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NAFLD Fibrosis Score – Is it ready for wider use in clinical practice and for clinical trials?

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Nonalcoholic fatty liver disease at large is relatively benign, but some individuals with nonalcoholic fatty liver disease (NAFLD) develop major hepatic and extrahepatic complications (NAFLD-at-risk). Hepatic complications of NAFLD include progressive liver disease leading to cirrhosis and liver failure and the development of hepatocellular carcinoma which is largely confined to those with advanced fibrosis and cirrhosis.[1,2] It has been suggested that NAFLD is an independent risk factor for accelerated cardiovascular disease, and in fact, several recent epidemiological and cohort studies have shown that cardiovascular disease is the most common cause of death in individuals with NAFLD.[3–5] Currently, the liver histology is the most widely used method to identify individuals with NAFLD who are at risk to develop cirrhosis and subsequent liver failure. Traditionally, the presence of steatohepatitis and advanced fibrosis are considered harbingers of adverse hepatic outcomes in individuals with NAFLD.[6] But, performing a liver biopsy on all individuals with NAFLD is not a practical proposition, and thus, there have been numerous cross-sectional investigations to non-invasively identify steatohepatitis and advanced fibrosis in individuals with NAFLD.[7] Some of these noninvasive tests and stratification methods are reasonably predictive of advanced liver histology, but to date, very few studies have investigated noninvasive tools to predict adverse hepatic outcomes in this patient population. In fact, the development of non-invasive tools which precisely predict long-term hepatic and extrahepatic adverse outcomes remains a holy grail in the NAFLD field.

The NAFLD Fibrosis Score (NAFLD-FS), BARD, APRI and FIB-4 are among the more widely investigated non-invasive tools to cross-sectionally predict advanced fibrosis in NAFLD. [8–11] These scoring systems are based on easily available clinical variables and each exhibited varying degrees of success depending on the patient population studied. The NAFLD-FS is calculated based on age, BMI, hyperglycemia or diabetes, AST/ALT, platelets, and albumin (www.nafldscore.com).[8] The BARD score was developed by

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Harrison et al., on a large cohort of patients with biopsy-proven NAFLD and it is based on BMI, AST/ALT, and the presence of diabetes.[9] The FIB-4(calculated based on age, AST, ALT and platelets), and the AST to platelet ratio index (APRI) were originally developed to predict advanced fibrosis in patients with chronic hepatitis C infection, but they were subsequently investigated for the same task in patients with NAFLD. [10–12] Of the four scoring systems, NAFLD-FS has received the most extensive validation and it has been recommended for clinical use in the recent US multi-society practice guideline on the diagnosis and management of NAFLD.[6]

In this issue of the Journal, Angulo et al., evaluated the performance of these 4 non-invasive scoring systems (NAFLD-FS, APRI, FIB-4, and BARD) to predict liver-related complications and death/liver transplantation in patients with NAFLD.[13] It was a retrospective, international study that included 320 patients from referral centers from the USA, Italy, Iceland, Thailand, UK, and Australia. The subjects were predominantly White (92%) and overweight or obese (95%) adults. As it generally is the case with cohorts reported from specialized referral centers, this cohort was enriched with NASH and advanced fibrosis accounting for nearly 50% of the patients. Subjects were followed for a median duration of 104.8 months (3–317 months). Per study protocol, 11 patients were excluded from the liver related-events analysis as those events occurred within first 3 months after the liver biopsy. None of the subjects received vitamin E, thiazolidinediones, or had bariatric surgery during the study period. Complete follow up was available on 80% of the subjects. The overall rate of liver-related adverse events and death/liver transplantation were 14% and 13%, respectively. Complications of cirrhosis were the third most common cause of death following cardiovascular events and non-hepatic malignancies. Interestingly, there was no greater frequency of liver-related adverse events or death/liver transplantation among patients with definite NASH or severe steatosis. However, there was significant difference in outcomes between patients with and without advanced fibrosis. The mean score of all of four non-invasive systems correlated well with the degree of fibrosis (fibrosis stage 0 vs 1–2 vs-3–4) on baseline liver biopsies. The AUROC for NAFLD-FS, FIB-4, APRI and BARD for predicting liver-related outcomes were 0.86, 0.81, 0.80, and 0.73 and for death/liver transplantation were 0.70, 0.67, 0.63, and 0.66, respectively. Subsequently, using their established cut-off points, the investigators categorized the study cohortinto low, intermediate, or high-risk groups. For liver-related events, the adjusted hazard ratio was significantly higher for intermediate and high-risk groups for NAFLD-FS, APRI, and BARD, but it was higher only in the high-risk category for the FIB-4. The risk of death/liver transplantation steadily increased in the intermediate and high-risk groups for NAFLD-FS, only in the high-risk groups for the APRI and FIB-4 scores, but was not associated any of the BARD risk groups. The authors concluded that NAFLD-FS was the best indicator of NAFLD-at-risk, based on hazard ratios. This study once again confirmed that it is the advanced fibrosis which is associated with long-term serious outcomes in patients with NASH.[13,14]

Angulo and colleagues should be thanked for investigating these commonly cited noninvasive tools to predict long-term patient outcomes in NAFLD. As the authors admit, this study is far from perfect and carries several important limitations as outlined in their discussion. But it compliments a recent population-based study reported by Kim et al.,[15]

which consisted of 11,154 participants of the NHANESIII conducted in 1988–1994 who were followed for mortality until December 2006 using the National Death Index. At entry, these participants had extensive evaluation including a gallbladder ultrasound which was later evaluated for the presence of hepatic steatosis. From this cohort, they identified 4,083 (34%) individuals with NAFLD based on clinical, laboratory and imaging criteria. They investigated if baseline NAFLD-FS, FIB-4 and APRI predicted patient outcomes among these individuals with NAFLD over a median follow-up of 14.5 years (range 0.3–18.1 years). There were 779 individuals with NAFLD who died during the follow-up with cardiovascular disease (37%) being the most common cause of death followed by malignancy in 21%, but there were very few liver-related deaths (2.4%). This very low rate of liver-related deaths was not surprising because the prevalence of advanced fibrosis at baseline as characterized by the non-invasive fibrosis markers was very low. For example, only 3.2% of the patients with NAFLD had advanced fibrosis using NAFLD-FS >0.676 as a surrogate. This study showed a progressive increase in overall mortality rate with increasing fibrosis scores after adjustment for other known predictors of mortality (Table 1). These authors have also shown that this increased overall mortality was almost entirely due to cardiovascular causes. Baseline fibrosis scores did not predict liver-related mortality, very likely because of very low liver-related mortality observed during the follow-up period.

To sum up these two studies, the NAFLD-FS predicted overall mortality in two separate NAFLD cohorts with varying underlying characteristics – NHANESIII cohort with low prevalence (3.2%) and Angulo's cohort with higher prevalence (23.4%) of high NAFLD-FS. These observations provide further evidence to the recommendation by the recent multi-society NAFLD practice guidelines that recommended NAFLD-FS may be used to identify NAFLD patients at high risk for advanced fibrosis.[6]

Another potentially important finding of the study by Angulo et al., was that there was no significant association between histologically evident definite NASH at baseline and overall or liver-related mortality among patients with NAFLD. If confirmed, this observation may have profound impact on the design of the clinical trials for patients with NASH. The improvement in the NAFLD activity score (NAS) and the resolution of NASH are widely used as primary endpoints for clinical trials in NASH. Recently, Younossi et al., have shown that NAS > 4 (typical eligibility cut-off for the NASH clinical trials) did not correlate with liver-related mortality (adjusted hazard ratio 2.92, 95% 0.95–8.95).[13] These evolving data call for the upcoming AASLD/FDA workshop "Trial Designs and Endpoints for Liver Disease Secondary to Nonalcoholic Fatty Liver Disease" (September 5–6, 2013 at Silver Springs, Maryland) tocritically discuss (a) the validity of NAFLD activity score and steatohepatitis as primary endpoints; (b) about enriching clinical trials with individuals with advanced fibrosis; and finally (c) if NAFLD-FS is ready to be incorporated as one of the primary endpoints for NASH clinical trials.

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Table 1

Relationship between baseline fibrosis scores and mortality among NHANESIII participants with NAFLD

	NAFLD-FS	APRI	FIB-4
All-cause mortality	**Hazard Ratio (95% CI)***	**Hazard Ratio (95% CI)***	**Hazard Ratio (95% CI)***
- Low score	Reference	Reference	Reference
- Medium score	1.26 (0.98–1.64)	1.32 (0.78–2.23)	1.46 (1.16–1.83)
- High score	1.69 (1.09–2.63)	1.85 (1.02–3.37)	1.66 (0.98–2.82)
Cardiovascular mortality			
- Low score	Reference	Reference	Reference
- Medium score	2.16 (1.41–3.29)	0.97 (0.40–2.34)	1.75 (1.26–2.43)
- High score	3.46 (1.91–6.25)	2.53 (1.33–4.83)	2.68 (1.44–4.99)
Liver disease mortality			
- Low score	Reference	Reference	Reference
- Medium score	0.49 (0.08–2.83)	6.08 (0.77–48.21)	0.68 (0.11–4.05)
- High score	0.07 (0.00–1.25)	3.01 (0.20–45.62)	1.32 (0.12–14.80)

*Hazard ratio adjusted for age, gender, race/ethnicity, education, income, diabetes, hypertension, history of cardiovascular disease, lipid lowering therapy, smoking, waist circumference, alcohol consumption, caffeine intake, total cholesterol, HDL-cholesterol, transferrin saturation, and C-reactive protein.

NHANESIII – National Health and Nutritional Examination Survey III; NAFLD – Nonalcoholic Fatty Liver Disease; NAFLD-FS: NAFLD Fibrosis Score; APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis 4 Score