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Accurate tests to identify high-risk individuals in a population that could progress to severe forms of the disease are crucial strategies when tackling the nonalcoholic fatty liver disease (NAFLD) epidemic. NAFLD is projected to increase from affecting 83.1 million people in 2015 to 100.9 million in 2030, and its more severe form, nonalcoholic steatohepatitis (NASH) is estimated to increase from 16.52 million to 27.00 million in the US alone (1). These staggering numbers emphasize the need to precisely identify patients with NASH who could potentially develop life-threatening cirrhosis and hepatocellular carcinoma (2). By doing so, patients can be correctly selected to enter clinical trials designed to treat NASH with new drugs targeting different stages of the disease.

Previous efforts to identify these at-risk patients focused on liver biopsy, and recognizing those patients with stage 2 fibrosis or higher (≥F2) who were at an increased risk of morbidity and mortality. However, current strategies have shifted to focus on non-invasive tests (NITs), including imaging and laboratory tests (such as magnetic resonance elastography [MRE], vibration-controlled transient elastography [VCTE], enhanced liver fibrosis [ELF], Fibrosis-4 [FIB4] score, NAFLD Fibrosis score [NFS]) (3). The disadvantage of these tests is that they can only estimate fibrosis stage only. Newsome and colleagues acknowledge this limitation and have taken it a step further to formulate a score designed to isolate NASH patients with elevated NAFLD activity score (NAS ≥4) and significant liver fibrosis (≥F2), who could benefit from therapies with anti-steatohepatitis and/or antifibrotic properties (4). The novelty of the study came in two parts. The first part generated the
FibroScan-AST (FAST) score by prospectively analyzing a derivation cohort that included 350 patients suspected of NAFLD. The FAST score combines liver stiffness measurements (LSM) by VCTE, controlled attenuation parameter (CAP) and aspartate aminotransferase (AST) levels. Using a best-fitting multivariable logistic regression model, the derivation dataset score performed satisfactorily and was well calibrated (C-statistic 0.80, 95% CI 0.76–0.85). The second part validated the score by applying it to global external validation cohorts, which confirmed the calibration and had good discrimination across all seven validation cohorts (C-statistic range 0.74–0.95, 0.85; 95% CI 0.83–0.87 in the pooled external validation patients’ cohort; n=1026).

The meticulous way Newsome et al. have designed their study to incorporate the FAST score to a global validation cohort, to isolate these high-risk patients with NASH and fibrosis ≥2 and NASH + NAS ≥4 deserves praise. However, as with previous scores, the shortfall in the FAST score is the “grey zone”. The FAST score uses the dual cutoff approach, where the cutoff for a fixed sensitivity at ≥90 was 0.35 and fixed specificity at ≥90 was 0.67 in the derivation cohort. This led to a positive predictive value (PPV) of 0.83 (84/[84+17], 95%CI 0.75-0.87) and a negative predictive value (NPV) of 0.85 (93/[93+17], 95%CI 0.77-0.88) in the derivation cohort, of which 39% of patients fell into the grey zone. Applying the dual cutoff approach to the external pooled validation cohorts resulted in a similar number of patients in the grey zone (32%). Thus, with varying NPV, PPV and AUROC values across the international cohorts and a third of patients being excluded due to values falling in the grey zone, it raises the questions on how accurate the FAST score will be in large population-based or real-world cohorts, and how do we overcome or narrow this grey zone?

We propose an alternative approach for the grey zone issue and its cutoff values by adopting a traffic light system (Figure 1). This system considers sequential testing by combining different scores and tools, a concept that has been proposed in the past (5,6). By applying sequential testing, we do not solely rely on the accuracy of one score. We combine and analyze multiple scores for each patient, as no score will fit all situations and patient characteristics. We must be open minded and look at the threshold and values generated across multiple scores and tests in order to narrow this grey zone and achieve highest accuracy.

With this in mind, sequential testing will use NITs that will rely on fibrosis alone scores, such as VCTE, ELF test or MRE, but when these are not available, liver biopsy can be considered as a last
Thus, ideally reducing the number of patients being subjected to an invasive liver biopsy. NFS and FIB-4 scores can also be considered, but they have reduced accuracy for detecting patients with earlier fibrosis stages such as F2 and who may benefit from therapeutic interventions (5). In the future, other tests such as ELF or procollagen type-III N-terminal peptide (Pro-C3) could be incorporated into this system, but further data on their performances are warranted.

Additionally, the FAST score rely heavily on AST levels, which raises concerns. Previous studies have shown that a large number of patients with normal liver enzymes have advanced liver fibrosis on their liver biopsy (7). This may be less of an issue in a specialist clinic with gastroenterologists, hepatologists and some endocrinologists, as they are familiar with VCTE and enzyme interpretation, stiffness/fibrosis central role in prognosis, the sensitivity and specificity of VCTE readings. However, relying on AST alone may raise an issue in primary care settings and should be exercised with caution. To offer a clinical example, a patient with CAP score of 360 dbB/m, LSM score of 14 kPa and AST of 20 U/L (within normal range), will equate to a FAST score of 0.32, which means this patient will not be referred to a specialist, or be excluded from clinical trials and consequently potential effective treatment. However, this patient has a concerning LSM score (14 kPa), consistent with cirrhosis with high specificity (8); applying the traffic light system to this patient means they would fall within the green light (Figure 1) (which equals not doing liver biopsy or recommending treatment). Thus, significant fibrosis could be missed if someone is “too fast” to interpret the FAST score, and inevitably a large number of patients with fibrosis at advanced stages will be overlooked. This concept of relying heavily on AST and missing an important fibrosis stage can also be seen in the grey zone. For example, a patient with a CAP score of 350 dbB/m, LSM score of 12 kPa and AST of 41 U/L (slightly above the normal limit), will have a FAST score of 0.65 and falls within the grey zone despite having abnormal AST and advanced fibrosis by LSM. For this reason, close attention to the LSM of the VCTE should be considered while calculating the FAST score. Patient management is key, so when adopting the FAST score, all elements need to be thoroughly evaluated in case additional tests are warranted to confirm the fibrosis degree and select the right patients for clinical trials and drug therapy. In addition, the FAST score should be tested and compared in real-life
experiences outside the context of clinical trials on patients who are referred to primary and secondary care settings.

Finally, it is worth mentioning that all these NITs are being compared with liver biopsy (as a gold standard), which has its limitations such as sample variability, interobserver discordance, and many others. It has been suggested that NITs may predict meaningful clinical changes in NASH patients (such as changes in liver enzymes and weight) better than liver biopsy (9), but it will be interesting to see how the FAST score compares when it is used in different cohorts and settings.

In summary, the FAST score is a step forward in managing NASH patients, but more research and validation are needed. Our clinical judgement and attention to detail should always be on high alert when using NITs in the management of NASH patients. None of the NITs we use are perfect; will there ever be one? However, Newsome and colleagues have targeted the gap of existing scores and offer a more comprehensive approach to evaluate these high-risk patients. As with all these scores, caution and flexibility should be executed, especially when the amber light is flashing.
References


Figure legend

Figure 1. Combining the FAST score with a traffic light system to narrow the grey zone. The idea would be to incorporate sequential testing to patients who have values for controlled attenuation parameter (CAP), liver stiffness measurements (LSM) and aspartate aminotransferase (AST) outside the level of normal.
The cutoff **0.67** for specificity of 0.90 or greater is at a high probability of NASH with significant fibrosis.

**Enroll in NASH clinical Trials**

Patients who fall in the grey zone (~30% of patients) would benefit from **sequential testing** with another test after the FAST score (e.g. ELF, MRE or even liver biopsy).

- The cutoff **0.35** for sensitivity of 0.90 is at a low probability to identify patients at risk of active NASH with significant fibrosis.
- Patients with high LSM values would benefit from **sequential testing** with another test after the FAST score (e.g. ELF, MRE or even liver biopsy).