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How to Identify Advanced Nonalcoholic Fatty Liver Disease in the Primary Care Setting

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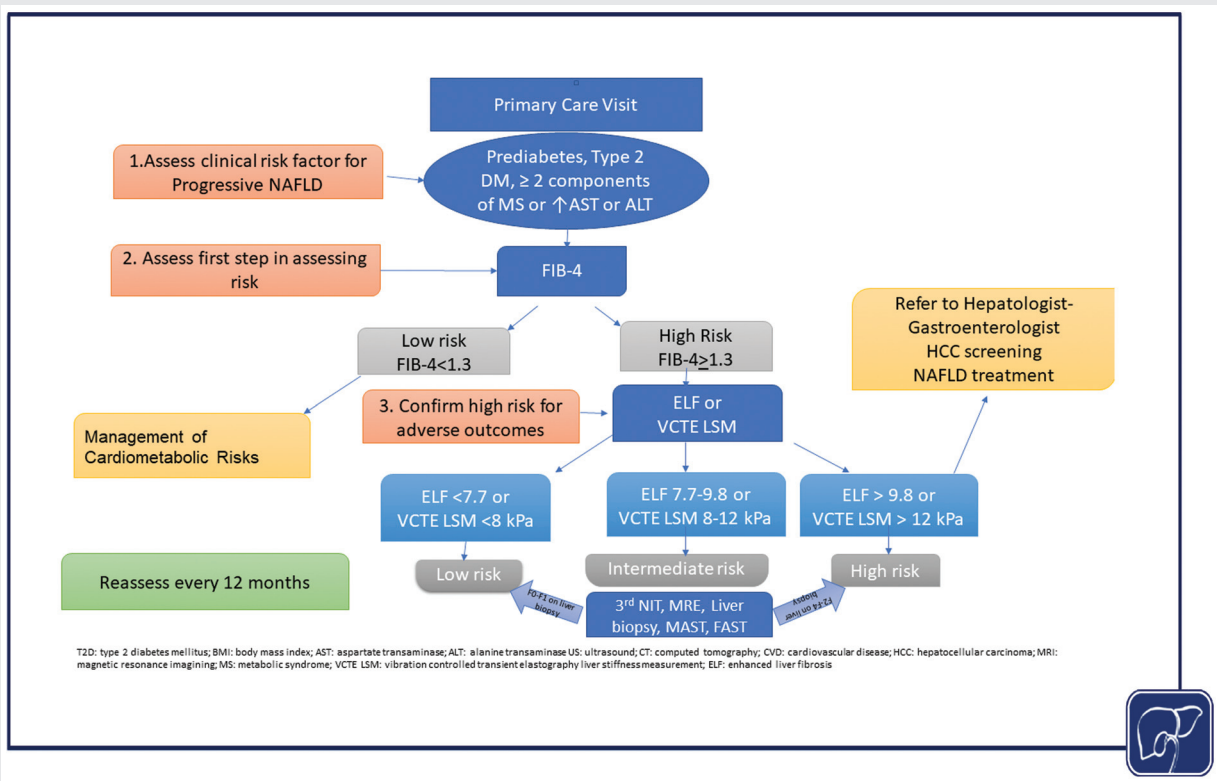
Graphical Abstract



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Abstract

Nonalcoholic fatty liver disease (NAFLD) affects 30 to 40% of the population globally and is increasingly considered the most common liver disease. Patients with type 2 diabetes, obesity, and cardiovascular diseases are at especially increased risk for NAFLD. Although most patients with NAFLD do not have progressive liver disease, some patients progress to cirrhosis, liver cancer, and liver mortality. Given the sheer number of patients with NAFLD, the burden of disease is enormous. Despite this large and increasing burden, identification of NAFLD patients at risk for progressive liver disease in the primary care and diabetology practice settings remains highly suboptimal. In this review, our aim is to summarize a stepwise approach to risk stratify patients with NAFLD which should help practitioners in their management of patients with NAFLD.

Keywords

- nonalcoholic fatty liver disease
- risk stratification
- advanced disease
- noninvasive tests
- primary care

Nonalcoholic fatty liver disease (NAFLD) affects over a third of the world population.[1–3] NAFLD has been defined as fat accumulation in more than 5% of hepatocytes, in the absence of secondary causes of liver disease, such as excessive alcohol consumption, viral hepatitis, and autoimmune liver disease.[4] The prevalence of NAFLD has been on the rise for decades in almost every region of the world. This is partly due to a rapid increase in the rates of obesity, type 2 diabetes (T2D), and metabolic syndrome. Due to its close associations, NAFLD has been regarded as the hepatic manifestation of metabolic syndrome.[5] It is now well established that the increasing number of components of metabolic syndrome components not only increases the risk of nonalcoholic steatohepatitis (NASH) or having advanced hepatic fibrosis, but also higher rates of liver mortality.[6] This risk is especially high for NAFLD patients with T2D.[7]

Although most patients with NAFLD do not experience progressive liver disease, some will develop advanced fibrosis, cirrhosis, and liver cancer leading to an increased number of patients being listed for liver transplantation and increased liver mortality.[8–11] In this context, it is estimated that 10 to 15% of patients with NAFLD have the progressive type or NASH. Furthermore, it is estimated that 10 to 20% of patients with NASH can progress to cirrhosis over a 10-year period.[12,13] Once cirrhosis is established, the risk of developing hepatocellular carcinoma (HCC) is about 2% yearly.[14] Nevertheless, this risk can be as low as 1% in those followed in clinical trials. In addition to the presence of T2D and other cardiometabolic risks, stage of fibrosis is an independent predictor of mortality.[15] In fact, multiple meta-analyses have established that NAFLD stage less than 2 is associated with increased risk for overall and liver-related mortality.[16–19] Although establishing the diagnosis of NAFLD or NASH may be important, identifying the stage of liver disease in these patients is of paramount importance to risk stratify patients with NAFLD. It is also important to note that diagnosis of NASH is based on pathologic criteria established by liver biopsy.[15] Furthermore, association of stage of fibrosis with adverse outcomes was based on histologic stage seen on liver biopsy.[15–17] Given the limitations of liver biopsy which includes its invasiveness, poor acceptability, sampling variability, and cost, the use of noninvasive tests (NITs) to estimate the stage of fibrosis has gained significant popularity. These NITs and their combinations have been used to develop algorithms to risk stratify these patients.

Management of NAFLD is based on the cornerstone of prescribed lifestyle modification which can lead to sustainable weight loss. Additionally, new drug regimens are being tested in clinical trials and may provide additional options for treatment of these patients. Therefore, identifying NAFLD patients at high risk of progressive liver disease is becoming increasingly important. In this context, most patients at risk for progressive NAFLD who present with a number of cardiometabolic risks are seen at the primary care or diabetology practices. Despite the growing number of patients seen in these clinical settings, awareness about this liver disease and its potential burden is quite low. This lack of awareness in the primary care practices regarding the importance of NAFLD represents a major conundrum. Therefore, programs that combine raising awareness in the primary care setting with algorithms using validated NITs to identify "high-risk" NAFLD patients have become increasingly important.[20–27] These algorithms should combine clinical data with a combination of different types of NITs to optimize their performance. Once established, the cost-effectiveness of these pathways to identify high-risk NAFLD patients should be considered.

Identifying NAFLD and Fibrosis by Imaging Techniques

Traditional imaging modalities such as ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) have been frequently used to establish the presence of hepatic fat and to diagnose NAFLD. Even though US is widely available and relatively cheap, it falls short in its sensitivity to detect mild steatosis.[23,28] Conventional MRI performs better than US but cost and access remain important challenges.[29] Abdominal CT does not have any advantages over US but introduces the unnecessary exposure to radiation.[30,31] Finally, none of these imaging technologies (US, CT, and conventional MRI) can accurately estimate the stage of hepatic fibrosis.

Magnetic resonance spectroscopy (MRS) seems to better quantify lipid fraction relative to water in hepatic parenchyma, but cost, access, and inability to determine stage of fibrosis still remain challenges.[32]

Transient elastography (TE) is a modality that can estimate hepatic fibrosis by measuring liver stiffness and quantifying liver fat by using controlled attenuation parameter.[33] It is noninvasive and can be performed at point-of-care. In addition to estimating hepatic steatosis, TE can estimate stages of fibrosis.[34] However, in those with visceral obesity, its yield seems to be limited.[35] Another elastography technique is called acoustic radiation force impulse (ARFI) elastography, which include point-shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE).[36] This method uses high-intensity US waves, as opposed to TE which uses mechanical waves via the probe. For this reason, pSWE and 2D-SWE seem to provide more valid measurement of hepatic steatosis than TE, even in patients with high body mass index (BMI). Use of ARFI involved targeting the 5- the 10-mm region of hepatic tissue by B-mode US, transmitting short pulses generated by US probe, and tracking quantifiably shear wave speed.[37] ARFI has been shown to have similar diagnostic efficacy with TE, but also has similar disadvantages in patients with obesity.[38]

Application of magnetic resonance technology for estimating liver stiffness has led to higher accuracy. In fact, magnetic resonance elastography (MRE) is more accurate for detecting hepatic fibrosis than TE. Unlike TE and ARFI, which can study only a small portion of liver parenchyma, MRE can analyze the entire liver and its results are easily reproducible. Combining MRE with MRI–proton density fat fraction (MRI-PDFF) which estimates hepatic fat brings both assessment of hepatic fibrosis and hepatic steatosis together in a single imaging test. Again, costs and limited access can be important limitations of this technology in clinical practice.[39,40]

Serum Single Biomarkers for Detection of NASH and Fibrosis

Numerous serum biomarkers have been studied for use in noninvasive detection of NASH or fibrosis, details of which are beyond the scope of this article. Briefly, one of the first fibrosis biomarkers was hyaluronic acid (HA), which is a component of the extracellular matrix.[41] Individually, HA does have interindividual variability making it less desirable for large-scale testing. Cytokeratin-18, which is an intermediate filament protein, was found to be associated with hepatocyte apoptosis and was thought to be a promising marker for diagnosing NASH, but its external validity and appropriate certain cutoff for NASH diagnosis has not been established.[42] Other markers of chronic inflammation and fibrosis, including but not limited to fibroblast growth factor 21, interleukin 1 receptor antagonist, pigment epithelium-derived factor, and osteoprotegerin, have all been studied, but their use is limited to research.[43]

Biomarker Panels for NAFLD, NASH, and Fibrosis

There have been several noninvasive panels that combine clinical variables with different biochemical markers and are used to establish NAFLD, NASH, or stage of fibrosis.

A test that is used to establish NAFLD is fatty liver index (FLI). This test combines BMI, waist circumference, triglyceride level, and gamma glutamyl transferase (GGT), and gives a quantitative estimate of hepatic steatosis. FLI has scores ranging between 0 and 100, where FLI less than 30 rules out steatosis, while FLI greater than 60 rules in fatty liver.[44] The hepatic steatosis index (HSI) is another test that uses BMI, AST/ALT ratio, the presence of diabetes, and gender to estimate hepatic steatosis. With a score less than 30, HSI ruled out NAFLD with a sensitivity of 92.5%, while a score greater than 36 could detect NAFLD with a specificity of 92.4%.[45] The usefulness of FLI and HSI in clinical practice is very limited. In this context, FLI and HSI have been used in population studies where US or other modalities to estimate fat are not available.

Index of NASH (ION) was developed as a potential NIT for establishing NASH. ION uses waist-to-hip ratio, triglyceride level, ALT, and HOMA score. In this context, ION score of 50 or more identified histologically proven NASH with a specificity of 92%.[46] Again, the utility of ION and its external validity in clinical practice have not been established. Recently, NIS-4 algorithm has been developed to identify patients at risk of NASH which combines miR-34a-5p, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin. A NIS-4 score less than 0.36 ruled out high-risk NASH with a sensitivity of 82%, while a score greater than 0.63 ruled in high-risk NASH with a specificity of 87%.[47] Again, the utility of NIS-4 in clinical practice has not been fully established.

Given the importance of hepatic fibrosis, several other NITs have been developed to estimate the stage of fibrosis. Of these, the BARD score combines BMI, AST/ALT ratio, and the presence of diabetes to estimate the presence of fibrosis in NAFLD. Despite its use in clinical practice, BARD score has a high false-positive rate.[48] Other tests include AST/ALT ratio and AST/platelet ratio (APRI), which were initially developed for chronic hepatitis C.[49,50] Although APRI has been used in studies of NAFLD, its widespread use in clinical practice remains suboptimal.

Two other tests have been advocated for use in clinical practice. NAFLD fibrosis score (NFS) includes the presence of impaired fasting glucose/diabetes, BMI, platelet count, albumin, AST/ALT ratio, and age.[51] The developers reported that use of NFS could avoid liver biopsy in a large number of patients with NAFLD. Although NFS seems to be a good initial test to risk stratify NAFLD, its utility in clinical practice seems to be limited.[52] Finally, FIB-4 index was developed to estimate the stage of fibrosis for patients with chronic hepatitis C. FIB-4 index includes platelet count, AST and ALT levels, and age.[53] In fact, FIB-4 index has been widely validated among patients with NAFLD. Using the previously reported cut-off of less than 1.3 and greater than 2.67 for the absence and presence of advanced fibrosis, it

was shown that FIB-4 can be used to avoid liver biopsy in 78 to 90% of patients.[54] Additionally, FIB-4 index has been shown to predict long-term outcomes among patients with NAFLD.[55] Given the accumulating evidence supporting the validity of FIB-4 index, it is being proposed as the initial test to risk stratify patients with NAFLD.

FibroTest combines five biomarkers, haptoglobin, a2-macroglobulin, apolipoprotein a1, total bilirubin, and GGT, and adjusted according to age and gender.[56] Although this test has been marketed for use in NAFLD, its validity for the spectrum of NAFLD-related stages is lacking.

Another test, Hepascore, combines four biomarkers, HA, a2 macroglobulin, total bilirubin, and GGT, and adds age and gender as other variables. It was reported to have good high specificity and positive predictive value for predicting advanced fibrosis.[51] Fibrometer is a patented formula that combines AST, ALT, GGT, urea, alpha-2-macroglobulin, prothrombin index, and platelet count, and was found to have an area-under-the-curve of 0.82 in determining the presence of F3 fibrosis.[57] Again, the validity and utility of Hepascore and Fibrometer in large-scale use in clinical practice have not been established.

The enhanced liver fibrosis (ELF) panel combines three biomarkers, HA, tissue inhibitors of metalloproteinase 1, amino terminal peptide of pro-collagen 3, and adds age as the fourth variable.[58] Later, five additional variables were added to the original ELF panel (BMI, presence of diabetes or impaired fasting glucose, AST/ALT ratio, platelet count, and albumin, resulting in an increase in diagnostic efficacy for severe, moderate, and no fibrosis).[59] ELF test has been widely validated in different clinical and research settings. ELF has been shown to assess active, dynamic fibrosis which is important in patients with NAFLD. In 2018, the U.S. Food and Drug Administration approved ELF as the first prognostic tool for patients with advanced fibrosis (F3 or F4) due to NASH.[60] Furthermore, ELF has been recommended by National Institute for Health and Care Excellence (NICE) in the United Kingdom for the assessment of fibrosis among NAFLD.

Combination of Imaging with Biomarkers

Combining newly developed imaging modalities with other biomarkers can be used to develop combination biomarkers that may enhance performance and validity of a single test. Combination tests such as the FAST, MAST, MEFIB, and Agile score combine imagining and biomarkers to determine those with "at-risk" NASH. Among these, the FAST score combines the liver stiffness measurement (LSM) from FibroScan with AST level from blood work. A FAST score of 0.67 is indicative of F2 fibrosis with 90% specificity, while a cut-off level of 0.76 is indicative of F3 fibrosis with 92% specificity.[61] Another method is combining MRI with AST levels, known as MAST score. Validation and comparison studies suggest that MAST score resulted in fewer proportion of patients with intermediate results than NFS or FIB-4, and compared to FAST, MAST had higher AUC level.[62] The MEFIB is a combination of MRE and the FIB-4 score. The MEFIB index is considered to be positive with a MRE score of 3.3 kPa or higher and FIB-4 of 1.6 or higher. MEFIB can be used to identify a population with low risk for liver-related events.[63] Finally, Agile score was recently developed based on the combination of aspartate aminotransferase/alanine aminotransferase ratio, platelet count, diabetes status, sex, age, and LSM by TE to identify advanced fibrosis (Agile 3+) and cirrhosis (Agile 4).[64,65] Obviously, the advantages and disadvantages of TE and MRE will still be applicable to these combination tests.

Recommendations for a Stepwise Algorithm Using Noninvasive Tests

As noted previously, the sheer volume of patients with NAFLD and cardiometabolic risks leads to a large group of patients at risk of advanced liver disease. Therefore, it is crucial to identify those "high-risk" NASH patients and link them to targeted and aggressive medical management. Given the limitation in hepatology manpower, a great deal of this risk stratification can occur at the primary care setting where most of these patients are being managed for their cardiometabolic risks. In this context, patients with low-risk NAFLD can be managed by primary care providers and only those with high risk should be linked to gastroenterology-hepatology care. To help with this risk stratification, several algorithms have been proposed.[12,66–71] The majority of these algorithms have initially focused on clinical risk factors of progression, including the presence of T2D or two other components of metabolic syndrome as well as those with chronically elevated aminotransferases. Once the population is enriched with those with metabolic risk factors, FIB-4 index has been recommended as the first-line NIT. Those considered to have low risk (FIB-4 < 1.3) should be managed by primary care providers to optimize their cardiometabolic risks. On the other hand, those considered intermediate risk and high-risk by FIB-4 should be further evaluated. In this context, use of TE or ELF can further risk stratify those with high risk who should be linked to specialty care.[12,67] It is also important that occasionally, patients may have two conflicting results of these two NITs. A third step using NITs (FIB-4–ELF–then TE or FIB-4–TE and then ELF) or a liver biopsy may be considered. The use of other tests such as MRE, FAST, MAST as a third test can be considered based on availability and clinical scenario (►**Fig. 1**).

Conclusions

Some patients with NAFLD are at an increased risk of disease progression. Identifying those at high risk of progression using simple and easy-to-use NIT algorithms can help risk stratify these patients. Given the high number of potentially affected individuals, a stepwise approach for risk stratification has been an unmet need in the daily clinical practice, especially in the primary care setting, which was recently addressed by algorithms recommended by different guidelines. These algorithms should be easy to implement and combined with programs to raise disease awareness. These algorithms can help in managing patients with NAFLD and provide clinicians with practical care pathways.

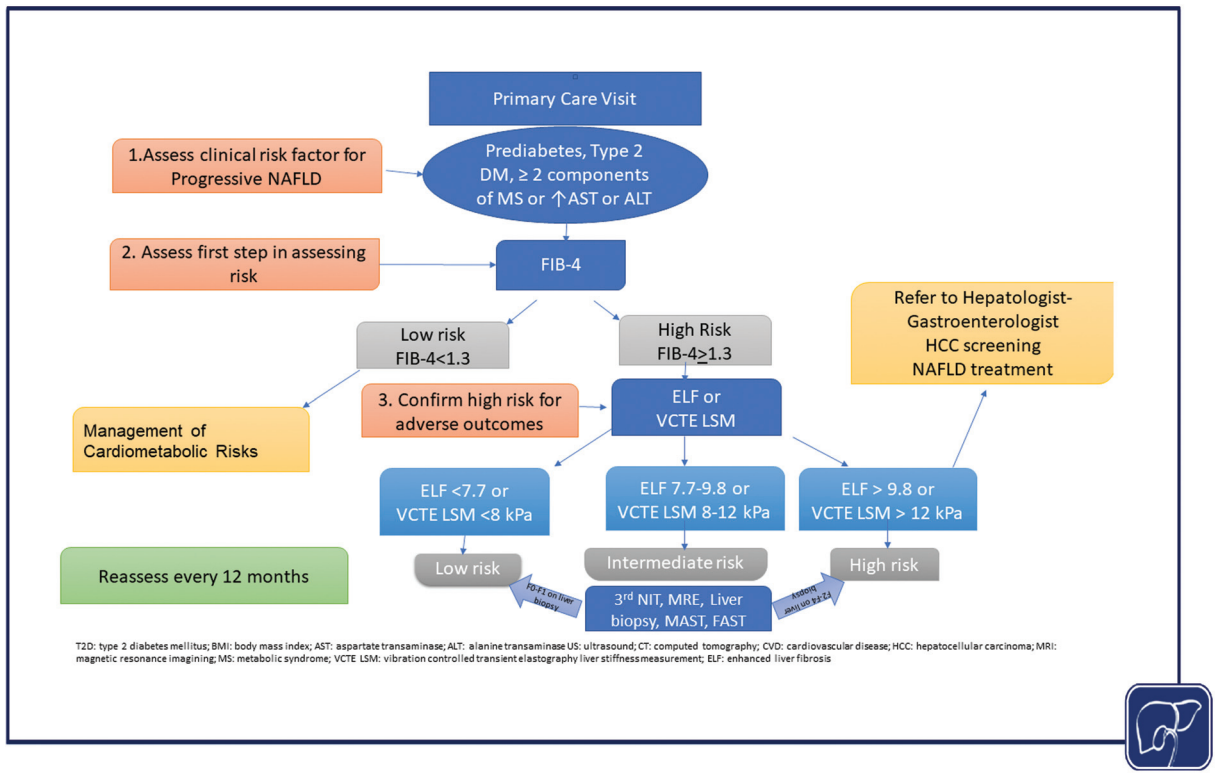

Fig. 1 Risk stratification of patients with nonalcoholic fatty liver disease (NAFLD).

Conflict of Interest

ZYM is consultant to Abbott, AstraZeneca, Bristol-Myers Squibb, Gilead Sciences, Intercept, Madrigal, Merck, Novo-Nordisk, and Siemens Healthineers. None of the other authors have conflicts of interest.

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