Two are better than one: noninvasive assessment of liver fibrosis in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease in many regions, affecting 15–40 % of the general population [1, 2]. One of the key challenges in managing NAFLD is differentiating simple steatosis from advanced disease, i.e., those with nonalcoholic steatohepatitis (NASH), advanced fibrosis or even cirrhosis [3]. The challenge is further substantiated by the poor correlation between liver fibrosis and routine blood tests, e.g., the serum alanine aminotransferase (ALT) level [4]. Patients may have progressed to advanced fibrosis or cirrhosis without any abnormalities in these common blood parameters [5]. Liver biopsy is not always feasible or acceptable to patients, especially to those largely asymptomatic subjects; this has promoted the popularity of noninvasive assessments of liver fibrosis for NAFLD patients (Table 1) [6, 7].

Among the numerous noninvasive assessments, liver stiffness measurement (LSM) by transient elastography is one of the most popular tools [8]. This tool out-performed other serum parameters in detecting advanced fibrosis or cirrhosis [9]. Nonetheless, a false-positive diagnosis of advanced fibrosis is not uncommon, in addition to LSM results lying in the gray zone [9]. This would be an even

more serious problem in obviously obese subjects, as the LSM is higher among those with a body mass index (BMI) above 30 kg/m² in the same fibrosis stage [10]. On the other hand, the NAFLD fibrosis score (NFS) is the best-studied serum-based combined clinical algorithm; it was recommended in the latest American practice guidelines for NAFLD [11]. All these observations have raised the interest in combining these two well-studied noninvasive parameters. On the other hand, magnetic resonance elastography (MRE) is probably even more accurate than LSM and NFS [12]. Nonetheless, MRE is not as widely available as these two tools.

Recently, Chan et al. [13] evaluated the diagnostic performance a novel two-step approach combining NFS and LSM. The beauty of this study was the robust methodology of including two independent groups of patients as the training and validation cohort, respectively. The detailed comparison of the performance of various approaches, be it either parameter alone or combining two parameters in different fashions, established this novel two-step approach as the best among the five to avoid liver biopsy. Similar approaches have been proposed in patients with chronic hepatitis B [14, 15]; this was the first time in NAFLD patients.

The unresolved questions remaining include the suboptimal performance of NFS in Asian subjects because of the different BMI cutoffs for obesity [16]. This was echoed by the relatively low sensitivity (40 %) of NFS to predict advanced fibrosis in Chan's study. Investigators should pay special attention when applying any parameters derived from the west to Asian patients, such that different cutoffs or even different algorithms should be considered. It would be helpful if another serum parameter with better performance could be found. Cytokeratin-18 (CK18) fragments have been investigated extensively as novel biomarkers for

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Table 1 Noninvasive parameters for advanced fibrosis in nonalcoholic fatty liver disease [6, 9, 12]

Parameters	Cutoffs	Components	Sensitivity	Specificity
Liver stiffness measurement (kPa)	7.9 9.6	N.A.	0.77 0.64	0.69 0.84
NAFLD fibrosis score	−1.455 and 0.676	Age, hyperglycemia, BMI, platelet, albumin, AST/ALT ratio (dual cutoffs)	0.77	0.96
BARD score	2	BMI, AST/ALT ratio, diabetes	0.62	0.66
AST/ALT ratio	1.0	AST, ALT	0.21	0.90
APRI	0.5 and 1.5	AST, platelets (dual cutoffs)	0.65	0.97
ELF	0.3576	Hyaluronic acid, TIMP1, PIIINP (dual cutoffs)	0.80	0.90
FIB-4	1.30 and 2.67	Age, AST, platelet, ALT (dual cutoffs)	0.74	0.98
FibroTest	0.70	Total bilirubin, GGT, α_2 -macroglobulin, ApoA1, haptoglobin (dual cutoffs)	0.88	0.99
MRE (kPa)	3.63	N.A.	0.86	0.91
C-caffeine breath test ^a	1.27	N.A.	0.90	0.76

ALT alanine aminotransferase, *ApoA1* apolipoprotein A1, *APRI* AST-to-platelet ratio index, *AST* aspartate aminotransferase, *BMI* body mass index, *ELF* enhanced liver fibrosis panel, *GGT* gamma-glutamyl transpeptidase, *MRE* magnetic resonance elastography, *NAFLD* nonalcoholic fatty liver disease, *PIIINP* procollagen III amino-terminal peptide, *TIMP1* tissue inhibitor of matrix metalloproteinase 1

^a The cutoff of 1.27 on the C-caffeine breath test was used to diagnose histological cirrhosis

NASH [17, 18], but in the latest guideline it was considered premature to recommend them in routine clinical practice [11].

Another big area for further investigation is the prospective longitudinal assessment of liver fibrosis in NAFLD subjects. Luckily a grossly elevated ALT level is uncommonly seen in NAFLD subjects such that the confounding effect of ALT on LSM [19] would be minimal. The current major limitation of all these noninvasive tools is that they have largely been investigated in cross-sectional studies; thus, their utility in monitoring a disease's natural history and predicting outcomes or responses to therapeutic interventions remains to be defined. Since liver fibrosis changes relatively slowly compared to liver fat, with short-term lifestyle modifications [20], studies of sufficiently long follow-up duration would be prudent to demonstrate the change in liver fibrosis [21]. Recently, NFS was found to be valuable in predicting liver-related events and deaths in a study with a median follow-up duration of nearly 9 years [22]. More data from similar studies would be useful to ascertain the role of these noninvasive tools.

A newly published phase 2 study by the NASH Clinical Research Network tested the use of obeticholic acid, a farnesoid X receptor agonist, in NASH (the FLINT trial) and first demonstrated that a pharmacological agent improved liver fibrosis after 18 months of treatment. This exciting observation not only shed the light on the therapeutic aspect of NASH, it also shows the need for noninvasive tools to assess the on-treatment response of liver fibrosis [23].

In conclusion, the study by Chan et al. provides valuable data on this novel two-step approach combining NFS and LSM to improve the accuracy of predicting advanced fibrosis and reducing the need for liver biopsy. Future study should be directed toward the values of these tools in a longitudinal fashion.

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Grace Wong has received honoraria for lectures for Echosens and Furui. Henry Chan is a consultant for Furui and has received an honorarium for a lecture for Echosens.

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