

Original Article

Assessment nonalcoholic fatty liver disease fibrosis score for staging and predicting outcome

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is emerging as one of the leading disorders of liver worldwide. NAFLD fibrosis score (NFS) is a noninvasive simple test for staging fibrosis in patients with NAFLD, with an acceptable diagnostic performance and extensively validated in various populations. In clinical practice, the suboptimal diagnostic accuracy however makes it clinically valuable only in excluding severe fibrosis, or in a combination with other complimentary approaches. Nevertheless, the NFS could be used as a helpful tool to monitor disease progression and to evaluate efficacy of potential therapies for NAFLD adults. This review describes the implementation of NFS in fibrosis staging and outcome predicting. The outcome prediction of NAFLD traditionally depends on baseline histology of biopsy specimen, and advanced fibrosis is best associated with overall and liver-related mortality among the individual pathologic features. Accordingly, NFS exhibits an intriguing ability for outcome prediction, including the long term mortality, hepatic and extra hepatic complications and whether liver related or not. Its merit in predication for long-term outcomes could derive substantially from its ability in fibrosis evaluation, as a moderately prognostic accuracy was replicated by FIB-4, another good noninvasive simple test for identifying liver fibrosis, in our study and others. In addition, this ability could be explained by the incorporated variables. In more detail, lower level of albumin, older age and the concomitant injury of glucometabolism, all suggest an overall poorer outcome in complications whether liver related or not for NAFLD patients. Here we propose to calculate NFS in newly diagnosed patients with NAFLD and recalculate annually to timely monitor disease progression. Nonetheless, the appropriate cutoff values of the NFS for different purposes remain to be determined.

Keywords: Nonalcoholic fatty liver disease, NAFLD fibrosis score, staging, natural history, mortality

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, the prevalence of metabolic syndrome linked with obesity. The high prevalence of metabolic syndrome and obesity acknowledged as a major worldwide public health concern. The incidence rate is as high as 15% in adult Chinese [1, 2]. Generally, (> 80%) NAFLD is recognized as benign disease, however, some individuals may develop major hepatic and extra-hepatic complications (also defined as NAFLD-at-risk) [3-6]. Liver biopsy is widely used to differentiate among patients with simple steatosis (SS) and non-alcoholic steatohepatitis (NASH) which can progress to cirrhosis, hepatocellular

carcinoma, and liver-related mortality. NASH with advanced fibrosis (stage 3-4) is associated with the highest risk [1, 4]. A recently reported cohort study showed that fibrosis stage is one of the leading predictors for both liver-related and overall mortality, regardless of the inflammatory degree [7]. Additionally, a major portion (37%~64%) of SS patients can progress to NASH and clinically significant fibrosis within limited time (3.7~6.6 years), consistent to stage 1 of progression over 14.3 years (versus 7.1 years for patients with NASH), as suggested by paired biopsy cohorts [8-10]. These studies challenge the traditional view that SS and NASH have distinct nature and SS is a stable histological subtype of NAFLD and provides a potential explanation for the increased morbidity and

mortality of SS patients than that of matched healthy controls [4, 11, 12]. Therefore, it is critical to stage fibrosis precisely and identify prognostic factors with in time during daily management of NAFLD [13].

To date, staging of fibrosis is an important tool that based on histological examination of a tissue specimen collected through liver biopsy which is an invasiveness procedure with inherent sampling variability. Besides, complexity of the procedure also limits its use in clinical practices. A high prevalence of NAFLD globally calls for a more efficient means for histological evaluation [14, 15]. In the last several decades, consistent efforts have been made in the development of alternative noninvasive strategies for the staging of NAFLD and noninvasively simple tests to identify patients at higher risk of disease progression [1, 14]. Among these approaches, a group of predictive scores for advanced fibrosis derived from routine laboratory tests and clinical variables by multivariate analyses, usually named noninvasive simple panels, standout attributing to its convenience and low cost [14]. Among those simple panels, the NAFLD fibrosis score (NFS) is an intriguing one with its acceptable diagnostic performance in advanced fibrosis assessment and promising use in risk stratification for long term prognosis of NAFLD. NFS can be conveniently scored on excel or online at the following website: <http://www.naflscore.com/> [3, 4, 14, 16].

The NFS, together with transient elastography have been recognized as a most validated tool for staging of liver fibrosis, although it requires further optimization [14]. It allows confident diagnosis of severe fibrosis and selection of subgroups of patients who might benefit the most from a liver biopsy for fibrosis staging purpose [14]. As a result, the NFS has been recommended for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis by the U.S practice guideline for the diagnosis and management of NAFLD [17]. And its value in risk stratification for prognosis is gaining wider attention [3].

Therefore, this Review discusses the advantages and limitations of using NFS as an important reference for the management of adults with NAFLD, focusing on following two aspects: 1) The NFS as a noninvasive test for fibrosis staging and its clinical implementation; 2) NFS as a prognostic tool for outcome prediction.

NFS as a noninvasive test for fibrosis staging and its clinical implementation

NFS alone as a noninvasive test to stage fibrosis

NFS is a scoring system incorporating 6 routinely measured and readily available clinical and laboratory variables data which used to separate NAFLD patients with or without advanced fibrosis. It was proposed by Angulo *et al.* in 2007 in a multicenter large cohort study of patients with liver biopsy-proven NAFLD (n=733) predominate (90%) of Caucasian [18]. Briefly, six independent predictors of advanced fibrosis such as age, hyperglycemia, body mass index (BMI), platelet count, albumin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR) were used in multivariate analysis, which were combined into a regression formula $(-1.675 + 0.037 \times (\text{age} [\text{years}]) + (0.094 \times \text{BMI} [\text{kg}/\text{m}^2]) + (1.13 \times \text{impaired fasting glucose or diabetes} [\text{yes} = 1, \text{no} = 0]) + (0.99 \times \text{AAR}) - (0.013 \times \text{platelet} [10^9/\text{L}]) - (0.66 \times \text{albumin} [\text{g}/\text{dl}])$. For fibrotic severity prediction, an area under the receiver operating characteristic curve (AUROC) of 0.88 and 0.82 were obtained in estimation group (n=480) and validation group (n=253), respectively. Several authors stated that a liver biopsy would have been avoided in 549 (75%) of the 733 patients, with a correct prediction in 496 (90%), if this model had been used. In addition, NFS may be a better reflection of fibrosis severity in the whole organ than that of liver biopsy analysis given the uneven distribution of fibrosis in the livers of NAFLD patients [18].

Subsequently, the diagnostic analysis of the NFS for advanced fibrosis has been extensively validated in various other independent populations of NAFLD and shown a concordantly confident ability in ruling out severe fibrosis [19]. In several Studies using the NFS in Chinese populations also demonstrated that it had a reliable negative predictive value (NPV) of 88%~91% in excluding advanced fibrosis, while the accuracy is somehow suboptimal in defining advanced fibrosis [19, 20]. In a meta-analysis included 3,064 patients from different ethnic populations (including American Caucasians, blacks, and Hispanics, Europeans, and Asians), distributions of fibrotic severity (10%~37%), ages, and obesity and diabetes status from 13 eligible studies, Musso *et al.* reported a pooled AUROC of 0.85 (95% confidential interval [CI],

0.80-0.93) for NFS, with a sensitivity of 90% and a specificity of 97% for diagnosing advanced fibrosis [4]. The conflicting observations from different studies are indicating the differences of clinical feature of patients involved, the sampling variability of liver biopsy and the suboptimum of fibrotic semi-quantitative score system rather than quantitative image analysis used as a diagnostic reference [21-23].

Compared with other noninvasive panels

Several studies compared the diagnostic performance between the NFS and other noninvasive simple tests or panels using direct markers of liver fibrogenesis [19, 20, 23-28]. Although it was complicated by a slightly lower AUROC than the FIB-4 index in some research, the NFS usually maintains an AUROC of clinical use (≥ 0.8) and is able to reliably exclude advanced fibrosis in a high proportion (52%~72.4%) of patients with NAFLD [19, 20, 24-26]. And its performance remains stable in NAFLD patients with normal ALT levels [29, 30] and morbidly obese patients [31], though a slight change of cutoff value for ruling out advanced fibrosis in those with normal ALT levels may be important.

Comparison between the NFS and TE

In comparison with TE, a favorable approach using imaging modality to detect severe fibrosis and cirrhosis, the NFS usually performs less satisfying when the analysis was limited to those patients with successful liver stiffness measurements (LSMs), but not when all patients originally recruited were analyzed [32-34]. However, additional to the requirement for a dedicated device, TE suffered from the high rate of failure (no valid shot) or unreliable results, particularly in those morbid obese patients [14, 35]. Thus the NFS remains to be an important choice in noninvasive approaches for fibrosis estimation in spite of popularity of TE. Furthermore, due to the good feasibility in all patients, NFS scoring has been proposed as the initial step in a sequential diagnostic procedure to reduce the chance for liver biopsy especially when LSM fails [4].

Combining with other noninvasive approaches

The precision of NFS alone for the diagnosis of severe fibrosis in clinical practice is still poor. Stepwise combination of the NFS with other

simple noninvasive tests seems insufficient to improve its diagnostic accuracy [36], LSM, in contrast, complemented NFS quite well [37]. In a study aiming to evaluate the performance of combined noninvasive tools for identifying advanced fibrosis, the combination of LSM plus NFS performed best against LSM, NFS, FIB-4 alone or other combination strategies [37]. In the training cohort, the combination of LSM plus NFS provided false positive, false negative and uncertainty area rates of 0%, 1.1% and 48% respectively, and similar results were obtained in the validation cohort. The evident advantage of multiple vs. single tests is the ability to reduce both false negative and false positive results, although the number of patients in uncertainty increases. However, the advantages of this approach need further evaluation in independently prospective studies [37].

Describing the histological severity in epidemiologic study

Considering its noninvasive nature and the extensively validated diagnostic application against other simple tests, the NFS has already been used in tracking the histological severity in large population-based epidemiologic studies. Armstrong *et al.* [38] depicted the range of disease severity of NAFLD using the NFS in patients with incidental abnormal liver function tests (LFTs) in a primary care setting in UK. According to the original cutoff value of NFS to diagnose (> 0.676) or exclude (< -1.455) advanced fibrosis, 7.6% of NAFLD patients were predicted to have possible advanced liver fibrosis and 57.2% were confidently absent of advanced fibrosis [38]. Based on NFS result, subjects with suspected advanced fibrosis identified by primary care practitioners can be timely transited to secondary care for early disease management, while patients with an unspecified NFS will receive closer monitoring in primary care. The NFS, with the BARD score, was also applied to evaluate fibrotic severity in a Korean study that investigated the role of the PNPLA3 I148M polymorphism in the liver fibrosis of NAFLD, and the effect of the established risk allele G of PNPLA3 rs738409 on liver fibrosis was verified by this noninvasive tool [39]. In the general Hong Kong Chinese populations, Wong *et al.* reported the prevalence of advanced fibrosis estimated by TE in 264 NAFLD patients

diagnosed by ^1H -MRS (proton magnetic resonance spectroscopy) [40]. Eight (3.7%) patients with a LSM ≥ 9.6 kPa were diagnosis with advanced fibrosis. However, when the cutoff of 0.676 of NFS was applied, none of advanced fibrosis was identified in the cohort, compared with the figure of 0.4% by FIB-4 (score ≥ 2.67) and 0% by APRI (score ≥ 1.5). The selection criteria (community population vs. subjects with abnormal LFTs in primary care), diagnosis tool for NAFLD (^1H -MRS vs. ultrasonography) and different BMI (22.8 vs. 28.7 kg/m²) maybe contribute to the difference of fibrotic severity estimated by NFS in a similar prevalence of NAFLD (28.6% vs. 26.4%) [38, 40]. However, Wong's study provided comprehensive epidemiological data on Chinese NAFLD in community in which liver-biopsy is unpractical. But care should be taken when we interprets these data, as the NFS tend to underestimate while TE overestimate the fibrotic severity of NAFLD. For the best utilization of the NFS in this case, a combine strategy with TE or other noninvasive tools would be reasonable.

Additionally, Dvorak *et al.* [41] used the NFS as well as other serum biomarkers to analyze the histological severity of NAFLD patients who were not indicated for liver biopsy. The results showed that a substantial portion (up to 35%, estimated by serum hyaluronic acid, a better marker in defining advanced fibrosis than the NFS in those subjects) of them might have undiagnosed advanced fibrosis against those biopsied patients with a clinical suspicion of severe liver disease (30% per liver biopsy) [41]. This study emphasizes the importance of precise examination of those patients with suspected NAFLD but not indicated for a liver biopsy. The NFS would play a potential role in minimizing the underestimation of significant fibrosis in these subpopulations.

Identifying extrahepatic damage

NAFLD is associated with various clinical conditions however, liver per se, and cardio-vascular disease (CVD) are very common. The clinical use of NFS in assessing cardio-vascular organ damage among patients with ultrasonography-diagnosed steatosis was explored in a cross-sectional study reported from Italy [42]. Cardio-vascular organ damage was defined as increased carotid intima-media thickness (cIMT,

> 0.9 mm) and/or left ventricular mass index (LVMI, 115 [g/m²] for men and 95 for women), and the NFS was used to determine the probability of fibrosis. In comparison with those at low (< -1.455) probability of liver fibrosis, individuals both high (> 0.676) and intermediate ($-1.455 \sim 0.676$) probability of fibrosis showed an unfavorable cardio-metabolic risk profile after adjustment for smoking and metabolic syndrome. When the AUROCs used for identifying cases with vascular atherosclerosis or left ventricular hypertrophy were calculated, NFS produces a significantly higher AUROC than that of FIB-4, BARD, APRI and fatty liver index (FLI), and similar to that of the classical Framingham risk score. Thus the NFS is able to discriminate NALFD patients with different degree of cardiovascular organ damage independently of other known factors [42]. Similarly, the same group [43] analyzed the association of severity of liver fibrosis with the prevalence of chronic kidney disease (CKD) in individuals with NAFLD using the NFS. The authors concluded that advanced liver fibrosis identified by the NFS is also associated with CKD independently from other traditional factors including age, gender, BMI and diabetes [43].

Evaluating the response to treatment

Lifestyle modification is the basis for management of NAFLD. OH *et al.* [44] reported a retrospective analysis of middle-age obese men who had completed a 12-wk supervised exercise training program to determine the effect of exercise without dietary restrictions, and a group of surrogate markers such as the NFS were selected to quantify changes of the pathophysiology [44]. Exercise training improved hepatic inflammatory condition and its related oxidative stress levels, showing its beneficial effect on obesity-related liver diseases even without detectable weight loss. The NFS, however, showed little change after this exercise training program, which was in line with the difficulty in fibrosis reversal by exercise itself [45].

The NFS has also been used to evaluate the efficacy of bariatric surgery for avoiding a postsurgical liver biopsy [46]. In a prospective cohort study aimed to determine the evolution of liver disease 12 months after Rouxen-Y gastric bypass (RYGB), 63 eligible patients were enrolled and mean NFS decreased from 1.142

to 0.066 after surgery, with a resolution rate of advanced fibrosis of 55% (22/40) assessed by this method [46]. Thus the NFS is an easy and adequate way to assess the influence of the surgical procedure on liver diseases, and its application in this aspect should be encouraged. Although it does not replace liver biopsy, the authors stated that, the NFS has no related morbidity and no restraints from modality can easily and promptly determined through routine studies, thus it is very suitable for clinical follow-up purposes [46]. If validated, the utilization of NFS, including other noninvasive simple tests could be introduced in clinical trials assessment.

Monitoring disease progression

Several studies explored the use of NFS in monitoring disease progression of the NAFLD. In a cohort study investigating disease progression of the NAFLD, the NFS, TE and other simple tests were applied for staging fibrosis after a 4 years' follow up for 36 biopsy-proven Japanese patients with NAFLD [47]. TE identified 9 (25%) patients with fibrosis progression and 10 (27.8%) with fibrosis remission, these observations were consistent with that from biopsy based study [47, 48]. As for those noninvasive simple tests, changes of FIB-4 and APRI, but not the NFS, correlated significantly with the LSM alteration [47]. The small size of sample made it difficult to use for final conclusion, yet all these noninvasive strategies could be useful in monitoring the progression of hepatic fibrosis in NAFLD patients.

In a retrospective study to analyze the risk factors of HCC in patients with NAFLD, patients with a higher score of APRI (> 1.5) had a mean HR of 25 in contrast with those score no more than 1.5 [49]. The potential value of the NFS in this scenario has not been reported and is highly expected.

NFS as a prognostic tool for outcome predicting

In addition to its application in fibrosis assessment, the NFS could be a useful predictor for long-term outcomes in NAFLD patients. This was supported by several biopsy- or ultrasonography-based cohort studies of NAFLD reported from different regions.

The prognostic relevance of liver fibrosis in NAFLD

Non-alcoholic fatty liver disease is associated with elevated mortality due to cardiovascular failure, malignancy and liver-related deaths [1]. Assessment of various components of pathologic features individually revealed that advanced fibrosis (stage 3 fibrosis and cirrhosis), but not grades of steatosis, lobular inflammation, or ballooning degeneration, causes higher risk of liver-related mortality in NASH [7]. Advanced fibrosis individually is a leading cause of long-term liver-related mortality in the individual pathologic features [7, 12, 50]. Additionally, NAFLD patients with advanced fibrosis, irrespective of their inflammatory degree, had also increased mortality ([hazard ratio, HR]=3.3) after a mean 26.4 years of follow-up in a Sweden cohort of NAFLD, indicating the strongest predictive value of fibrosis stage for both liver-related and overall mortality [7]. As mentioned above, liver biopsy remains the gold standard for assessing stage of disease, but its invasive nature makes it impractical for routine use as a prognostic tool. However, simple tests such as the NFS are most practical.

The NFS in overall and liver-related mortality prediction

In a cohort study to determine the mortality effect of NAFLD and advanced fibrosis in NAFLD on the basis of the National Health and Nutrition Examination Survey data-a representative sample of the non-institutionalized civilian population of the U.S ($n=11,154$, NAFLD 4,081), Kim *et al.* [51] selected NFS, APRI, and FIB-4 score to estimate the presence of liver fibrosis. According to their results, ultrasonography-diagnosed NAFLD itself was not associated with increased mortality after a median follow-up of 14.5 years; advanced fibrosis, as determined by noninvasive fibrosis marker panels, however, was an outstanding predictor of mortality independent of other known factors. Compared with the individuals with a low probability of advanced fibrosis recognized by NFS, patients with a high probability had a 69% increase and those with intermediate score had a 26% increase in overall mortality. Cause-specific mortality analyses showed that the increase in mortality associated with fibrosis was essentially driven by cardiovascular events,

and the number of liver related deaths (37/1795) is too small to address the association between severe NAFLD with hepatic mortality statistically [51]. Similar analysis was implemented to patients with NAFLD from the Rochester Epidemiology Project of the U.S [52]. Among the 302 NAFLD patients with a follow-up of 12 (≥ 5) years, it was estimated that 181 (60%) subjects had a low probability (NFS < -1.5) while 13 (4.3%) had a high probability (NFS > 0.67) of advanced fibrosis at baseline, and 39 (13%) died during the follow-up. According to the NFS calculated, liver fibrosis in most patients (60%) were stable, 37% were progressive and only 3% were regressive. The annual NFS alteration (median 0.1 for all patients) in patients who died was significantly higher than those in patients who survived (0.14 vs. 0.07) during the follow-up. A higher NFS at baseline and the presence of new-onset coronary heart disease (CHD) were independently predictive of death by multivariate analysis. A baseline NFS of -0.9 was the best cutoff value with a sensitivity of 62%, specificity of 76%, positive predictive value of 28%, NPV of 93% and AUROC of 0.7 to predict overall death [52]. Thus for baseline risk stratification and follow-up of fibrosis progression in general population, it is reasonable to calculate NFS in newly diagnosed patients with NAFLD and to recalculate it annually.

In our retrospectively hospital-based cohort study with ultrasonography-diagnosed NAFLD patients, we validated the predictive performance of NFS for overall mortality in Chinese adults [53]. In brief, 180 eligible patients (median age 39 years; 96 males) were included, with 12 deaths over a median follow-up of 6.6 (range: 0.5-14.8) -year. The NFS other than 3 other scoring systems (FIB-4, APRI and BARD) was identified as the only predictor of all-cause mortality [HR=2.743] by Cox model analysis. As for the performance to predict overall mortality, the NFS yielded the highest AUROC of 0.828 (95% CI 0.728~0.928, $P < 0.05$), followed by FIB-4, APRI and BARD with their AUROCs of 0.806, 0.732 and 0.632 respectively ($P < 0.05$, except for BARD). Although performed on a less-robust cohort with limited information, the prognostic power of the NFS for overall mortality has been evaluated in a Chinese population of NAFLD and clearly manifested a good ability of prediction over a shorter period.

As ultrasonography is insensitive in detecting hepatic steatosis and unable to distinguish fibrosis, NASH- especially the burned-out one from SS. Angulo *et al.* [16] confirmed the prognostic value of the NFS and other simple tests in a cohort of biopsy-proven NAFLD from specialized referral centers. In this retrospective, international, multicenter cohort of biopsy-based NAFLD patients (n=320), 13% of the patients died or underwent liver transplantation with a median follow-up of about a decade (104.8 [range 3-317] months). CVD, non-liver malignancy and complications of cirrhosis were the most common causes of death. The diagnostic accuracies of the four scores (NFS, APRI, FIB-4, and BARD) at baseline to distinguish between patients with and without risk for death/liver transplantation were as follows: NFS 0.70, APRI 0.63, FIB-4 0.67 and BARD 0.66. The cumulative probability of death/liver transplantation estimated by Kaplan-Meier analysis was significantly different among the three risk categories for each of the four scores, while the NFS was the best one as both the intermediate and high risk categories of the NFS increased significantly the likelihood to die as compared to the low risk category (HR=4.2, 9.8, respectively).

Interestingly, the NFS failed to predict mortality in a prospective cohort study of general population aimed to compare the predictive ability of several noninvasive hepatic steatosis scoring systems. Instead, ^1H -MRS derived NAFLD liver fat score (LFS) gave the best performance, and the association between LFS and mortality suggested a prognostic value independent of fibrosis during a median follow-up of 14.7 years [54]. Which test is better and whether a combination of the NFS with LFS could improve the performance of prognosis prediction requires further study with large-scale NAFLD cohorts. Besides, the relevance of the NFS with cause-specific mortality remains to be determined in future.

The NFS in hepatic complication prediction

Two studies reported the role of the NFS with hepatic complication. In the analysis, patients with NAFLD from the Rochester Epidemiology Project of the U.S [52], liver complications found in 6 subjects; compared with those with a low probability of advanced liver fibrosis (NFS

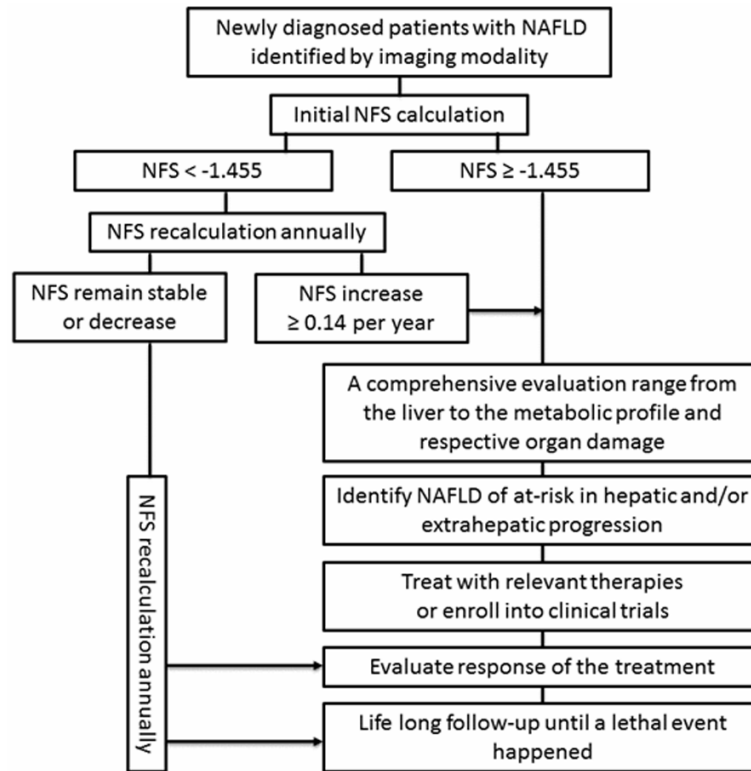


Figure 1. A proposed diagram for a comprehensive use of the NFS in the management of patients with NAFLD.

< -1.5), patients with a high probability of advanced liver fibrosis (NFS > 0.67) had a significant higher frequency of liver complications (4.1% vs. 0.6%, $P=0.03$). Using the biopsy-proven NAFLD cohort, Angulo *et al.* addressed the predictive ability of the NFS for liver-related issues [16]. During the follow-up, 14% of the subjects developed liver-related problems, predominately gastroesophageal varices, ascites and portosystemic encephalopathy. The predictive accuracies of the four scores (NFS, APRI, FIB-4, and BARD) at baseline for liver-related events were as follows: NFS 0.86, APRI 0.80, FIB-4 0.81 and BARD 0.73. For either liver-related events or overall mortality analyzed, the NFS had the highest AUROC compared to the other three scores.

The NFS in extra-hepatic events prediction

So far, few studies have explored the NFS in extra-hepatic events prediction. A prospective study of the adult Japanese who took part a routine medical checkup analyzed the relationship between two noninvasive fibrosis scores, NFS and FIB-4, and systemic complications of

NAFLD during a 3 years of follow-up [55]. It was estimated that 130 out of 434 cases with ultrasonography-diagnosed NAFLD developed liver fibrosis of any stage by the NFS (≥ -1.455), 100 by FIB-4 (≥ 1.45), and 76 by both. When the NFS was used to group the entire cohort ($n=1559$, including 1125 healthy control), new cases of diabetes was 4.5% versus 1.2%, that of cerebral-cardiovascular diseases was 5.0% versus 0.9% in cases with a NFS ≥ -1.455 and those < -1.455 , respectively. The FIB-4 shown similar result in this context, thus the NFS and FIB-4 are useful in identifying cases with high risk of systemic complications of NAFLD. Moreover, Chang *et al.* [56] examined that whether ultrasonography diagnosed NAFLD and its severity reflected by the NFS can predict the development of diabetes in a cohort

of apparently healthy adult Koreans. During 175,996 person-years of follow-up, 2,025 participants developed diabetes. An increase across NAFLD categories on the basis of their NFS was in parallel with an increased risk of diabetes in both the cross-sectional and cohort studies. Multivariate adjusted model indicated that the HRs for diabetes in NAFLD with low NFS (< -1.455) and NAFLD with intermediate or high NFS (≥ -1.455) vs. no NAFLD were 2.00 and 4.74 respectively; and this association remained significant even in subjects with a euglycemic range of glucose and HbA1c [56]. This prognostic value of the NFS in Chinese and Western populations is yet to be determined.

Mechanisms underlying the prognostic value of the NFS

In our opinion, this interestingly prognostic value of the NFS could derive substantially from its ability in detecting fibrosis, because a moderately prognostic accuracy was replicated by FIB-4 in our study and others. From another perspective, each component of the NFS (i.e. lower albumin level, older age and especially

the concomitant occurrence of diabetes) suggests an overall inferior outcome for NAFLD patients, including both liver-related and unrelated outcomes, thereby suggesting an overall better predictive value than the other tests. The exact mechanism address such link needs further investigation.

Concluding remarks

Together, noninvasive simple scores for staging may assist clinicians in patient counseling and monitoring, and the NFS looks to be a superior choice for outcomes prediction for both liver and other diseases associated with NAFLD. Considering the importance of noninvasive assessment in the era of global pandemic of obesity and its hepatic sequel, the abovementioned features make the NFS a versatile clinical tool to help with the management of NAFLD in various clinical problems. On the basis of various observations summarized in this Review, we propose a diagram for a comprehensive use of the NFS in order to improve the current state of NAFLD management (**Figure 1**). For any patient with an image diagnosis of NAFLD from screening, NFS calculation should be an indispensable component among baseline assessments. After initial evaluation, NFS may be monitored in the lifelong follow-up and the possible treatment course. Than at any time, a triage strategy in monitoring the disease progression and in prescribing can be checked based on calculated NFS. For a better clinical implementation of the NFS, however, both combinations with other variables and modification of relevant cut-offs in a given context are recommended.

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Disclosure of conflict of interest

None.

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