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Mini Review

Referral of Intermediate and High-Risk Non-Alcoholic Fatty Liver Disease Patients to Hepatology Based on Noninvasive Tests

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ABSTRACT

Nonalcoholic Fatty Liver Disease (NAFLD) is the most common liver disease that affects a quarter of the global population. Fibrosis is the only histological feature associated with liver-related events. The clinical challenge of endocrinologists and primary care practitioners is to screen for patients likely to have significant fibrosis (≥ F2), from a patient population that has a lower prevalence of advanced fibrosis, and therefore the screening tests are penalized with lower positive predictive values9. Most of the patients with NAFLD can remain in the primary care setting while a selected subset benefits from referral. FIB-4 can identify patients with baseline advanced fibrosis and future liver-related events. FIB-4 and VCTE combination has been shown to sequentially risk stratify patients based on the risk of advanced fibrosis. Despite the available tools and society guidelines, there is a lack of disease awareness among patients and primary care practitioners leading to reduced referrals of high-risk patients to hepatology and over-referral of low-risk patients.

Keywords: Metabolic associated fatty liver disease; Nonalcoholic fatty liver disease; Steatohepatitis; Fibrosis

INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) is the most common liver disease that affects a quarter of the global population [1]. The disease spectrum includes patients with and without steatohepatitis (AKA nonalcoholic steato hepatitis or NASH), as well as with and without significant fibrosis (i.e. stage 2, F2). The prevalence of NAFLD is projected to increase in the coming years due to the increasing prevalence of obesity, diabesity, and metabolic syndrome. Only a minority of patients with NAFLD eventually develop end-stage liver disease and hepatocellular carcinoma. Fibrosis is the only histological feature associated with liver-related events, specific mortality, and all-cause mortality is increased [2], even after adjustment for steatohepatitis [3,4]. Baseline fibrosis is also the most important risk factor for fibrosis progression [5]. Steatohepatitis remains a relevant histological factor because it also affects fibrosis progression and is often an inclusion criterion for NASH clinical trials. The prevalence of advanced fibrosis is estimated to be 3.2 in the general population, and 1.7% among patients with NAFLD [6,7]. The prevalence of NAFLD is up to 70% and advanced fibrosis up to 9% in patients with type 2 diabetes (T2D) in primary care and diabetes clinics [8].

The clinical challenge of hepatologists is to identify selected NAFLD patients with significant fibrosis (≥ F2). Patients may benefit from intensive lifestyle modifications, pharmacotherapy for weight loss, bariatric surgery, certain classes of diabetes medications, and clinical trial enrollment. Patients with advanced fibrosis (≥ F3) and cirrhosis (F4) may additionally benefit from ultrasound for hepatocellular carcinoma surveillance and endoscopy for esophageal varices prevention. The clinical challenge of endocrinologists and primary care practitioners is to screen for patients likely to have significant fibrosis (≥ F2), from a patient population that has a lower prevalence of advanced fibrosis, and therefore the screening tests are penalized with lower positive predictive values [9]. Most of the patients with NAFLD can remain in the primary care setting while a selected subset benefits from referral. Some endocrinologists and primary care practitioner offices may not have

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access to ordering Enhanced Liver Fibrosis (ELF) and Vibration-Controlled Transient Elastography (VCTE) which poses additional challenges.

Noninvasive Tests (NITs) are available clinical decision aids to identify patients at risk for advanced fibrosis. These include the NAFLD Fibrosis Score (NFS), Fibrosis-4 (FIB-4) indexes, various elastography methodologies, and the ELF. The FIB-4 and ELF are the most widely used serum marker while the VCTE is the most widely adopted elastography method [9].

LITERATURE REVIEW

NFS and FIB-4 can identify patients with baseline advanced fibrosis and future liver-related events [10]. However, both have limitations in younger patients and patients with T2D [11]. A higher cut point of 2.0 for those <65 has often been used. Non-invasive tests can be combined to better stratify patients based on their risk of advanced fibrosis. FIB-4+VCTE and FIB-4+ELF strategies have been developed to identify future liver-related events [12,13]. In a prospective longitudinal study in the United Kingdom, a 2-step algorithm of FIB-4 followed by ELF testing was introduced. ELF testing is only required given intermediate risk FIB-4 (1.30–3.25). Patients are referred to hepatology if ELF is intermediate to high risk (>9.5) or FIB-4 is high risk (≥ 3.25). This approach detected 5 times more cases of advanced fibrosis and cirrhosis while reducing unnecessary referrals to hepatology by 81%. Performing ELF in patients with intermediate FIB-4 identified 84% of patients subsequently found to have advanced fibrosis or cirrhosis.

In a large cross-sectional study of patients with biopsy-proven NASH, FIB-4 and VCTE combination has been shown to sequentially risk stratify patients based on risk of advanced fibrosis [14]. Another multicenter study aimed to evaluate the prognostic accuracy of FIB-4 and VCTE combination for the prediction of liver-related events in NAFLD. VCTE is used as a second step to stratify patients with FIB-4 ≥ 1.30. Patients with FIB-4 <1.3 or VCTE <8.0 have the lowest risk (HR1.0, reference), followed by VCTE 8.0 - 12.0 (HR3.8, increased risk), and VCTE >12.0 (HR12.4, high risk).

Moving into the near future, machine learning using a random forest model with 17 commonly available laboratory biomarkers, has recently been shown to be superior to FIB-4 and VCTE in identifying advanced fibrosis [15]. Translating a random forest model, which are the consensus votes of 100–500 decision trees, into a website calculator, remains a technical challenge.

Clinical societies have provided guidelines on the use of NITs to screen for advanced fibrosis. While the previous version of the American Association for the Study of Liver Diseases (AASLD) guideline in 2018 had some revisions over which population to screen for advanced fibrosis, a recent revision in 2022, along with the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO) guideline of 2016, and the EASL guideline on NITs updates in 2021, all agreed that screening for advanced fibrosis in patients age >50, T2D, and metabolic syndrome is indicated [16-19]. A normal liver enzyme should not preclude screening for advanced fibrosis. After initiation of advanced fibrosis screening, the AASLD and EASL guidelines have subtle differences in the referral algorithm [17,19]. Both guidelines promote FIB-4 as the first-line screening for risk stratification. The prevalence of advanced fibrosis is low in a primary care setting as such; the widely available, least expensive FIB-4 is the most appropriate initial test [9]. Patients with low-risk FIB-4 can remain in the primary care setting. According to the AASLD guideline, patients with intermediate-risk FIB-4 (1.3-2.27) should be further risk stratified by VCTE or ELF. Patients should be referred to hepatology if VCTE and ELF are not available, VCTE >8k pa or ELF >7.7, or FIB-4 >2.67. The EASL guideline differs in those patients with FIB-4 >1.30 is to be referred to have VCTE before or after referral to hepatology according to local availability.

Despite the high prevalence of NAFLD patients, there is a lack of disease awareness among patients and primary care practitioners leading to reduced referrals to hepatology. Fewer than 5% of people with NAFLD are aware of their disease compared to other chronic liver diseases such as viral hepatitis [20]. In a global survey of over 2200 physicians recently, the greatest knowledge gap among endocrinologist and primary care practitioners are in epidemiology and diagnostics of NAFLD [21]. Another survey of 751 clinicians including primary care practitioners indicated that the most significant knowledge gap is the underestimation of the prevalence of MAFLD in patients with T2D [22]. As a result, only 10% of patients are referred to a specialist and early intervention opportunity is missed [23].

DISCUSSION

We have recently demonstrated that the majority of patients referred to hepatology for evaluation of NAFLD are of low-risk FIB-4, and the vast majority of patients with high-risk FIB-4 have not been referred [24]. We analyzed 2174 patients with FIB-4 >3.25 and T2D who had visited the internal medicine, family medicine, and endocrinology clinic. Only 290 (13.3%) were referred to the hepatology clinic before their initial hepatic decompensation. Notably, the referred patients had the same rate of biochemical decompensation, but a substantially higher rate of diagnosis in cirrhosis and cirrhosis complications, including ascites, hepatic encephalopathy, and liver cancer. The referred patients had a lower overall mortality risk. We speculate that the survival difference is due to the increased recognition of cirrhosis and cirrhosis complications in the referred populations [24]. In addition, we also noticed that half of the referrals that we received in the hepatology clinic are of low-risk FIB-4. Our study is echoed by a real-world community study in Spain [25]. Only 1.6% of patients had FIB-4 in the high risk (>3.25) category, and most are not recognized by physicians. A large portion of those patients has evidence of advanced fibrosis.

We are still placing too much emphasis on standard Liver Function Tests (LFTs) [26]. LFTs do not correlate with the severity of liver disease. The prevalence of clinically significant liver disease including cirrhosis has been described by at least 19 studies [27]. Simple NITs (i.e. NFS, FIB-4) are as accurate in patients with normal *vs.* elevated LFTs. Despite this, primary care physicians continue to rely on LFTs to determine candidacy for hepatology referral. This is a reason for the over-referral of

the low-risk populations and under-referral of the high-risk populations. Therefore, our screening strategy for advanced fibrosis should deemphasize LFTs and emphasize underlying metabolic risk factors (i.e. T2D, metabolic syndrome).

CONCLUSION

In summary, while MAFLD is a very common liver condition, only selected patients with advanced fibrosis are at risk for the liver-related outcome. Despite the disease prevalence, is a lack of disease awareness among patients and providers. There is often a false reassurance of normal liver enzymes. Patients with metabolic risk factors should be screened for advanced fibrosis, regardless of whether the liver enzyme is elevated or not. The least expensive and widely available FIB-4 should be the first step. Low-risk FIB-4 patients can be managed by primary care practitioners. Intermediate risk and high-risk patients can be further risk stratified by ELF, VCTE, or referred based on local availability. With limited resources, we simultaneously suffer from over-referral of the low-risk populations and under-referral of the high-risk populations.

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