REVIEW ARTICLE

Work-up for Incidentally Detected NAFLD: How Far is It Worth?

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Abstract

The incidence of nonalcoholic fatty liver disease (NAFLD) has seen a steep rise in parallel with the global obesity and metabolic syndrome epidemic. The presence of NAFLD contributes to significant socioeconomic burden due to healthcare costs, progression of liver disease as non-alcoholic steatohepatitis (NASH), and later cirrhosis and hepatocellular carcinoma (HCC). With the advent of widely available imaging, it is also being detected as an incidental diagnosis in individuals with systemic disease like metabolic syndrome, diabetes, chronic cardiac disease, polycystic ovarian syndrome, etc. or in asymptomatic persons on presurgical evaluation or even annual health assessments. Gastroenterologists, hepatologists, physicians and surgeons need to be updated about the new diagnostic criteria of Metabolic (dysfunction)-associated fatty liver disease, noninvasive tests (NITs) of liver fibrosis, new tools of elastography, and identification of those with high-risk disease. In this review, we appraise the relevance of new diagnostic definitions, steatosis and fibrosis estimation tests, advanced imaging like magnetic resonance elastography and proton density fat fraction and discuss the diagnostic algorithm for incidentally detected NAFLD.

Keywords: Acoustic radiation force impulse, Incidental NAFLD, Liver fibrosis, Metabolic (Dysfunction)-associated fatty liver disease, Magnetic resonance imaging-proton density fat fraction, Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Transient elastography.

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Background

In clinical practice, it is quite common to encounter patients who present with an imaging finding (usually an ultrasound abdomen) suggestive of fatty liver. Mostly these patients are under evaluation for other ailments during which hepatic steatosis is incidentally detected. The primary aim in such patients should be to find the cause of steatosis, determine the severity of underlying liver disease and identify concomitant comorbidities if any. Alcohol, drugs, and viral hepatitis are the common secondary causes of fatty liver.[1] The incidence of NAFLD, in association with metabolic risks factors like obesity, diabetes mellitus, dyslipidemia, and/or hypertension, has seen a steep rise globally.[2–4]

Nearly one-third of the world population has NAFLD, with a much higher prevalence in the Middle Eastern and South American countries.[1,5] Prevalence is even higher (up to 60–70%) in patients with one or more metabolic risk factors.[1,2] More than 50% healthy blood donors were found to have NAFLD on screening in a study from Northern India.[6] One-third of these patients are likely to have NASH, an aggressive form, which may progress to cirrhosis and HCC quite rapidly.[7–9] Nonalcoholic fatty liver disease is a hepatic manifestation of systemic metabolic syndrome.[2,10] Liver-specific and overall mortality rates among NAFLD and NASH have been found to be 0.77 per 1,000 and 11.77 per 1,000 person-years and 15.44 per 1,000 (range 11.72–20.34) and 25.56 per 1,000 person-years, respectively.[1]

With rapidly increasing incidence of a sedentary lifestyle, diseases such as diabetes, hypertension, dyslipidemia and obesity, fast food consumption, genetic predisposition, and rapid urbanization, NAFLD has already escalated into a major public health problem even in low-middle income countries.[4,5,11] In a systematic review and meta-analysis of the studies in the Asian population, the overall prevalence of NAFLD was 29.62% with a significant increase in prevalence from 25.28 to 33.9% between 1999 and 2017. The pooled annual incidence of NAFLD and HCC was 50.9 and 1.8 cases per 1,000 person-years, respectively.[5]

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Nonalcoholic fatty liver disease, along with alcohol, has become one of the leading causes of underlying cirrhosis among the liver transplantation (LT) waitlisted candidates without HCC.[3,12] Notably, among the LT-waitlisted patients with HCC, NASH was the possible etiology of cirrhosis in most patients.[4,12,13] With such high prevalence and increasing incidence of NAFLD, it is imperative to identify patients who are at higher risk of progression to NASH, cirrhosis, and HCC timely.

Most risk factors between Western and South Asian patients with NAFLD are similar with few noticeable differences.[14,15] South Asian NAFLD patients have relatively lower body mass index (BMI) and obesity rates, also known as the "Asian Paradox," which is primarily attributed to increased visceral fat content at a given BMI

when compared with their western counterparts.[1,2,5] The average BMI in South Asian NAFLD patients was found to be 26 kg/m^2 and therefore, a lower BMI (>22.9 kg/m^2) and waist circumference (≥90 cm in males and ≥80 cm in females) cut-offs are used to define metabolic syndrome and central obesity in the Asian population.[16,17]

In order to identify a specific cohort of patients at high risk of progression and complications in individuals presenting with incidentally detected NAFLD (ID-NAFLD), economical, easily available, acceptable, NITs are the need of the hour which can reliably rule-in or rule-out NASH and/or high fibrosis (≥F2) at presentation, that is, they should have high negative predictive value to exclude significant fibrosis. In this review, we will discuss the practical approach in patients who present to clinics with ID-NAFLD, what are the various NITs available along with their accuracy, and how to reliably identify and follow up ID-NAFLD patients at high-risk of adverse outcomes.

Metabolic (Dysfunction)-associated Fatty Liver Disease (MAFLD) and NAFLD

Nonalcoholic fatty liver disease, diabetes, dyslipidemias and obesity run in parallel. Recently, an expert consensus proposed a new acronym "MAFLD" instead of NAFLD.[10] Because patients with cirrhosis usually lose typical histopathological features of steatosis or steatohepatitis, the panel also proposed that patients who have past or present evidence of metabolic dysfunction with features suggestive of MAFLD in previous biopsy or steatosis on imaging should be considered as having MAFLD-related cirrhosis.[18] The definition of MAFLD requires the presence of hepatic steatosis in patients with diabetes, overweight/obesity or two other metabolic risk factors (central obesity, low HDL-cholesterol levels, hypertriglyceridemia, hypertension or on anti-hypertensive drugs, prediabetes, raised highly sensitive C-reactive protein levels, and homeostatic model for insulin resistance, HOMA-IR, ≥2.5) and does not require exclusion of excessive alcohol intake, viral hepatitis and other secondary causes of fatty liver.[10,18]

The rationale behind the proposed nomenclature is that metabolic dysfunction independently contributes to poor hepatic and overall outcomes even in the presence of other risk factors like alcohol or viral hepatitis. This has led to extensive debate in the hepatology community with proposers of the term MAFLD justifying it as being a more pathophysiologically appropriate, less stigmatizing (removal of term "alcoholic"), positive definition. On the other hand, the opposing group term the change as being premature with possible negative effects on policy-making and ongoing clinical trials given its heterogeneous nature, removal of term NASH (a primary endpoint of most clinical trials), and vague definition of "metabolic health".[19]

Clinical Presentation of ID-NAFLD

Most patients are asymptomatic and detected to have NAFLD by chance while following up for other diseases like diabetes, cardiac ailments, pre-surgical assessment or during annual health check-ups. About one-third of patients may have malaise or fatigue as a presenting complaint. Non-specific gastrointestinal symptoms or vague right upper quadrant discomfort may be present in up to 30–50% cases.[17,20] Nonalcoholic fatty liver disease may also be diagnosed during the evaluation of abnormal liver function tests i.e., elevated transaminases ordered for unrelated indications, or in imaging done for other purposes. Unfortunately, patients with compensated cirrhosis or high fibrosis may remain asymptomatic, and many patients can present at advanced stages with cirrhosis and its complications or HCC. In such patients, a retrospective diagnosis of NAFLD is usually based on historical pointers, maximum lifetime body weight, and the presence of one or more metabolic risk factors.[21]

Clinical Spectrum of ID-NAFLD

Nonalcoholic fatty liver disease is characterized by the presence of hepatic steatosis in the absence of significant alcohol intake [<21 units (<30 g/day) and <14 units (<20 g/day) standard drinks per week for males and females, respectively] and after ruling out other plausible causes of steatosis.[1,2,21,22] NAFLD is an umbrella term that includes Non-alcoholic fatty liver (NAFL) or simple steatosis, NASH, Cirrhosis, HCC (with/without cirrhosis) in increasing order of severity (Fig. 1). Macrovesicular steatosis involving >5% hepatocytes is the characteristic histological finding.[1] Simple steatosis and NASH can

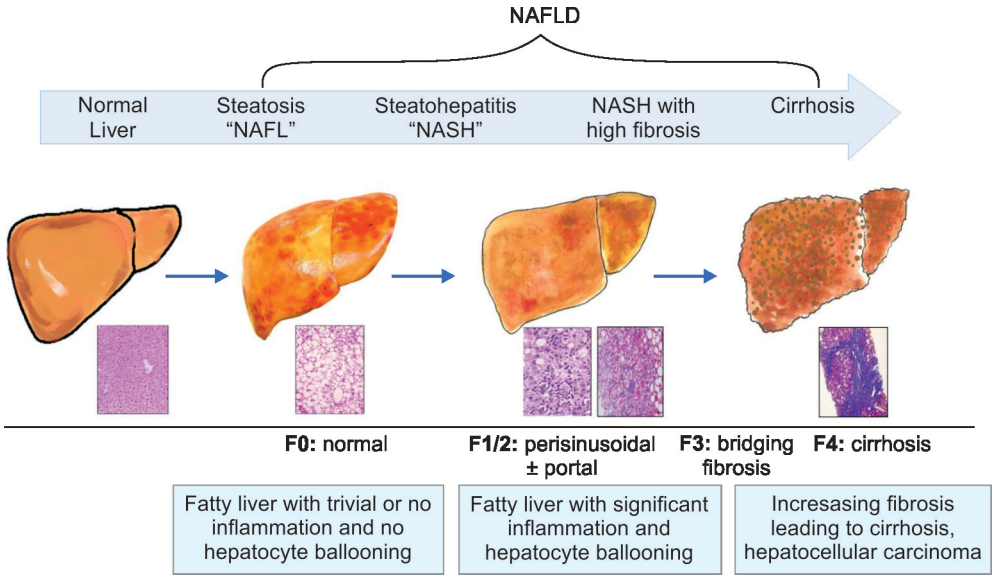


Fig. 1: Clinical continuum in incidental NAFLD

be differentiated by the presence of lobular inflammation and ballooning with or without fibrosis in the latter.[1] The presence of NASH signifies the progressive form of NAFLD and mandates appropriate intervention.[2,7,8] It is important to note that the level of serum transaminases cannot reliably distinguish between NAFL and NASH and correlate poorly with histological findings. More than 75% of patients with NAFLD and 50% with NASH may have normal serum transaminases.[6,7,14]

Diagnosis and Work-up for ID-NAFLD

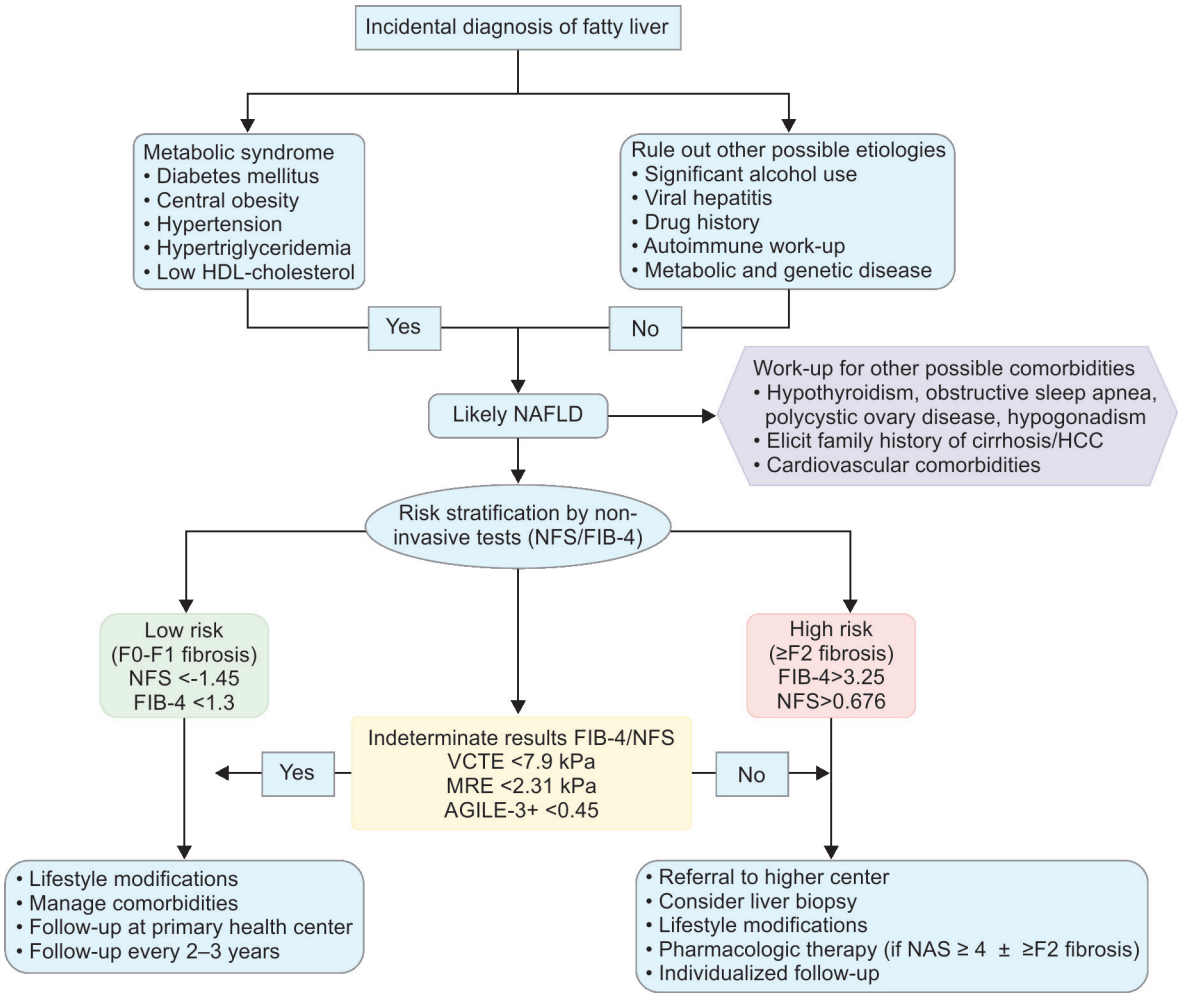
History, Physical Examination, and Laboratory Tests

The presumptive diagnosis of NAFLD is an example of diagnosis of exclusion.[1] A well-directed detailed history should be undertaken to exclude other probable causes of steatosis like significant alcohol intake and drug history.[1] Duration and amount of alcohol intake should be documented accurately along with lifestyle habits including diet and physical activity. Anthropometric measurements including waist circumference and BMI should be done in all patients and stratified as per local cut-offs.[1,16] Hepatomegaly may be present in up to 50% of patients. General physical examinations may reveal xanthomas/xanthelasmas, acanthosis nigricans and other cutaneous signs of dyslipidaemia and insulin resistance, respectively.[1,6,11,15,17] In patients with advanced cirrhosis of unknown etiology (cryptogenic), history should be taken to find out maximum lifetime body weight as the onset of advanced cirrhosis usually leads to sarcopenia i.e., loss of muscle mass, with fluid accumulation leading to ascites and pedal edema. This makes accurate estimation of weight difficult. Nearly two-thirds of patients with cryptogenic cirrhosis, especially those with metabolic risk factors, showed features consistent with NASH-related cirrhosis on explant pathology.[21,23]

All patients with ID-NAFLD should be evaluated for the presence of diabetes, dyslipidemia, and hypertension. A cardiopulmonary evaluation may be undertaken on a case-to-case basis. Hypothyroidism, obstructive sleep apnea, chronic kidney disease and polycystic ovary disease have also been found to have increased prevalence in NAFLD and require individualized work up.[1,11,14,15] Clinical predictors for the presence of NASH include older age, obesity, male gender, family history of NASH-related cirrhosis and number of metabolic risk factors (Flowchart 1).[1,15]

Alternate etiologies of hepatic steatosis and raised transaminases (if present), apart from alcohol intake, such as chronic viral hepatitis (hepatitis B, hepatitis C), drug-induced liver injury, autoimmune hepatitis, Wilson's disease, hemochromatosis and Celiac disease should be ruled out by appropriate tests.[1,2] Anti-nuclear antibody

Flowchart 1: Algorithm to evaluate incidentally detected fatty liver



AST, aspartate aminotransferase; FAST, fibroscan plus AST score; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; VCTE, vibration controlled transient elastography

positivity, as an epiphenomenon, may be seen in up to 25–30% patients with NAFLD which may confound the diagnosis and may require further work-up such as serum total immunoglobulins along with a liver biopsy to rule out for autoimmune hepatitis as per clinical scenario.[1]

Once the diagnosis of ID-NAFLD is confirmed, an accurate stepwise assessment of the severity of underlying chronic liver disease utilizing appropriate NITs should be undertaken. The presence of NASH and/or advanced fibrosis are the primary predictors of progression, morbidity, and mortality.[5] NASH can be conclusively diagnosed only on liver biopsy whereas many non-invasive have now been validated to rule-in or rule-out advanced fibrosis (F3–F4).[1,22,24,25]

Non-invasive Assessment of Hepatic Steatosis

Serum-based Tests

Fatty Liver Index (FLI) combines easily available variables such as waist circumference, BMI, serum triglyceride level and serum gamma-glutamyl transferase. An FLI of ≥30 has an AUROC of 0.834 (0.825–0.842) to detect NAFLD with 80% sensitivity and 72% specificity.[26] Other similar tests such as SteatoTest™, Hepatic Steatosis Index and the NAFLD-Liver fat score have also been evaluated with an acceptable AUROC of >0.80 to detect steatosis.[25] However, These tests usually do not add much to the already available information provided by routine clinical, laboratory and imaging parameters.[1,25]

Imaging-based Tests

Ultrasonography

Ultrasonography (USG) of the abdomen is the most frequently used and preferred initial imaging modality to detect hepatic steatosis[2,25] because of its acceptability, safety, low cost, and widespread availability. Furthermore, it gives other useful information like the presence of cirrhosis (coarse, nodular liver, ascites, hepatic space-occupying lesions) and other complications. The degree of hepatic steatosis can be qualitatively graded as grade I (increased liver echogenicity relative to kidney and spleen), grade II (blurring of intrahepatic vascular structures), and grade III (deep attenuation of the ultrasound signal).[27] Unfortunately, the diagnostic accuracy of USG is limited in patients with severe obesity and <30% steatosis. However, USG is limited by the fact that it is operator dependent, and only provides restricted information about fibrosis.

Controlled Attenuation Parameter

FibroScan-based evaluation with controlled attenuation parameters (CAP) allows objective quantification of hepatic steatosis. Head-to-head trials with USG are lacking. Although, there are no consensual cut-offs, steatosis can be graded as no steatosis (S0): <248 dB/m, mild steatosis (S1): 248–268 dB/m, moderate steatosis (S2): 268–280 dB/m, and severe steatosis (S3): >280 dB/m. A CAP value of >250 dB/m has >90% sensitivity and PPV to detect steatosis (Table 1).[28,29]

Non-contrast Computed Tomography-liver Attenuation Index

Normally, the liver and spleen have the same attenuation on non-contrast computed tomography (CT). However, a steatotic liver appears hypo-attenuated as compared to the spleen. The difference in attenuation between liver and spleen on non-contrast CT, known as liver attenuation index (LAI), is frequently used to evaluate hepatic steatosis in living donors for liver transplantation. An LAI of less than −10 HU is highly suggestive of moderate-severe macrovesicular steatosis whereas an LAI of more than +5 HU reliably rules out significant steatosis.[30] The diagnostic accuracy of CT is comparable to USG but lower than that of a Magnetic Resonance Imaging (MRI) based techniques.[31] Higher cost, limited availability and radiation exposure prohibits routine use of CT to assess steatosis.

MRI-based Techniques

Magnetic Resonance Imaging-based techniques have been developed to quantify hepatic steatosis either by direct [magnetic resonance spectroscopy (MRS)] or indirect [magnetic resonance proton density fat fraction (MR-PDFF)] assessment of chemical shift.[32] Magnetic resonance spectroscopy has excellent accuracy but is not widely available and requires expertise to interpret.[25,33] magnetic resonance proton density fat fraction measures the fraction of triglyceride-bound mobile protons to total protons (bound to triglycerides and water both) and the software can be incorporated into routine MRI machines.[32,34] The values lie between 0 and 100%. The AUROC values MRI-PDFF to detect steatosis ≥5%, ≥33%, and ≥66% were 0.98, 0.91, and 0.90, respectively with a pooled sensitivity and specificity of 93 and 94%, 74 and 90%, and 74 and 87%, respectively in a meta-analysis of six studies with 635 biopsy-proven NAFLD patients.[35] The major advantage of both MRS and MR-PDFF is in dynamic assessment of liver fat especially in clinical trials as repeated liver biopsy to assess response may be impractical and risky. A reduction in MRI-PDFF values by >30% or an increase by >15% has been found to correlate with outcomes and response positively and negatively in clinical trials,[34,36] respectively. Furthermore, MRI-based techniques, such as MR-elastography[37] (MRE) can also accurately evaluate hepatic fibrosis. In view of limited availability and costs, use of MRI-based techniques to assess hepatic steatosis/fibrosis remains confined to research settings.

Non-invasive Assessment of Fibrosis

Liver fibrosis is graded[38] from F0 (no fibrosis) to F4 (cirrhosis). Fibrosis stage ≥F2 suggests advanced fibrosis and directs management strategy. Non-invasive tests have particularly good sensitivities and negative predictive values but demonstrate poor specificity and positive predictive value for advanced fibrosis.[25] Most non-invasive scores perform quite well at the two extremes of fibrosis whereas their performance to rule-in or rule out F2–F3 fibrosis remains suboptimal.[25,33] They are therefore best utilized for risk stratification at the outset. A combination of two or more non-invasive serum-based tests simultaneously or sequentially have been found to be economical with improved overall performance in terms of specificity, predictive values, and diagnostic accuracy.[25,33,39] Patients stratified as low risk (F0–F1 Fibrosis) may be followed up at a primary health care facility whereas those stratified into high-risk category (F2–F4, advanced fibrosis) need referral to a higher centre for detailed evaluation which may include a liver biopsy.

Non-invasive, serum parameters based clinical panels to predict advanced fibrosis include non-proprietary, simple scores such as NAFLD fibrosis score[40] (NFS), FIB-4,[41] AST-platelet ratio index[42] (APRI), and proprietary, patented tests which incorporate expanded panels such as FibroTest,[25] enhanced liver fibrosis[43] (ELF) test and FibroMeter (Table 1).[44]

Elastography Techniques

Elastography uses the principle that vibrations travel faster in stiffer tissue and utilizes liver stiffness as a surrogate marker for the degree

Table 1: Summary of NITs to identify steatosis and fibrosis

	Serum-based tests	
AST to platelet ratio index[42] (APRI)	• At cut-off value of >1, predicts advanced fibrosis with more than 75% sensitivity and specificity with an AUROC of 0.80 • Most data in chronic hepatitis C patients	
FIB-4[41]	• Platelet count, Age, AST, ALT • Score of <1.3: >90% NPV rule out advanced fibrosis • Score of >3.25: 97% specificity and 65% PPV to rule in advanced fibrosis	• NITs should be used to rule out rather than rule in advanced fibrosis in low prevalence population • NFS and FIB-4 are as good as MRE for predicting F3–F4 fibrosis especially in patients with metabolic syndrome/risk factors • Higher cut-offs (<2 for FIB-4 and <0.12 NFS) should be used in older age
NAFLD fibrosis score[40] (NFS)	• Age, body mass index, hyperglycemia, platelet count, albumin, AST/ALT ratio • Score <−1.45: >90% NPV to exclude advanced fibrosis • Score >0.676: 67% sensitivity and 80–90% specificity to rule in advanced fibrosis • AUROC: 0.85	
™Enhanced liver fibrosis panel[43] (ELF)	• Hyaluronic acid, tissue inhibitor of metalloproteinase-1, and N-terminal procollagen III-peptide • Baseline ELF value of >9.8 and greater changes overtime predicts progression of fibrosis with 77% sensitivity and 66% specificity • AUROC: 0.90	
™FibroMeter[44]	• Age, weight, platelet count, ferritin, glucose, AST, ALT • <0.32 and >0.69 have >90% NPV and PPV for >F2 fibrosis	
	Imaging/ Elastography-based methods	
Ultrasonography[25,27]	• Detects ≥20–30% steatosis with sensitivity and specificity of >85% and >90%, respectively • Provides additional information • Easily available, safe and economical • Limited accuracy in patients with <20% steatosis, obesity • Interobserver variability	
Fibroscan-controlled attenuation parameter[28,29] (CAP)	• AUROC, sensitivity, and specificity based on severity of steatosis – ≥5–10%:0.82, 69%, 82% – ≥33%:0.86, 77%, 81% – ≥66%:0.88, 88%, 78% • >95% applicability especially with XL probe • Quality criteria: IQR <30 or 40 dB/m • MRI-PDFF outperforms CAP	
Fibroscan-transient elastography[46,47] (TE)	• <8 kPa rules out advanced fibrosis (>95% NPV). • >9.9 kPa has 95% sensitivity and 77% specificity to rule in advanced fibrosis with an AUROC of 0.93 (0.86–0.96). • LSM >12 kPa predicts liver-related complications. • LSM >20–25 kPa signifies clinically significant portal hypertension (especially if platelets are <1,50,000/mL) • 5–10% failure rate in obese patients • Sensitivity and accuracy reduced in presence of ascites, congestive hepatopathy, raised liver enzymes, and biliary obstruction	
ARFI[45] (point-shear wave elastography)	• Cut-offs (p-SWE) – ≥F2:1.34 m/s – ≥F3:1.72 m/s – ≥F4:1.81 m/s • AUROC of >0.90 with >85% specificity	
Magnetic resonance elastography[37] (MRE)	• Most accurate non-invasive method to stage liver fibrosis • Only slightly better in F3–F4 stages than other NITs (NFS, FIB-4) – Stage (F1): ≥2.61 kPa – Significant (≥F2): ≥2.97 kPa – Advanced fibrosis (≥F3): ≥3.61 kPa (sensitivity—86% specificity 91%) – Cirrhosis (F4): ≥4.69 kPa	

Magnetic resonance imaging-proton density fat fraction[34–36] (MRI-PDFF)	• AUROC, sensitivity, and specificity based on degree of steatosis – ≥5%:0.98, 93%, 94% – ≥33%:0.91, 74%, 90% – ≥66%:0.90, 74%, 87% • Accurate, reproducible, quantitative • Detects even <5% steatosis • Provides additional information • Can be used to follow up after an intervention • >15.7% may predict progression in fibrosis • Costly, limited availability
Combined tests	
FAST score[49]	• Devised to identify patients with active NASH (NAFLD Activity Score ≥4) or fibrotic-NASH F ≥2 non-invasively • Incorporates LSM by TE (Fibrosis), CAP (Steatosis), AST (inflammation) • <0.35 rule-out cut-off for active/fibrotic NASH with ≥90% sensitivity • >0.67 rule-in cut-off for active/fibrotic NASH with ≥90% specificity • Cut-off may vary based on local prevalence; rule-in and rule-out cut-offs were determined to be ≥0.78 (PPV-70) and ≤0.55 (NPV >90%) in Indian population[51]

™Proprietary tests; ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; AUROC, area under the receiver operator curve; kPa, kilopascals; m/s, metre/second; p-SWE, point shear wave elastography; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; TE, transient elastography

of fibrosis.[33,45] Vibration-Controlled Transient elastography[25,39] (VCTE or TE by Fibroscan, Echosens) has now been extensively validated for fibrosis prediction in NAFLD.[46] As opposed to VCTE which requires a separate machine, acoustic radiation force impulse (ARFI) elastography[25,45] techniques can be performed by incorporation into the conventional USG machines, which also enables selection of a region of interest (ROI). In Fibroscan, a mechanical probe generates vibrations, the speed of which is measured by a USG probe along the same axis mounted within the mechanical actuator and represented as liver stiffness measurement (LSM).[25] Acoustic radiation force impulse employs short bursts of high-intensity acoustic waves to displace tissue perpendicularly and displays the "displacement" at an ROI as a greyscale map of stiffness whereas in point-SWE "speed of secondary waves" rather than displacement is measured.[45] In 2D-SWE, multiple points are examined at a time which then generates a coloured quantitative elastogram over a B-mode image.[33,45]

Based on LSM values, fibrosis can be staged as F0–F1 (<7 kPa), ≥F2 (7–8.7 kPa), ≥F3 (8.7–10.3 kPa) and F4 (≥10.3 kPa) using FibroScan (Table 1).[1,25] Morbidly obese patients, presence of ascites, congestive hepatopathy, non-fasting (at least 3–4 hours), deranged liver enzymes and biliary obstruction can reduce the accuracy of VCTE.[47] An advantage of ARFI and 2D-SWE over TE is that it can be reliably performed in patients with ascites after choosing an appropriate ROI but requires additional training to have adequate expertise in performing the procedure (Fig. 2).[25] An advantage of FibroScan over ARFI is quantification of fat (CAP score and measurement of fibrosis).

MRE is the most accurate method[25,32] for detecting and staging fibrosis and also provides additional information (Table 1). It utilizes a special pulse sequence to image micron-level cyclic displacements caused by propagating waves along the liver parenchyma. It is can give reliable results even in patients who have morbid obesity and ascites.[25,32] However, its routine use is limited by cost and availability, especially in developing countries (Fig. 3).

Combined Scores

The importance of reliably differentiating NAFL/Simple steatosis from NASH at the outset cannot be further stressed. Patients in whom NITs like APRI, FIB-4, NFS and FibroScan have predicted advanced fibrosis are at a higher risk of underlying fibrotic-NASH.[48] At present, liver biopsy remains the only conclusive method to differentiate NAFL from NASH. Recently, Newsome et al.[49] in their multicentric study derived and validated a new non-proprietary score incorporates LSM (Fibrosis) and CAP (Steatosis) by TE with serum aspartate aminotransferase (AST, Steatohepatitis) level known as the FAST score to identify patients with NASH with significant fibrosis (≥F2) and inflammation (NAFLD activity score, NAS ≥4) on biopsy. The score can be determined using an online calculator. The sensitivity and specificity of rule-in and rule-out cut-offs may be affected by the local prevalence of NAFL, and NASH and population-specific cut-offs may be needed to increase accuracy and predictive values (Table 1).[50] MACK-3 is another recently described combined score[51] that incorporates HOMA-IR, AST, and CK-18 to predict the presence of fibrotic-NASH with similar performance.

Role of Liver Biopsy

Liver biopsy is the current gold standard to detect NASH and staging of fibrosis.[1,2,25] Routine use is limited as it is an invasive procedure with a small but definite risk of complications like bleeding and mortality. Therefore, its use is restricted to patients who are at elevated risk of having NASH or advanced fibrosis based on NITs as discussed above. Liver biopsy can also be considered on a case-to-case basis in those with inconclusive or indeterminate results on non-invasive assessment of fibrosis and in those with diagnostic confusion or suspected concomitant aetiologies.[25] Patients enrolled in clinical trials also usually undergo interval liver biopsies for response assessment. Apart from its invasive nature, sampling error and inter-observer variations are other limitations.[25]

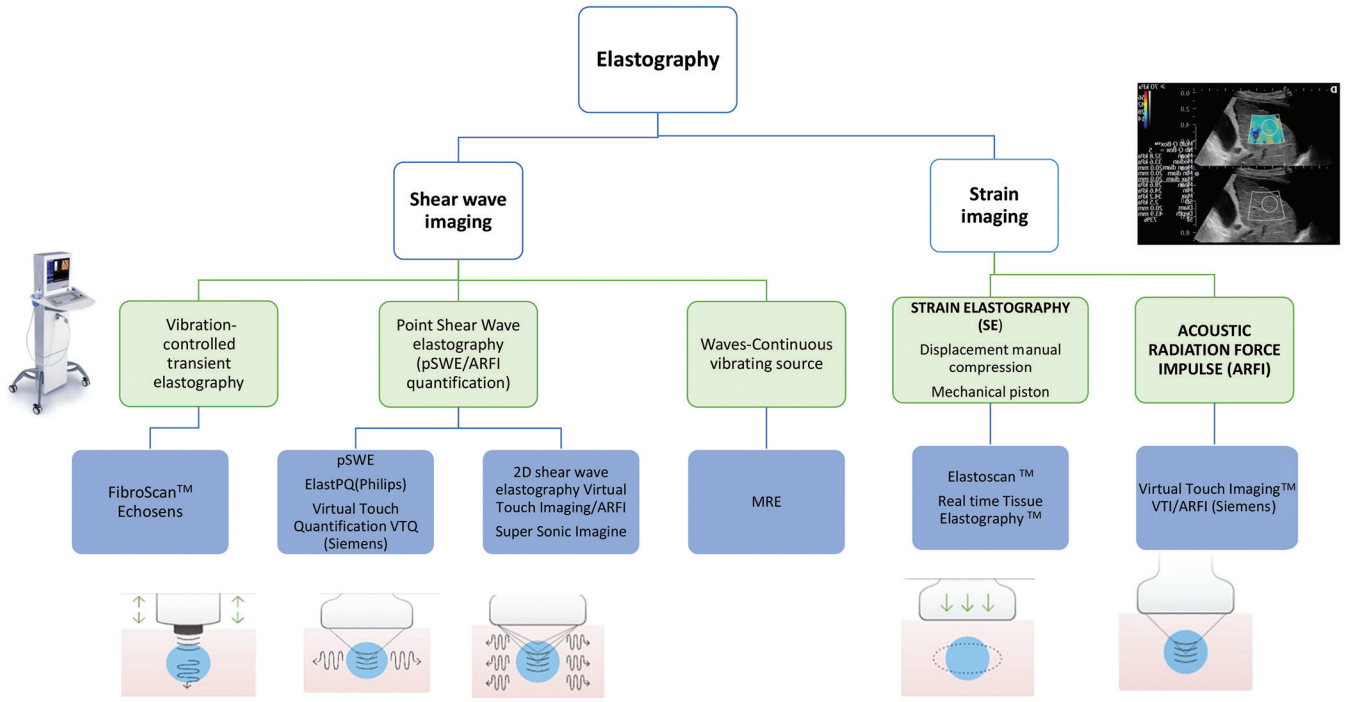
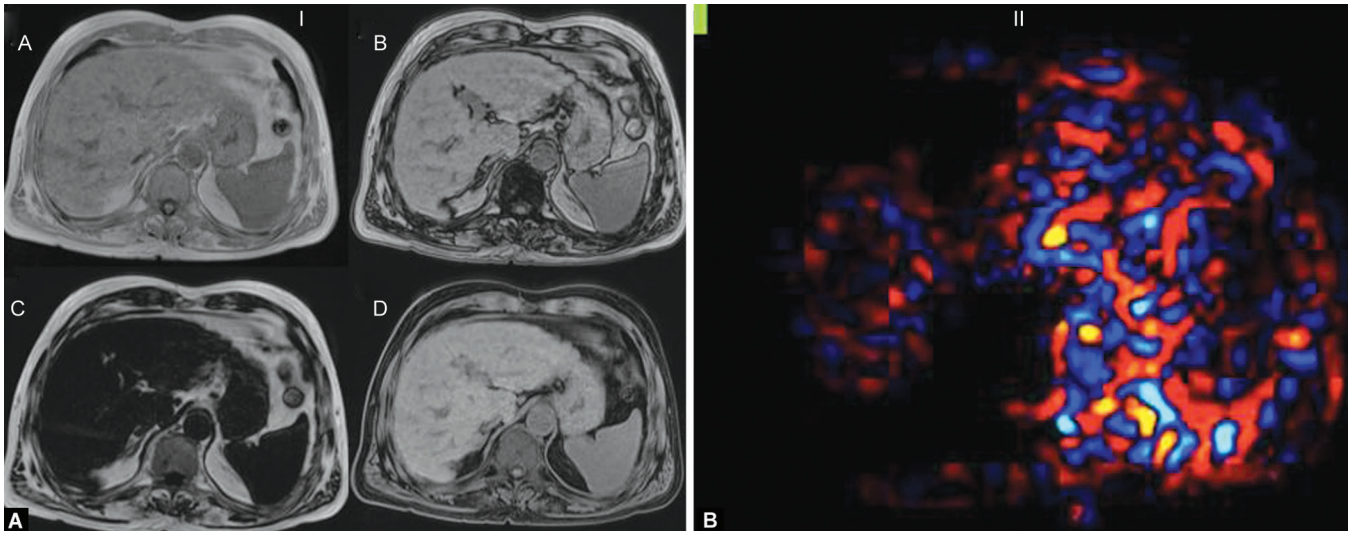


Fig. 2: Types of elastography



Figs 3A and B: Magnetic resonance elastography. Panel (I) MR Dixon sequences for fat detection, (A) In phase image; (B) Opposed phase image; (C) Fat-only image; (D) Water-only image, Panel (II) MR elastogram obtained using applicator placed over right hypochondriac region

How Far is it Worth Testing Further in ID-NAFLD?

Nonalcoholic fatty liver disease patients have an overall unhealthy metabolic pro-inflammatory profile. Unfortunately, even patients with NAFL/Simple steatosis, there is increased overall mortality (HR 1.94; range 1.28–2.92) as compared to matched control population without NAFL.[7,18,25,52] The mortality in ID-NAFLD is due to associated cardiovascular disease, risk of stroke, uncontrolled diabetes, and complications.[5,14] The degree of fibrosis followed by steatohepatitis (inflammation) are the primary determinants of liver-related outcomes. Nonalcoholic fatty liver disease is a dynamic disease with patients fluctuating between simple steatosis and steatohepatitis. A meta-analysis of 11 studies with available paired biopsies of 366 NAFLD patients showed that nearly 36% of patients show progressive fibrosis, 20% show regression, whereas 45% may remain stable.[7] A complex dynamic interaction between multiple inflammatory pathways, genetic and epigenetic modifications play a role in this unpredictable natural history of NAFLD.[7,53] Even patients with simple steatosis to begin with demonstrated progression albeit less rapidly than those with NASH.[7] The higher number of components of metabolic syndrome, the more rapid is the

progression.[7,11] Nearly 13% HCC occur without underlying cirrhosis and the presence of NAFLD has been found to be independently associated with the development of non-cirrhotic HCC probably as a result of adverse pro-carcinogenic local cytokine milieu.[1,7,10,11,25,53]

Given the rapid rise in global incidence and prevalence of metabolic syndrome, a pandemic of NAFLD has already begun. Early identification with highly sensitive, simple to use, and relatively economical tests at the primary health level can flatten the curve. Primary and pre-primary prevention with the inculcation of healthy dietary habits and increased physical activity among the younger generation is the need of the hour. Prevention strategies include mass awareness campaigns among school going children, adolescents, university students and young adults. Regular lectures on health goals and fitness with periodic reinforcement can improve healthy attitudes, diet and an active lifestyle. Public health mechanisms such as introducing extra tax on fast food and processed meals, school meal regulation, portion size control in restaurants and accurate nutritive value labels on food items will be able to flatten the obesity epidemic curve.

Problem of Lean NAFLD

There is no standard definition of Lean NAFLD, or BMI cut-off that can be applied to all ethnic or racial groups. Asians have a relatively higher risk of metabolic syndrome, adverse cardiovascular and overall outcomes at a lower BMI cut-off.[9,16,54] The interim results of the on-going real-life study from India (Indian Consortium on NAFLD—ICON-D) in 3,500 patients (mean BMI—27.6 ± 5.7 kg/m^2) showed the prevalence of overweight (BMI 23–24.9 kg/m^2) in 16%, obesity (BMI ≥25 kg/m^2) in 73% and lean NAFLD (BMI <23 kg/m^2) in 10.6% of patients.[55]

Lean NAFLD is characterized by the presence of steatosis or steatohepatitis in patients with a BMI <25 kg/m^2 (<23 kg/m^2 for Asian populations from India, China, Taiwan, Korea, and Japan etc.) in the absence of "significant" alcohol intake.[54] An international expert consensus statement[56] has defined new criteria for MAFLD in lean persons, in which the exclusion of alcohol was not essential, but evidence of hepatic steatosis, and two additional metabolic abnormalities were required to be present. In the published literature, 5–45% of lean individuals may have metabolic abnormalities, which are typically associated with obesity. Overall, the prevalence of lean NAFLD has been reported to be between 5 and 27% in various studies (Fig. 4).[10,56]

Clinical Significance

The complete spectrum of NAFLD, including simple steatosis/NAFL, imparts increased mortality due to both hepatic and non-hepatic causes. A stepwise approach using sensitive and specific NITs to stratify patients into low-risk and high-risk groups should be undertaken at the outset. High-risk patients (those with suspected NAS ≥4 and/or ≥F2 fibrosis) must be referred to higher centres for appropriate management by a multidisciplinary team including hepatologists, nutritionists and endocrinologists.[25] Lifestyle modifications, weight reduction and control of comorbidities remains the primary management modality with risk-based follow-up as effective pharmacologic therapies which can reduce inflammation and reverse/halt fibrosis are lacking at present.[57,58] NASH is a histological diagnosis, nonetheless non-invasive modalities like the TE and MRE for hepatic fibrosis, CAP and MRI-PDFF for hepatic steatosis and serum biomarkers like cytokeratin-18 (CK-18) for cellular apoptosis are of interest for the diagnosis of NASH and need further refinement.[25,39]

Future research also needs to focus on the role of an inflammatory gut microbiota which may have a bidirectional relationship with NAFLD and metabolic parameters. Specific microbiota signatures like Clostridium and Lactobacillus overlap between NAFLD and metabolic diseases (type 2 DM and obesity). The invasion of oral species like Veilonella and Prevotella in the distal intestine occurs in cirrhosis. Manipulation of the microbiome using pre and probiotics, antibiotics or fecal microbiota transplantation is of future interest.[59]

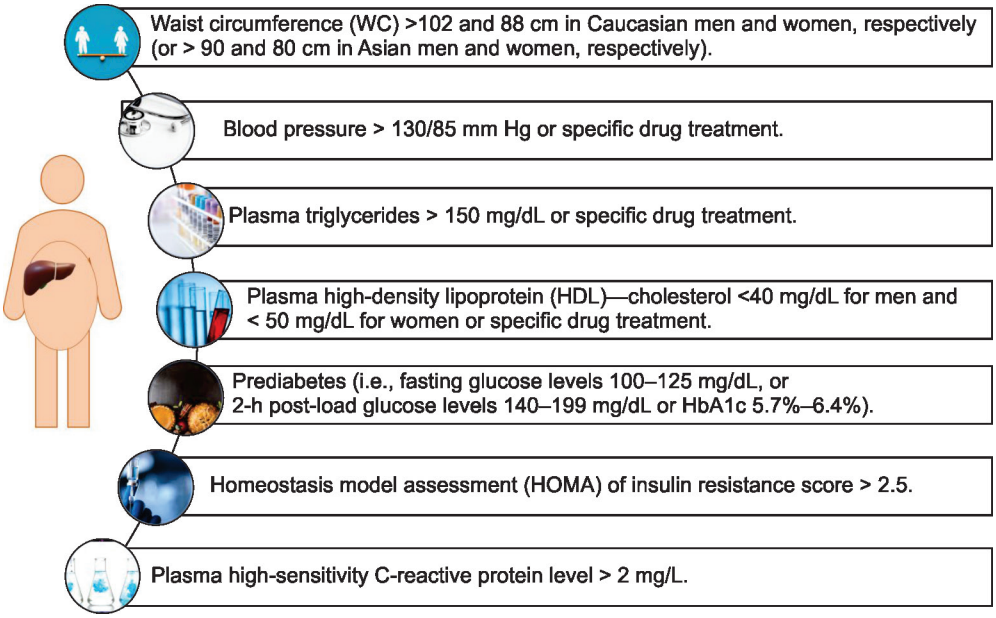


Fig. 4: Metabolic risk factors in NAFLD–MAFLD diagnostic conundrum

The Post COVID-19 Era and NAFLD

During the coronavirus disease-2019 (COVID-19) pandemic, several new factors have set in which may contribute to a spurt in cases of ID-NAFLD. With COVID-related emergency measures, a large proportion of workers shifted to "work from home", schools and universities started online education, with limited access to sports and outdoor exercise facilities. The increased morbidity and mortality of the SARS-CoV-2 virus in persons with NAFLD is also well recognized.[60] As such there is the opportunity for the recognition of NAFLD as a public health burden with direct and indirect healthcare and economic costs, and increased mortality due to cardiovascular risk or liver disease progression. As per the 2016 estimates of the World Health Organization (WHO), 39% of adults aged ≥18 years (39% of men and 40% of women) were overweight, and about 13% of the world's adult population (11% of men and 15% of women) could be categorized as obese. The World health Assembly adopted the "*WHO Global Strategy on Diet, Physical Activity and Health*" in 2004 and reiterated the same in in a 2011 revised political declaration on noncommunicable disease (NCDs) which describes the actions needed to support healthy diets and regular physical activity. This policy document calls upon all stakeholders at the global, state, and regional level to devise mechanisms to improve diets and physical activity patterns at the population level.[61] Following the collateral economic and societal impact of COVID-19 over the last two years, we expect a rise in undernutrition, malnutrition, and obesity. We also expect a worsening of metabolic control in persons with existing chronic diseases, as there was a global disruption in healthcare delivery systems, with unequitable access to medical care. We can expect an exponential rise in obesity in young adults and children globally due to the long period of economic and social containment. Keeping this in mind, we can expect steep rise of ID-NAFLD cases in the near future. Therefore, a sustainable global plan to educate people, and improve access to safe nutrition, active lifestyle, and national health policy framework to improve access to healthcare is essential to combat NAFLD.[62]

Conclusion

Metabolic syndrome is a multisystem disease, NAFLD being its hepatic manifestation. Numerous pathways (inflammatory, genetic, gut microbiota, environmental) converge and lead to progressive disease. Steep rise in metabolic syndrome and NAFLD will lead to a significant burden on healthcare services. Identification and treatment of patients at an early stage, by using a combination of sensitive NITs (stepwise or simultaneously) provides practitioners a chance to halt the progression of NAFLD, thus reducing overall morbidity and mortality. As ID-NAFLD is a common problem and cost is a major deterrent in Southeast Asian countries, a stratified approach, budget impact analysis, targeted screening and specific interventions have to be used to assess the prevalence and health economic impact of ID-NAFLD. The rising NAFLD/MAFLD curve has collateral morbidity and mortality association with cardiovascular and cerebrovascular diseases. Therefore, public health infrastructure and health policies should cater to ID-NAFLD as a non-communicable disease with high prevalence and consequent economic burden.

Author Contributions

SM, HB, LK, ASB and MP were all involved in the manuscript preparation. All the authors have read and approved the manuscript.

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