REVIEW

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The Impact of Nonalcoholic Fatty Liver Disease in Primary Care: A Population Health Perspective

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease worldwide, with rising rates in parallel to those of obesity, type 2 diabetes, and metabolic syndrome. NAFLD encompasses a wide spectrum of pathology from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis, which are linked to poor outcomes. Studies confirm a significant amount of undiagnosed NAFLD and related fibrosis within the community, increasing the overall burden of the disease. NAFLD appears to be more prevalent in certain populations, such as those with type 2 diabetes and metabolic syndrome. Early detection and lifestyle modifications, including weight loss and regular exercise, have been shown to improve outcomes. Adverse cardiovascular events are a key contributor to NAFLD-associated morbidity and mortality, and efforts to minimize their occurrence are essential. A targeted and algorithmic approach using noninvasive diagnostic techniques is promptly required to identify and risk-stratify patients with NAFLD. Patients at low risk of progression to NASH and advanced fibrosis can be managed in the primary care setting, while those at high risk of disease progression should be referred to hepatology specialists for surveillance and treatment. This review summarizes the key data of NAFLD's impact within primary care populations and proposes a potential algorithmic approach to identifying and managing such patients.
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KEYWORDS: Diagnosis; Nonalcoholic fatty liver disease; Primary care; Screening

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease globally, affecting a quarter of the world's adult population.[1] The prevalence of NAFLD in the United States is estimated to increase from 83.1 million in 2015 to 100.9 million in 2030.[2] The incidence of nonalcoholic steatohepatitis (NASH), decompensated cirrhosis, and hepatocellular carcinoma are also projected to increase by 63%, 168%, and 137%, respectively, by 2030.[2] All-cause mortality related to NAFLD is escalating, with recent data demonstrating an increase in the age-standardized death rate by 15% (12.94 to 14.90; average annual percentage change, 1.98%; $P < .001$) between 2007 and 2016.[3] Considering the economy, the annual direct cost of NAFLD in the United States is estimated to be $103 billion, with over $7 billion attributed to NASH alone.[4]

NAFLD encompasses a wide spectrum of pathology from simple steatosis to NASH, an entity that is associated with advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma.[5,6] Approximately 20%-25% of individuals with NAFLD are predicted to have NASH, accounting for 5% of the US adult population.[5,7] Up to one-third of the NASH population will develop fibrosis, and 20% cirrhosis, as part of disease progression.[8,9] The presence of NASH and advanced fibrosis directly impacts morbidity and mortality. A study comparing 71 individuals with NASH revealed significantly decreased survival rates (70% vs 80%; $P = .01$), increased liver (2.8% vs 0.2%; $P = .04$), and nonliver- (15.5% vs 7.5%; $P = .04$) related mortality, compared with controls.[10]

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Health-related quality of life is also negatively impacted in NAFLD, with those developing NASH and cirrhosis having a poorer quality of life.[11] Recent data from the Short-Form Health Survey and Chronic Liver Disease Questionnaires demonstrate significantly lower health-related quality of life in individuals with NASH when compared with age- and sex-matched counterparts.[12]

The immense clinical burden of NAFLD and NASH necessitates early targeting of the community population, where NAFLD is profoundly underdiagnosed. More than 75% of patients with NAFLD are undiagnosed in the community, and only 3% of those at high risk of developing fibrosis are referred for specialized care.[13] Lack of identification and untimely management of NAFLD delays diagnosis of NASH and advanced fibrosis, often leading to related complications fraught with potential irreversibility and insufficient therapies. Given the alarmingly high proportions of undiagnosed NAFLD and NASH within the community, general practitioners have a critical and frontline role in alleviating the growing burden of disease.

CLINICAL SIGNIFICANCE

- Nonalcoholic fatty liver disease is the leading cause of liver disease worldwide, yet remains profoundly underdiagnosed in the community.
- General practitioners are at the forefront of tackling this indolent yet clinically and economically significant disease.
- Early detection and lifestyle modifications, including weight loss and regular exercise, improve outcomes.
- A targeted and algorithmic approach using noninvasive diagnostic techniques is required to identify and risk-stratify patients with nonalcoholic fatty liver disease.

WHAT DO THE GUIDELINES SAY?

International medical associations now recommend NAFLD evaluation in high-risk patients, such as those with type 2 diabetes. In fact, the American Diabetes Association recommends NASH and liver fibrosis evaluation for patients with type 2 diabetes, prediabetes, elevated serum alanine aminotransferase (ALT) levels, or presence of fatty liver on imaging studies.[14] The European Association for the Study of the Liver recommends NAFLD evaluation for patients with insulin resistance independent of the presence of other metabolic comorbidities.[6] The American Association for the Study of Liver Disease recommends against routine screening for NAFLD, but advises physicians to suspect NAFLD and NASH in patients with type 2 diabetes.[5] Early identification, referral, and management of NAFLD is imperative and starts in the community frontlines.

Screening the general population remains controversial and is not currently recommended.[5] Arguably, screening has not been deemed cost-effective, partly due to the conceived lack of useful therapies.[5] However, early implementation of weight loss strategies through lifestyle measures alone or weight reduction surgery do, in fact, reverse hepatic steatosis and fibrosis.[15,16] Additionally, early diagnosis would allow patients the opportunity to enter into clinical trials for investigational drugs on the horizon.

WHO IS AT RISK IN THE PRIMARY CARE POPULATION?

A targeted approach for evaluating patients at a high risk of developing NAFLD should be considered in the primary care setting. Factors such as type 2 diabetes and metabolic syndrome portend an increased risk.[17] Type 2 diabetes, in particular, is a strong predictor for the development of NAFLD, advanced fibrosis, and hepatocellular carcinoma.[18,19] Approximately 20%-25% of NAFLD patients develop NASH.[8,9] Risk factors for NASH and advanced fibrosis include older age, abnormal aminotransferase levels, metabolic syndrome, type 2 diabetes, hyperlipidemia, visceral obesity, and hypertension.[18,20] Among patients with liver cirrhosis from NAFLD, those with type 2 diabetes have an approximately 400% percent increased risk of developing hepatocellular carcinoma (hazard ratio 4.2; 95% confidence Interval (CI), 1.2-14.2; $P = .02$).[19]

Considering disease prevalence, 2 studies revealed an NAFLD prevalence of 70% and 65%, respectively, in a large population of patients with type 2 diabetes, figures much higher than those encountered in the general population.[21,22] The increased prevalence of NAFLD among diabetics highlight the need to target this population early on. Sole reliance on abnormal aminotransferase levels is insufficient, as only a quarter of diabetics with NAFLD have an increased ALT.[22] A multifaceted noninvasive screening strategy incorporating other liver-related parameters is required to accurately identify individuals with NAFLD and further risk-stratify those with NASH and advanced fibrosis.

NONINVASIVE DIAGNOSTIC TECHNIQUES

Early identification and risk stratification are required to reduce costs associated with unwarranted specialist referral, but more importantly, to identify those who may benefit from timely Hepatology referral prior to going on to develop NASH-related complications such as hepatocellular carcinoma, portal hypertension, and liver failure. Detecting patients with high risk of disease progression is challenging, however, as they often lack symptoms and traditional liver function tests are unreliable.[22,23] Liver biopsy remains the gold-standard method of assessment, but is accompanied with high costs, potential sampling error, and a low risk of complications such as bleeding, infection, and pain, thereby limiting its use.[24-26]

The advent of new noninvasive fibrosis measurements has revolutionized the management of patients with liver

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Table Commonly Used Cutoff Values for Noninvasive NAFLD Assessment Tools With Their Respective Performance Characteristics in Detecting Advanced Fibrosis

Comparison of Noninvasive Tests for Detecting Advanced Fibrosis in NAFLD						
Noninvasive Test	Cutoff	Sensitivity	Specificity	NPV	PPV	Study
APRI score	0.452-0.50	72%	67%	89%	44%	Xiao et al[38]
ELF	0.3576*	80%	90%	94%	71%	Guha et al[39]
FIB-4 index	1.24-1.45	77%	71%	92%	40%	Xiao et al[38]
	>3.25	37%	95%	87%	72%	Xiao et al[38]
MRE	3.62-4.8	85%	90%	93%	71%	Xiao et al[38]
NFS	−1.455	72%	73%	91%	50%	Xiao et al[38]
VCTE	8.2	90%	61%	85%	69%	Cassinotto et al[40]

APRI = aspartate aminotransferase-to-platelet ratio; ELF = enhanced liver fibrosis; FIB-4 = fibrosis-4; MRE = magnetic resonance elastography; NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; NPV = negative predictive value; PPV = positive predictive value; VCTE = vibration-controlled transient elastography.

*"Discriminant Score = −7.412 + (ln[hyaluronic acid]*0.681) + (ln[peptide of pro-collagen III]*0.775) + (ln[tissue inhibitor of matrix metalloproteinase 1]*0.494)."

disease overall. Importantly, noninvasive fibrosis tests may help general practitioners differentiate patients at a high risk of disease progression to NASH/advanced fibrosis that require specialist referral from low-risk patients that can continue to be monitored and managed in the primary care clinic. These assessments include serology-based tests such as the fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and enhanced liver fibrosis (ELF), or imaging-based tests such as vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE).

The FIB-4 index is a scoring system that was originally intended for patients coinfected with hepatitis C virus and human immunodeficiency virus.[27] It combines patient age with basic laboratory tests (aspartate aminotransferase, ALT, and platelet count) to predict liver fibrosis and cirrhosis, and was found to be effective in patients with NAFLD.[27,28] Similarly, the NFS is a scoring system that combines patient characteristics (age, body mass index) and basic laboratory tests (fasting glucose, aspartate aminotransferase, ALT, albumin, and platelet count), aiming to identify NAFLD.[29] The ELF is a scoring system based on serum test results of inflammatory markers, namely, hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase 1, and has been shown to be effective in detecting liver fibrosis and steatohepatitis in patients with suspected or confirmed NAFLD.[30,31] Despite demonstrable efficacy in guiding the diagnosis of NAFLD, serologic-based tests could yield false negative results in certain populations such as individuals above 65 years of age or those with chronic renal failure.[32,33]

Nonserologic methods of noninvasive screening also exist. Namely, VCTE is a noninvasive ultrasound-based diagnostic modality that detects liver fibrosis and cirrhosis through liver stiffness measurement.[34] VCTE accuracy, however, is undermined in cases of operator inexperience, morbid obesity, narrow intercostal space, and ascites.[35,36] MRE is an imaging modality based on magnetic resonance technique that uses shear wave to detect liver fibrosis with very high accuracy.[37] General practitioners can combine such tools with their clinical judgment to dictate need for specialist referral. The Table summarizes the baseline properties of commonly used cutoff values for noninvasive NAFLD assessment tools with their respective performance characteristics.[38-40]

APPLICATION OF NONINVASIVE MEASURES — IS IT COST-EFFECTIVE?

Multiple studies have demonstrated the benefits of applying noninvasive techniques in evaluating for NAFLD, as it allows for a safer and more cost-effective approach in identifying and triaging patients at risk of progression to NASH and advanced fibrosis. Tapper et al[35] determined that using a VCTE cutoff score of <7.7 kPa to exclude advanced fibrosis in the primary care setting is reliable (100% sensitivity, 100% negative predictive value) and leads to 45% fewer liver biopsies performed. Considering an economic perspective, utilizing the NFS/VCTE combination in detecting NAFLD was shown to decrease costs by $2696/person.[41] In another study, implementing the NFS alone was deemed to be the most cost-effective strategy, with $2118-$13,585 less/person when compared with VCTE/NFS/liver biopsy referral combinations, with the largest cost reduction occurring in the primary care setting.[24] In Canada, the annual NAFLD screening of high-risk populations using serologic diagnostic tools with MRE as confirmation of fibrosis has also been shown to be cost-effective, with an incremental cost-effectiveness ratio of C$26,143 per quality-adjusted life year gained.[42]

THE DATA OF AN ALGORITHMIC APPROACH

An algorithmic approach facilitates and standardizes the detection of patients at risk of developing NAFLD and its associated complications, namely NASH, advanced fibrosis, and cirrhosis. Recent studies propose pathways that combine noninvasive assessment tools to detect advanced fibrosis and cirrhosis in a high-risk population in a precise and cost-effective manner.[43,44] Davyduke et al[43] demonstrate a noninvasive stepwise approach incorporating the

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FIB-4 and VCTE with a "FIB-4 first strategy." They utilized a FIB-4 cutoff score of 1.3 for managing patients in the primary care setting and referred scores above 1.3 for VCTE. VCTE scores below 8 kPa returned to the general practitioners for management, while scores above 8 kPa underwent Hepatology referral. The FIB-4 cutoff score of 1.3 led to fewer unnecessary VCTE studies, and the combined 2-step approach (FIB-4 >1.3 and VCTE >8 kPa) resulted in fewer unwarranted Hepatology referrals, with only 4% of the total patient population being referred (95% CI, 2%-6%), a reasonable measure given the staggeringly high and fast-growing NAFLD prevalence within the general population.[43] Similarly, Srivastava et al[44] proposed an NAFLD pathway combining the FIB-4 and ELF. They also used a FIB-4 cutoff score of 1.3 for managing patients in the primary care setting, with scores above 3.25 triggering Hepatology referral.[44] "Indeterminate" FIB-4 scores between 1.3 and 3.25 prompted the use of ELF for further risk stratification, with a cutoff threshold of 9.5.[44] ELF scores above 9.5 prompted Hepatology referral. By following this pathway, there was an 80% reduction in Hepatology referrals and a significant improvement in advanced fibrosis detection (odds ratio 5.18; 95% CI, 2.97-9.04; $P < .0001$).[44] Primary care management would focus on reversing NAFLD risk factors such as metabolic syndrome and optimizing cardiovascular health.

These studies propose a pragmatic approach to identifying patients with NAFLD, and more importantly, those at a high risk of progression to NASH/advanced fibrosis. They allow for specialized care for patients who need it, while simultaneously saving patients with low risk of disease progression from unnecessary referral, a change that would improve resource utilization, enhance patient satisfaction, and reduce health care costs.

NAFLD MANAGEMENT IN THE PRIMARY CARE SETTING

NAFLD management does not solely entail treatment of the diseased liver, but also includes tackling of concurrent metabolic issues such as dyslipidemia, diabetes, and visceral obesity. In fact, pharmacologic treatments aimed directly at treating liver disease should be reserved for patients with biopsy-proven NASH and fibrosis.[5] The management of NAFLD should instead entail a multimodal approach aimed at promoting weight loss and exercise, decreasing risk of cardiovascular events, and reducing heavy alcohol consumption.

Cardiovascular disease is a key component in NAFLD and a top contributor to NAFLD-associated morbidity and mortality.[45] Current American Association for the Study of Liver Disease guidelines recommend adequate cardiovascular disease risk-stratification for patients with NAFLD and timely initiation of appropriate treatment accordingly.[5] Mildly elevated aminotransferase levels are not a contraindication to statin therapy, and statins can be safely administered for patients with NAFLD or NASH, based on cardiovascular risk profile.[5] As a matter of fact, lipid-lowering medications such as statins have been shown to significantly improve serum aminotransferases and decrease incidence of cardiovascular events in patients with abnormal aminotransferase levels attributed to NAFLD.[46]

Weight loss is considered the cornerstone of NAFLD management, with 2 large studies demonstrating significant hepatic histologic improvement with 5%-10% body weight reduction.[47,48] Bariatric surgery in eligible obese individuals with NAFLD is among the treatment options for weight loss, as it leads to improvement in hepatic histology and reduction of metabolic syndrome complications.[5,15] Regular exercise also reduces aminotransferase levels independent of weight reduction and has been associated with prevention of NAFLD and even improvement in those with existing disease.[49,50] A combination protocol of calorie-restricted diet and exercise has been shown to improve hepatic histopathology through decreasing inflammation, ballooning, and fibrosis.[48]

Vitamin E, an antioxidant, has been studied in patients with NASH. Its use has been shown to decrease hepatic steatosis, steatohepatitis, aminotransferase levels, and lobular inflammation in NASH.[51] Expert recommendations include it as first-line therapy in patients with NASH who do not have type 2 diabetes.[5]

Insulin desensitizers also appear to have a role in NAFLD management. Pioglitazone decreases insulin resistance, aminotransferase levels, hepatic steatosis, inflammation, and ballooning, and is therefore recommended for use in biopsy-proven NASH.[52] Furthermore, its association with significant reduction in death, myocardial infarction, and stroke in diabetics make it an attractive option for individuals with NASH and type 2 diabetes, although long-term safety data are lacking.[53] Similarly, canagliflozin, a sodium glucose co-transporter 2 inhibitor (SGLT2i), has been shown to decrease body weight, hemoglobin A1c, triglycerides, and aminotransferase levels in patients with type 2 diabetes and NAFLD.[54] Furthermore, recent studies on SGLT2i use in diabetics revealed a decreased incidence of major cardiovascular events in those with atherosclerotic disease, thus, proposing SGLT2i as a potentially promising treatment option in diabetics with NAFLD.[55]

Although these measures alone have proven beneficial, additional pharmacologic therapies that can be considered are on the horizon. Early identification of disease to encourage such interventions is crucial to prevent progression of disease. This prompt identification starts in the frontlines at the community practices.

PUTTING IT ALL TOGETHER

It is evident that NAFLD is increasing in prevalence, and its assessment should begin in the primary care office. General practitioners are on the forefront of tackling this indolent yet clinically and economically significant disease with a burden that is only expected to worsen. Early diagnosis will help timely implementation of current and future treatment

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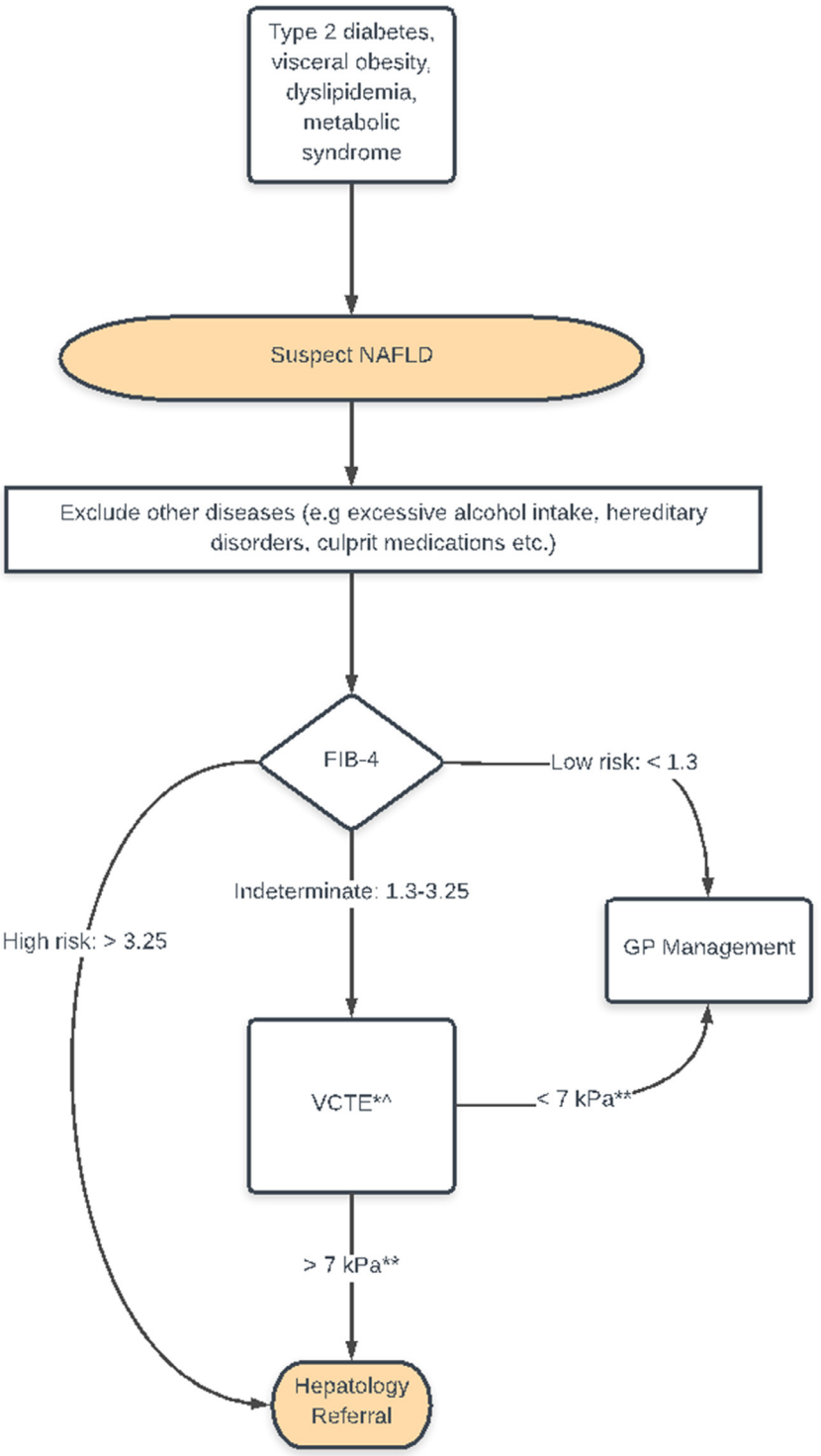

Figure A proposed algorithm for identifying and managing patients with a high risk of NAFLD in the primary care setting.
FIB-4 = fibrosis-4 score; GP = general practitioner; kPa = kilopascal; NAFLD = nonalcoholic fatty liver disease; VCTE = vibration-controlled transient elastography.
*VCTE limitations include perihepatic ascites, morbid obesity, alanine aminotransferase >100 U/L, in which case magnetic resonance elastography can be considered instead.
^Access to VCTE is variable, and patients may need Hepatology referral first.
**Lower VCTE cutoff score used to capture more patients with advanced fibrosis.

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strategies on the horizon while also triaging referral to specialists for chronic liver disease screening measures.[56,57] The majority of the recommended NAFLD interventions can be safely implemented in the primary care setting. Based on our review of the literature, we propose a simple, cost-effective, and noninvasive approach for general practitioners to follow in patients with high risk of developing NAFLD (Figure). A lower VCTE cutoff was used to detect more patients with advanced fibrosis. Although substantial advances have been made in this arena, the ultimate algorithmic approach for identifying NAFLD patients in the primary care setting remains to be determined. It is our hope that timely identification of disease and successful discovery of effective treatments will limit the escalating trend of NAFLD/NASH-related morbidity and mortality.

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