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LETTER FROM THE EDITOR

An Algorithmic Approach to NAFLD Screening: From PCP to Specialist

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BURDEN OF NAFLD

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease worldwide, and its prevalence is increasing in parallel with metabolic syndrome, obesity, and type 2 diabetes. About 20%–25% of patients with NALFD develop nonalcoholic steatohepatitis (NASH), and one-third of those patients develop advanced fibrosis or cirrhosis.[1,2] Patients with NASH and advanced fibrosis or cirrhosis are at heightened risk of complications with increased cardiovascular mortality, hepatocellular carcinoma (HCC), and liver failure. In fact, those with type 2 diabetes and cirrhosis have a particularly high risk of HCC.[3] In addition, NASH and cirrhosis impair health-related quality of life and dramatically increase healthcare costs.[4,5] Emerging evidence shows that early diagnosis and management of NAFLD may mitigate these complications while also reducing health-related and economic burden of disease.

DO GUIDELINES RECOMMEND SCREENING?

International guidelines do not specifically recommend screening patients for NAFLD, but newer data suggest that it may be beneficial. Although the United States Preventive Services Task Force does not make any recommendations, the American Association for the Study of Liver Disease currently recommends against screening.[6] However, American Association for the Study of Liver Disease's recommendation, based on a single study, suggests screening to not be cost effective because of incurred side-effect profile of existing interventions and not based on incident HCC or need for liver transplantation.[7] Newer studies proving the cost-effectiveness of screening are emerging.[8] As new evidence surfaces, screening for NAFLD may become commonplace and will likely be driven by primary care physicians (PCP) in the community where NAFLD is prevalent.

WHO TO SCREEN FOR NAFLD?

Those who are at risk of NAFLD include persons with metabolic syndrome, type 2 diabetes, and obesity, conditions most prevalent within the community where PCPs serve as the frontline practitioners. The unreliability of traditional liver tests and relative asymptomaticity of NAFLD make it challenging to identify. Targeting high-risk populations, such as those with type 2 diabetes, is one strategy to enhance diagnosis of NAFLD and related fibrosis. The presence of type 2 diabetes is an independent predictor for the development of NAFLD, NASH, advanced fibrosis, and HCC.[9,10] In fact, in patients with cirrhosis from NAFLD, those with type 2 diabetes have a 400% increased risk of HCC (hazard ratio: 4.2, 95% confidence interval: 1.2–14.2, $P = 0.02$).[3] Pending further investigation, selectively targeting those with type 2 diabetes for NAFLD screening therefore may be justified.

HOW TO SCREEN: THE ROLE OF NONINVASIVE TESTING

The optimal screening strategy for NAFLD is not yet known. A low cost, noninvasive, highly sensitive, and specific screening method that is applicable to a large cohort population is promptly warranted. Liver biopsy is invasive and has a small inherent risk of complications. The advent of noninvasive serologic and nonserologic tests, however, has revolutionized the way specialty hepatologists triage liver disease. Noninvasive tests can help PCPs differentiate patients with NAFLD who are at high risk of progressing to advanced fibrosis or cirrhosis and prompt specialist referral, from those patients who are low risk and can be monitored within the primary care clinic. Different noninvasive testing strategies continue to surface. The most commonly used serologic tests in NAFLD

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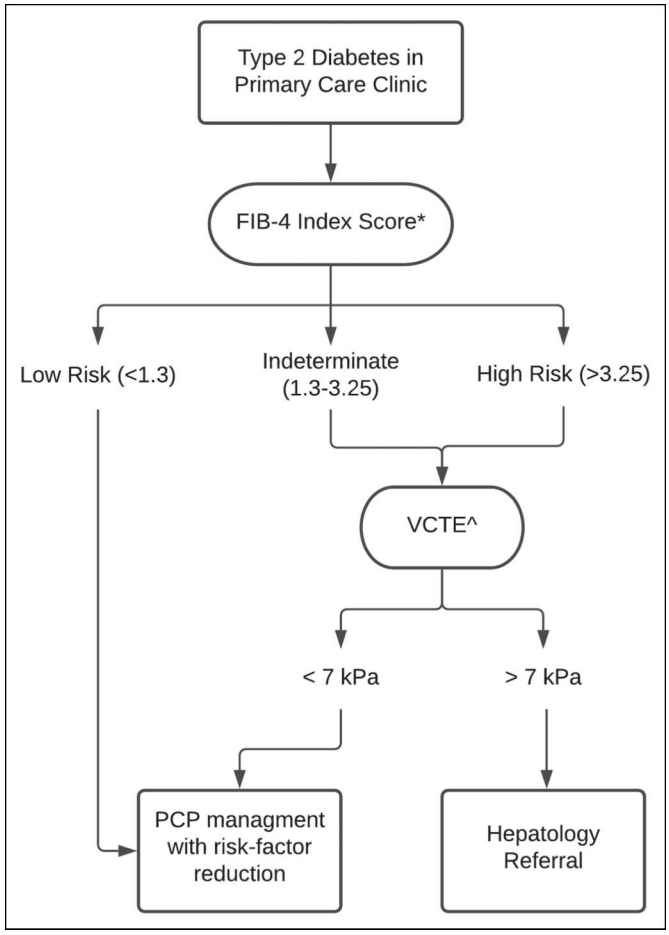

Figure 1. This is a proposed algorithm for identifying and managing patients with a high risk of NAFLD in the primary care setting. *FIB-4 index score should be interpreted with caution in patients <35 and >65 years of age. ^Access to VCTE is variable, and patients may need hepatology referral first. VCTE limitations include perihepatic ascites, morbid obesity, and ALT >100 U/L, in which case an MRE can be considered. FIB-4, Fibrosis-4; kPa, kilopascals; PCP, primary care physician; VCTE, vibration-controlled transient elastography.

include the fibrosis-4 (FIB-4) index and NAFLD Fibrosis score, whereas vibration-controlled transient elastography (VCTE) and magnetic resonance elastography are the most commonly used nonserologic strategies.

Although serologic tests alone are fraught with a false negative rate in certain populations (ie, above 65 years of age, renal failure), studies combining different noninvasive strategies to detect patients with NAFLD at high risk of NASH or fibrosis have shown efficacy.[11,12] One such study implements a "FIB-4 first strategy" where they incorporated FIB-4 and VCTE in an algorithmic approach to identify patients with advanced fibrosis and cirrhosis within PCP practices.[13] A combined two-step approach (using FIB-4 cutoff > 1.3 and VCTE cutoff > 8 kPa) significantly reduced unwarranted hepatology referrals with only 4% of patients being referred. Similarly, Srivastava et al demonstrated that a combination pathway using FIB-4 index with Enhanced Liver Fibrosis (ELF) score reduced hepatology referrals by 80% while enhancing detection of advanced fibrosis (odds ratio: 5.18, 95% confidence interval: 2.97–9.04, $P < 0.0001$).[14] Recent expert consensus recommends using FIB-4 as the initial noninvasive test because of simplicity and ease of use.[15] For nonserologic tests, VCTE alone has been shown to reliably exclude advanced fibrosis within the primary care setting with 100% sensitivity and a 100% negative predictive value when using a cutoff score less than 7.7 kPa and reducing need for liver biopsy.[16] Magnetic resonance elastography, which is also reliable, is more costly and not widely available. However, similar results reproduced in diabetic cohorts would be useful.

AN INTEGRATIVE APPROACH

A standardized and integrative approach to detect high-risk features of NAFLD in the community setting is imperative to reduce the overall burden of disease. Proper education of PCPs on the utilization and interpretation of these tests is paramount. Unnecessary referrals of mild NAFLD to specialty hepatologists leads to undue burden on patients and their caregivers while increasing

health-related costs. On the other hand, those with high-risk features of NAFLD are going unnoticed in the community and often present to specialists in late stages of disease with advanced fibrosis or HCC. A simple algorithm, accessible to all PCPs, targeting a specific high-risk population (ie, type 2 diabetes) is paramount. Figure 1 demonstrates a practical and concise approach for PCPs to screen for high-risk features of NAFLD and implement a selective referral strategy while awaiting data from larger cohorts with proper validation.

DISCLOSURES

Author contributions: HD Trivedi contributed to the manuscript in its entirety and is the article guarantor.

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