

# The impact of scoring system in the evaluation of Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

## Abstract

Nonalcoholic fatty liver disease (NAFLD) is an increasingly prevalent disease that has become the leading cause of liver-related morbidity and mortality in industrialized countries. It encompasses a spectrum of pathological manifestations that range from fatty infiltration without liver damage, to inflammation which can progress to fibrosis and cirrhosis. Individuals with features of the metabolic syndrome are at high risk of developing NAFLD. A major challenge is to find the reliable non-invasive diagnostic tool for the different aspects of NAFLD, particularly steatosis, steatohepatitis, and fibrosis. Currently, a liver biopsy is the definitive diagnostic test, but it is invasive and carries the risk of overt complications, and provides information on a very small portion of the liver. In this review, we discussed the various scores for diagnostic evaluation of patients with NAFLD and NASH.

**Keywords:** nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, fibrosis, diagnostic score

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**Abbreviations:** NAFLD, nonalcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; NFS, fibrosis score; AURCO, area under the receiver operating characteristic curve; CI, comprehensive index; SNPs, single nucleotide polymorphisms; FLI, fatty liver index; ELFP, enhanced liver fibrosis panel

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common etiologies of liver diseases in the United States.<sup>1</sup> NAFLD is a spectrum of pathological manifestations in non-alcoholic individuals which range from fatty infiltration of liver to steatohepatitis and cirrhosis. It is further categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) based on histological findings. NAFL is defined as the presence of  $\geq 5\%$  hepatic steatosis without evidence of hepatocytic injury while NASH is defined as the presence of  $\geq 5\%$  hepatic steatosis and inflammation with hepatocyte ballooning injury with or without fibrosis.<sup>1,2</sup> NAFLD is a highly prevalent disease and has been reported to affect about one billion individuals in the world.<sup>3</sup> Recent studies suggest that up to 30 to 40% of Americans have NAFLD in the United States.<sup>4-9</sup> Approximately 20% of NAFLD affected individuals are at risk of progression to NASH which is the second most common etiology for liver transplantation in the United States and is expected to be the leading cause in the next few years.<sup>10,11</sup> Screening for NAFLD is challenging because most patients are asymptomatic until the development of cirrhosis. Asymptomatic individuals come to attention due to blood tests performed for other indications.<sup>12</sup> Compared to the general population, patients with NAFLD have a significantly higher all-cause mortality, an increased incidence of cancer, diabetes and cardiovascular diseases, which is

also the most common cause of death in pre-cirrhotic NAFLD.<sup>1,13,18</sup> Considering these challenges, there is a need to establish a practical and effective approach for the evaluation and early detection of NAFLD particularly in those individuals who are at risk of developing fibrosis. Various biochemical marker and imaging modalities are being used for the diagnostic evaluation of both NAFLD and NASH. In this review we focused on the role of various scoring system in the evaluation of NAFLD and its progression to NASH and advanced liver fibrosis.

## The NAFLD fibrosis score (NFS)

NFS is commonly used scoring system to estimate advanced liver fibrosis. The NFS can only be used to determine the severity of liver fibrosis rather than diagnosis of NASH.<sup>2</sup> The NFS is based on the following parameters; age, BMI, hyperglycemia, albumin, platelet count and AST/ALT ratio. Using these 6 parameters, Angulo et al. differentiate between advanced and minimal fibrosis with an area under the receiver operating characteristic curve (AURCO) 0.88 and 0.82 in the estimation and validation group respectively.<sup>19</sup> They also determined a cut off value of NFS less than -1.455 to exclude and greater than 0.676 to predict advanced liver fibrosis. Using low cut off value, the fibrosis was excluded with high accuracy (NPV up to 93%), while fibrosis was diagnosed using high cutoff value with high accuracy (PPV up to 90%). Although the precision rate is very high to predict or exclude advanced fibrosis ( $\geq F3$ ) using these cutoff values, however NFS does not clear the stage of liver fibrosis (F1-2) if the value is between -1.455 to 0.676. Liver biopsy is needed in these cases of intermediate stage of liver fibrosis. Further studies are needed to overcome these limitations of NFS in the differentiation of steatosis and NASH.

## Fibrosis-4 (FIB-4) index

FIB-4 index is a non-invasive method to determine advances fibrosis in NAFLD and is calculated by documenting the age of a patient and the values of AST, ALT and platelet count obtained from a routine blood test, which emphasizes the ease of obtaining the FIB-4 score in a patient. A recent retrospective cohort study suggests that the FIB-4 index can provide a definitive diagnosis of NASH with a 67% sensitivity and 73% specificity. The same study also concluded that FIB-4 is also well equipped to identify NASH with mild fibrosis out of a NAFLD study population (57% sensitivity, and 75% specificity).<sup>20</sup> A recent study determined the cutoff value of FIB-4 score for evaluation of advanced fibrosis.<sup>21</sup> A cutoff value of <1.45 excludes advanced fibrosis and has 74% sensitivity, 71% specificity, 22% PPV, 73% NPV giving an AUROC of 0.87. Similarly, a higher cutoff value >3.25 predicts advanced fibrosis and has 26% sensitivity, 98% specificity, 75% PPV, 85% NPV giving an AUROC of 0.88. The efficiency of FIB-4 score between 1.45 to 3.25 is still undetermined and there is a scarcity of studies that have assessed the efficacy of FIB-4 in the clinical setting. Further studies need to be performed to determine its usefulness in diagnosing NASH and NAFLD. For detection of advanced liver fibrosis (F3) or cirrhosis (F4), both NFS and FIB-4 index are recommended to be useful tools in current guidelines.<sup>1</sup> Both NFS and FIB-4 are equivalent to MRE and better than other indices (like ASL/ALT ratio, BRAD score) for detection of advanced fibrosis in biopsy-proven NAFLD patients.<sup>22</sup>

## Comprehensive index (CI)

The comprehensive index (CI) combines six different serum biomarkers (weight, BMI, waist circumference, AST/ALT, triglycerides and fasting blood glucose) with different anthropometric denominations via a multivariate logistic regression analysis to detect NAFLD at an earlier stage. The sensitivity of CI was 90% while the specificity was 76%.<sup>23</sup> The CI can also take into account the development of single nucleotide polymorphisms (SNPs) in genes that regulate lipid metabolism. The incorporation of known gene mutations in CI can further enhance its sensitivity and specificity for detection of NAFLD. CI is unable to discern between various pathologic stages of NAFLD such as simple fatty liver, hepatic steatosis and its complicated advancements such as liver cirrhosis and HCC, which explains the narrow use of this index in current practice.

## Fatty liver index (FLI)

FLI is a simple and one of an accurate predictor of hepatic steatosis in the general population. It is based on an algorithm that accounts for four parameters including BMI, waist circumference, triglycerides, and  $\gamma$ -glutamyl transpeptidase. A study on 8626 patients determined the cutoff value of FLI in the evaluation of middle-aged and elderly patients with NAFLD.<sup>24</sup> A cutoff value of 30 was found to be promising in the identification of patients with NAFLD with 80% sensitivity, 72% specificity, giving an AUROC of 0.83.<sup>24</sup> FLI is a practicable computing tool because it uses clinical and laboratory values that are readily performed in both inpatient and outpatient settings which enhances its applicability. This allows for effective screening of patients at risk of developing the disease and subsequent introduction of lifestyle modifications that can curb the development and/or progression of this ailment. It can also help in siphoning candidates with suspected NAFLD who can then take part in research models that target further screening, investigations and treatment.<sup>25</sup>

## Fibro test

FibroTest is a noninvasive panel of serum markers to predict liver fibrosis with high NPV in advanced liver fibrosis.<sup>26-29</sup> The serum markers in this panel are haptoglobin, alpha2 microglobulin, total bilirubin,  $\gamma$ -glutamyl transpeptidase, and apolipoprotein A1. A recent study used FibroTest to predict advanced fibrosis in NAFLD.<sup>30</sup> The authors found AUROC of 0.81-0.92 in detecting F3-4 fibrosis and 0.75-0.86 in predicting F2-4. They determined the cutoff value of 0.30 and 0.70 for advanced liver fibrosis with 90% NPV and 73% PPV. The diagnostic performance of FibroTest was evaluated in a study of 600 biopsy-proven NAFLD patient by comparing FibroTest with BRAD score, FIB-4 index, and NFS.<sup>31</sup> The non-binary AUROC for FibroTest (0.877) was found to be superior to BRAD score (0.836), FIB-4 index (0.845) and comparable with NFS (0.866)<sup>31</sup>. Although FibroTest can detect liver fibrosis effectively, however, the routine application of this test is difficult due to unavailability of some of serum markers in most laboratories assay.

## Enhanced liver fibrosis panel (ELFP)

ELFP is commercially available markers of matrix turnover including PIIINP, hyaluronic acid (HA) and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). A recent study utilized ELFP in NASH patients showed AUROC of 0.90 and 0.82 in detecting stage F3-4 and F2-4 of advanced fibrosis respectively.<sup>32</sup> The ELFP cutoff value -0.2070 was found to have 61% sensitivity and 80% specificity to rule out liver fibrosis in NASH patients. ELFP is better diagnostic panel than NFS for detection of moderate fibrosis (AUROC 0.90 vs 0.86) and severe fibrosis (AUROC 0.93 vs 0.89), combination of these tests performs even better than individual test for detection of moderate (AUROC 0.93) and severe fibrosis (AUROC 0.98).<sup>32</sup>

## BRAD core

BRAD core is utilized to detect advanced liver fibrosis F3-4 in NAFLD. The BRAD score is based on BMI, AST/ALT ratio, and status of type II diabetes in suspected patients with NAFLD. A cutoff score value <2 is a reasonable predictor in exclusion of advanced fibrosis (NPV 95-97%), while a cutoff score >2 is associated with advanced liver fibrosis F3-4 with sensitivity and specificity of 88% and 89% respectively, and an AUROC of 0.865.<sup>33</sup> The BRAD has limited diagnostic value for detection of early stages of fibrosis and can only be utilized to predict severe fibrosis.

## Conclusion

Diagnostic evaluation of patients with NAFLD/NASH is challenging. The scoring system is a promising tool for identification of NAFLD and its progression to NASH. Further validation studies are required for clinical utilization of scoring system for assessment of various stages of disease progression.

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## Conflicts of interest

The authors have no conflicts of interest.

## Author's contribution

- a. Muhammad Nadeem Yousaf: Manuscript writing
- b. Fiaz S. Chaudhary: Manuscript and data review
- c. Wajahat Z. Mehal: Manuscript writing and overall supervision.

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