, Cummings OW, Sandrasegaran KE, Hameed T, Tonascia J, Chalasani N. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic Fatty liver disease. Clin Gastroenterol Hepatol. 2009 Apr;7(4):481-6. doi: 10.1016/j.cgh.2008.12.015

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