Indian National Association for Study of the Liver (INASL) Guidance Paper on Nomenclature, Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (NAFLD)

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Nonalcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease globally and in India. The already high burden of NAFLD in India is expected to further increase in the future in parallel with the ongoing epidemics of obesity and type 2 diabetes mellitus. Given the high prevalence of NAFLD in the community, it is crucial to identify those at risk of progressive liver disease to streamline referral and guide proper management. Existing guidelines on NAFLD by various international societies fail to capture the entire landscape of NAFLD in India and are often difficult to incorporate in clinical practice due to fundamental differences in sociocultural aspects and health infrastructure available in India. A lot of progress has been made in the field of NAFLD in the 7 years since the initial position paper by the Indian National Association for the Study of Liver on NAFLD

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; ALD: alcohol-associated liver disease; ALT: alanine aminotransferase; APRI: AST-platelet ratio index; AST: aspartate aminotransferase; BMI: body mass index; CAP: controlled attenuation parameter; CHB: chronic Hepatitis B; CHC: chronic Hepatitis C; CK-18: Cytokeratin-18; CKD: chronic kidney disease; CRN: Clinical Research Network; CVD: cardiovascular disease; DAFLD/DASH: dual etiology fatty liver disease or steatohepatitis; EBMT: endoscopic bariatric metabolic therapy; ELF: enhanced liver fibrosis; FAST: FibroScan-AST; FIB-4: fibrosis-4; FLIP: fatty liver inhibition of progression; FXR: farnesoid X receptor; GLP-1: glucagon-like peptide-1; HCC: hepatocellular carcinoma; INASL: Indian National Association for Study of the Liver; LAI: liver attenuation index; LSM: liver stiffness measurement; MAFLD: metabolic dysfunction-associated fatty liver disease; MetS: metabolic syndrome; MRE: magnetic resonance elastography; MR-PDFF: magnetic resonance – proton density fat fraction; NAFL:: nonalcoholic fatty liver; NAFLD: nonalcoholic fatty liver disease; NAS: NAFLD activity score; NASH: nonalcoholic steatohepatitis; NCPF: noncirrhotic portal fibrosis; NCD: noncommunicable diseases; NFS: NAFLD fibrosis score; NHL: non-Hodgkin's lymphoma; NPCDCS: National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke; OCA: obeticholic acid; PPAR: peroxisome proliferator activated receptor; PTMS: post-transplant metabolic syndrome; SAF: steatosis, activity, and fibrosis; SGLT-2: sodium-glucose cotransporter-2; T2DM: DM: type 2 diabetes mellitus; USG: ultrasound; VAT: visceral adipose tissue; VCTE: vibration controlled transient elastography; SWE: shear wave elastography

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in 2015. Further, the ongoing debate on the nomenclature of NAFLD is creating undue confusion among clinical practitioners. The ensuing comprehensive review provides consensus-based, guidance statements on the nomenclature, diagnosis, and treatment of NAFLD that are practically implementable in the Indian setting. (J Clin Exp Hepatol 2023;13:273–302)

Nonalcoholic fatty liver disease (NAFLD) has emerged as a major public health problem globally.[1,2] It is predominantly related to overweight/obesity and other metabolic risk factors secondary to sedentary lifestyle and high calorie consumption.[3] Globally and in Asia, around 25–29% of the general population has NAFLD.[4–7] In India, the prevalence of NAFLD in the general population varies from 9 to 53% with geographical and rural–urban differences in the prevalence.[8–10] A recent meta-analysis of studies published from India reported a NAFLD prevalence of 38.6% in adults and 35.4% in children.[11] The prevalence is reported to be higher in high-risk groups like those with metabolic syndrome (MetS) and its individual components.[3,12–15] In a multicentric study conducted in 101 Indian cities, the prevalence of NAFLD among patients with type 2 diabetes mellitus (T2DM) was reported to be 56.5%.[12] Overall, the pooled prevalence of NAFLD among high-risk Indian adults who are obese or overweight or have T2DM has been estimated to be 52.8%.[11] Nonalcoholic steatohepatitis (NASH) is a severe form of NAFLD which in addition to hepatic steatosis is associated with hepatic inflammation and fibrosis and has the higher propensity to progress on to cirrhosis of the liver and hepatocellular carcinoma (HCC).[16,17] Recent data from India suggest that NAFLD is responsible for significant number of patients with advanced fibrosis or cirrhosis and HCC, and the incidence has been steadily increasing over the years.[18,19]

NEED FOR THE GUIDANCE DOCUMENT

Management guidelines for patients with NAFLD are available from various international scientific societies. However, many of those strategies may not be applicable to Indian patients with NAFLD having altogether different socioeconomic and cultural issues.[20–23] For instance, the dietary habits of Indians including staple dietary constituents and cooking media are quite different from Western individuals. As such, recognition of patients who have progressed on to NASH and/or significant/advanced fibrosis or patients with NAFLD who are likely to have progressive disease is an important step in reducing the liver disease burden in any country including India.[1,24] Liver biopsy is seldom carried out in day-to-day practice in India due to lack of facilities and poor patient acceptance. Simple and practical diagnostic tools at the primary and secondary healthcare levels and clear guidelines for referral of patients to tertiary healthcare levels are required to improve the management of patients with NAFLD in a resource-constrained setting like India and optimize utilization of services of subspecialists like hepatologists and gastroenterologists who are mainly available in urban and tertiary centers. Of note, many of the proprietary noninvasive tests for detection of fibrosis are neither available in India nor have they been validated in Indian patients. As of now, India is the only country where a specific pharmacotherapy has been approved by a national regulatory agency [the drug controller general of India (DCGI)] for the management of NASH as discussed later.

The last position paper by Indian National Association for Study of the Liver (INASL) on NAFLD was published in 2015, and since then, a lot of progress has occurred in the diagnosis and treatment of patients with NAFLD including the approval of saroglitazar by DCGI.[25] A group of experts recently also suggested a change in the nomenclature from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD).[26] Despite the astoundingly high burden of NAFLD in India, only a fraction will ever develop clinically significant liver disease. Thus, risk stratification and guidance on referral using noninvasive tests is the need of the hour for optimal utilization of limited health resources in the country. INASL-NAFLD Taskforce on NAFLD thus decided to come out with a comprehensive new guidance document on NAFLD predominantly focusing on the nomenclature, spectrum, diagnosis, and treatment of patients with NAFLD.

PREPARATION OF THE GUIDANCE DOCUMENT

A core committee of 11 INASL-NAFLD task force members was initially constituted which unanimously agreed upon an "INASL-NAFLD Working Party" of 31 members consisting of researchers from across the country working in the area of NAFLD. Members of the working party were divided into seven groups. Each group headed by a captain and 4–5 other members. Each group was given research questions pertaining to a specific research area. The literature was reviewed by the respective groups, and the answers to the questions were prepared as per the GRADE system. The level of evidence and grade of recommendations are depicted in Table 1. Because of the ongoing COVID-19 pandemic, multiple meetings were held virtually (December 2020 to April 2021) with each group presenting

its consensus statements and supporting literature in 1–3 sessions. These presentations were made to the entire group of (31 members), which then ratified the statements after detailed discussions.

The purpose of this guidance paper is to provide a short and concise guidance document to the practicing hepatologists, gastroenterologists, and physicians.

NOMENCLATURE AND SPECTRUM

NAFLD vs. MAFLD

Recently, a group of experts suggested the change in name from NAFLD to MAFLD.[26] The reasons given for this change included: the name "NAFLD" is heterogeneous, is based on negative criteria, or is a diagnosis of exclusion, metabolic risk factors which are so commonly associated with this disease are not mentioned in the name, the word "non" in the "nonalcoholic" trivializes the importance of this clinical condition and the word "alcohol" in "nonalcoholic" is stigmatizing for the patients.[26]

Based on the available literature, the members of the working party suggested that the proposed change in nomenclature from NAFLD to MAFLD is more of eminence rather than evidence based. NAFLD is a heterogeneous disease with multifactorial pathogenesis, and mere name change would not make it homogenous.[27] Moreover, there is no accepted definition of "metabolic dysfunction," which is included in the new suggested name of MAFLD. Further, besides NAFLD, there are so many diseases that have prefix of "non" like non-Hodgkin's lymphoma, noncirrhotic portal fibrosis, noncommunicable diseases, and so on, and the prefix "non" does not trivialize these diseases.[28] Similarly, the word "nonalcoholic" in NAFLD does not seem to be stigmatizing. In fact, patients may feel happier when they learn that their liver disease is not related to alcohol. Significant progress has been made in last 2 decades in the biomarker and drug development for NAFLD, and the change in nomenclature may have a negative impact on these efforts. The working party agreed that based on the reasons suggested by some of the experts, there was no compelling need for this change in nomenclature. In fact, the members felt that the change in nomenclature may create confusion not only among the hepatologists but also among physicians and nonhepatologists who manage these patients or do research in the area of NAFLD.[29] However, the working party suggested the need for a wider consensus and collection of more evidence on this subject (see section on future research).

Lean vs. Obese NAFLD

Global, Asian and Indian data suggest that around 10–20% of patients with NAFLD may have normal body mass index

Table 1 Level of Evidence and Grade of Recommendations (Adapted From GRADE System).

Level of evidence[a]		**Confidence in the evidence**
High or I	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
Moderate or II	Data derived from a single RCT or multiple nonrandomized studies.	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Low or III	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.
Recommendations – Grade[b]		**Wording associated with the grade of recommendation**
Strong		''must", ''should", or ''INASL recommends"
Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost		
Weak		''can", ''may", or ''INASL suggests"
Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption		

INASL: Indian National Association for Study of the Liver; MRI-PDFF: magnetic resonance imaging derived proton density fat fraction; RCT: randomised controlled trial.

[a]Level was graded down if there was a poor quality, strong bias or inconsistency between studies; Level was graded up if there was a large effect size.

[b]Recommendations reached by consensus of the 'Working Party' and included the quality of evidence, presumed patient important outcomes and costs.

as per the population-specific cut-offs (<23 kg/m^2 for Indians) and are labeled as "Lean NAFLD."[8,19,27,30–45] An in-house meta-analysis of 17 Indian studies revealed that the pooled proportion of lean individuals among patients with NAFLD is 16.97% (95% CI: 13.6–20.6%), and the pooled prevalence of lean NAFLD in the general community is 6.5% (95% CI: 5.1–8.2%).[10,15,19,27,35–37,39,41–49]

In comparison to obese NAFLD, lean patients with NAFLD have been shown to have milder liver histology. Even though the data are conflicting, long-term outcome may be better in lean NAFLD than in obese NAFLD. But all-cause mortality/cardiovascular mortality has been shown to be higher in patients with lean NAFLD in comparison to lean non-NAFLD subjects. Even though, the pathogenesis, histological severity, and outcome of patients with lean NAFLD have been reported to be different from those with obese-NAFLD, most of the data on patients with lean NAFLD also suggest the role of visceral adipose tissue (VAT) and insulin resistance.[33,36,43,50–52] Central obesity that is measured clinically by waist circumference has been shown to correlate well with VAT and with the risk and severity of NAFLD and extra-hepatic diseases like cardiovascular disease (CVD).[53] On the other hand, BMI has its own limitations. Indeed, a muscular individual with high fat-free mass would still have a high BMI despite acceptable body fat percentage. Further, BMI is not being a good marker for the evaluation of VAT or central obesity.[54–56] Although other modalities like bioimpedance analysis and dual-energy X-ray absorptiometry are more accurate for assessment of adiposity, they are not widely available and cannot be advocated in routine clinical practice. Based on the available data, working party suggested including a normal waist circumference (a marker of central obesity and VAT) in addition to normal BMI in the definition of "Lean NAFLD." Population-specific cut-offs for waist circumference (90 cm and 80 cm for Indian males and females, respectively) should be used to define central obesity with waist circumference measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a stretch-resistant tape[57] (Appendix 2).

Spectrum of NAFLD

NAFLD is considered a spectrum ranging from nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), NASH with fibrosis, NASH-cirrhosis, and NASH-HCC.[17] Traditionally, NASH has been considered to be the progressive form of NAFLD. However, current evidence suggests a dynamic cycling between NAFL and NASH in the early stages of the disease. None the less, progression of fibrosis is possibly faster in those with NASH. The presence of underlying fibrosis is the key determinant of both histologic and clinical outcomes. Progression of fibrosis is slow in the vast majority of the patients although there may be rapid progression of fibrosis in around 20–30% patients.[17]

Indian data suggest that NAFLD is not only an important cause of unexplained rise in hepatic transaminases but an important cause of cryptogenic cirrhosis and non-HBV, non-HCV HCC, and is becoming an important indication for liver transplantation in this country.[18,58–63] In addition to increasing the risk of HCC in patients with NASH cirrhosis, NAFLD is emerging as an important cause of HCC in patients without cirrhosis or advanced fibrosis.[18,64,65]

Most patients with NAFLD are either detected incidentally or present with nonspecific symptoms unless the disease has progressed to cirrhosis or HCC. In the absence of other etiologies, the diagnosis of NAFL is easy and can be made noninvasively with the help of an ultrasound (USG) abdomen or other imaging modalities showing evidence of hepatic steatosis.[18,19] The diagnosis of NASH in addition requires documentation of specific histology (lobular inflammation, hepatocyte ballooning) and/or hepatic fibrosis of which hepatic fibrosis can be predicted noninvasively.[66] Even though the diagnosis of cirrhosis (compensated or decompensated) can be made noninvasively based on blood tests, elastography, and imaging, the specific etiological diagnosis of NASH-cirrhosis again requires liver histology and absence of other etiologies. As per the recommendations of the international societies, the diagnosis of NASH cirrhosis requires the present or past histological evidence of steatohepatitis in the absence of other etiologies.[20] In clinical practice, however, the acceptance rate of liver biopsy in patients with NAFLD is not very high in India and may be done predominantly as part of clinical trials.[19,67] Moreover, hepatic steatosis tends to decrease with increasing hepatic fibrosis/cirrhosis.[68] Hence, diagnosis of NASH-cirrhosis may have to be made in many patients without present or past histological evidence of steatohepatitis. Since, NAFLD is closely associated with metabolic risk factors, commonest being obesity or central obesity, the diagnosis of NASH-cirrhosis or NASH-HCC can be made in the absence of other etiologies and the presence of obesity or central obesity in addition to another MetS risk factor. Since the metabolic profile tends to change with the onset of cirrhosis (body weight, blood pressure and lipids decrease and glucose intolerance increases), the history of these metabolic risk factors may be equally important in making the diagnosis of NASH-cirrhosis or NASH-HCC.[25]

In addition to causing significant liver disease, NAFLD has been found to be associated with various extra-hepatic diseases.[69] In fact, the risk of chronic kidney disease (CKD), and fatal and nonfatal CVD have been shown to increase in patients with NAFLD independent of the presence of

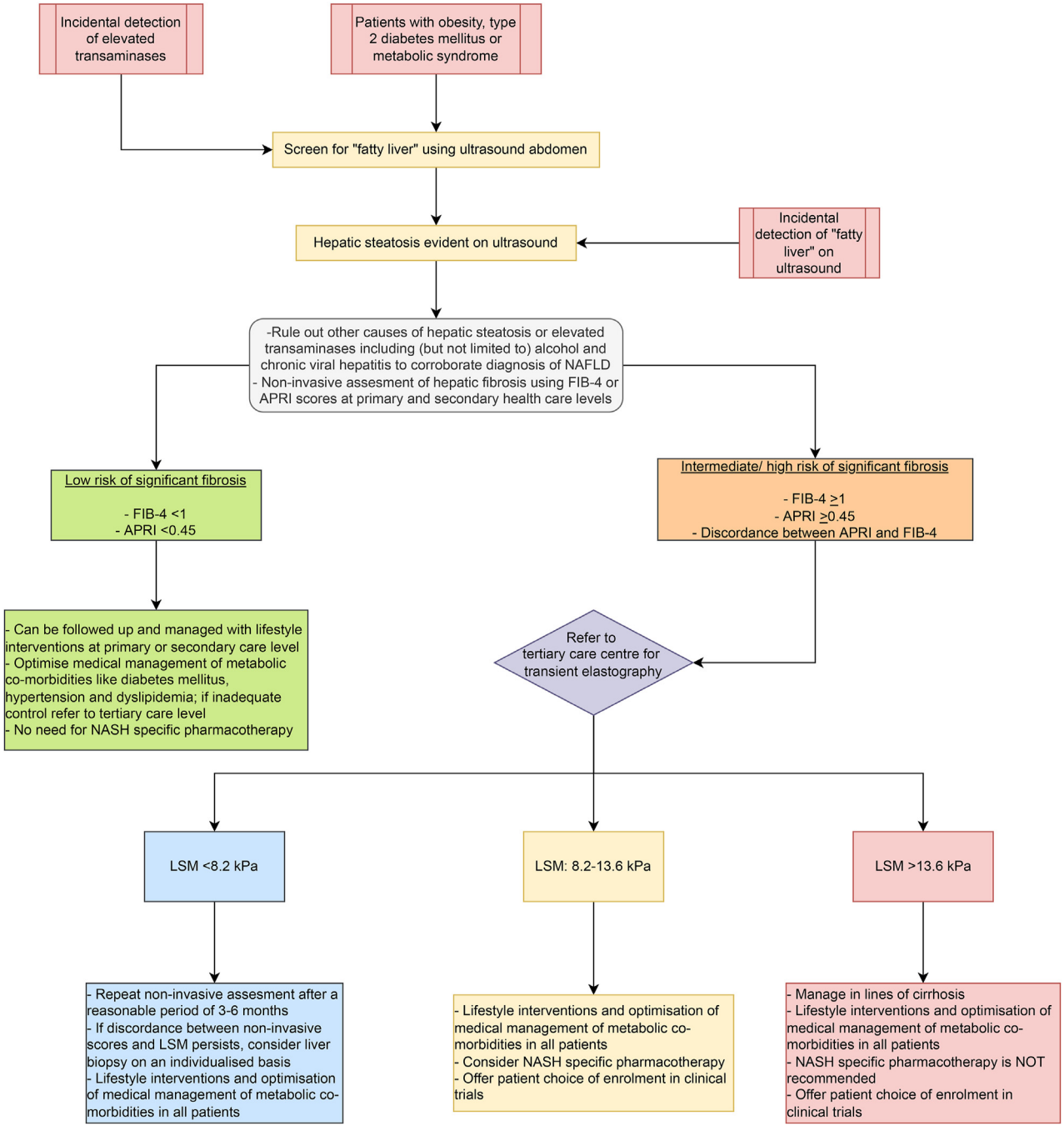

Figure 1 Risk stratification and management algorithm in nonalcoholic fatty liver disease.

metabolic risk factors.[70–77] Even though there is suggestion to screen patients with NAFLD (especially those with NASH, NASH with significant fibrosis and metabolic risk factors especially type 2 DM) for both CKD and CVD, there is a lack of consensus on the modalities to be used for screening in these patients.[78] NAFLD has also been associated with other extra-hepatic conditions including osteopenia and osteoporosis, obstructive sleep apnea, hypothyroidism, and polycystic ovarian syndrome.[79–84] In addition to HCC, NAFLD has been shown to increase the risk (1.5–2 times) of long-term development of various extra-hepatic malignancies including carcinoma colon, gastric cancer, carcinoma pancreas, uterine, and breast carcinoma.[85]

Because of the high prevalence of NAFLD in the general population, NAFLD may co-exist with other liver diseases and can increase the severity of fibrosis, risk of cirrhosis and HCC in patients with chronic hepatitis B (CHB), chronic hepatitis C (CHC), and alcohol-associated liver disease (ALD).[86–88] Indian data suggest that dual etiology fatty liver disease or steatohepatitis (DAFLD/DASH) comprising of alcohol and metabolic risk factors is not uncommon in clinical practice and increases the severity of liver disease.[89,90] Hence, in addition to the treatment of basic disease, these patients should be given special attention toward the control of metabolic risk factors (contributing to NAFLD).

Consensus Statements

- INASL suggests that in the absence of a compelling evidence, nonalcoholic liver disease (NAFLD) may be continued as the preferred terminology instead of metabolic dysfunction-associated fatty liver disease (MAFLD) (III, Weak).
- INASL suggests that in addition to normal BMI, the absence of central obesity (assessed by waist circumference) may be taken into account while defining "lean NAFLD" (III, Weak).
- INASL suggests that the diagnosis of NASH-cirrhosis and NASH-HCC can be made in the absence of other etiologies of liver disease and in the presence or history of obesity or central obesity and presence or history of another metabolic risk factor (III, Weak).
- Presence of hepatic steatosis (NAFLD) in patients with CHB and CHC augments the risk of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (I).
- Presence of metabolic risk factors in patients with alcohol-associated liver disease (ALD) increases the severity of ALD (II).
- INASL suggests that patients with NASH with or without advanced fibrosis and those with concomitant type 2 DM may be evaluated for impairment in renal functions (II, Weak).
- INASL recommends that patients with NASH with or without advanced fibrosis and those with concomitant type 2 DM should be evaluated for the presence of CVD (II, Strong).
- NAFLD is associated with an increased risk of extrahepatic cancers such as colon, stomach, pancreas, uterine, and breast (II).

DIAGNOSIS

Even though most patients with NAFLD are detected incidentally on USG abdomen done for dyspepsia or asymptomatic rise in transaminases, there are recommendations to suggest screening for NAFLD in patients with type 2 diabetes mellitus, obesity, or MetS[21,66] (Figure 1).

The diagnosis of NAFLD requires the documentation of hepatic steatosis of variable severity on imaging or histology and exclusion of secondary causes of hepatic steatosis (Appendix 1). Testing for these alternate causes of steatosis should be tailored according to the clinical scenario. However, at the very least, history of significant alcohol intake and screening for chronic viral hepatitis [Hepatitis B surface antigen (HBsAg)and Hepatitis C antibody (anti-HCV)] should be done in all patients. In Indian patients, significant alcohol intake is defined as consumption of >20 gm per day in both males and females.[25] Up to one third of the patients with NAFLD may have autoimmune markers like antinuclear antibodies and anti-smooth muscle antibody as an epiphenomenon. This should be interpreted as per the clinical scenario and the need for further investigations to rule out autoimmune hepatitis (including liver biopsy) should be taken accordingly. The diagnosis of NAFL can be made only by the presence of hepatic steatosis. The diagnosis of NASH in addition requires the additional presence of hepatic inflammation with or without hepatic fibrosis.

Noninvasive Assessment

Noninvasive tests (NITs) have come a long way for the assessment of hepatic fibrosis but still have limited role in the assessment of hepatic inflammation in NASH.[21,91] In patients with NAFLD, liver histology still remains the gold standard to assess all the three components of hepatic steatosis, inflammation, and fibrosis.[92] However, liver biopsy is an invasive procedure, is not free of complications, and is not the preferred modality by most patients.[17,59,79]

Assessment of Hepatic Steatosis

USG abdomen remains the easiest and simplest method to detect the presence and grade the severity of hepatic steatosis. Even though limited by its accuracy in patients with less than 30% of hepatic steatosis and those with severe obesity and overall subjective interpretation, USG remains the most preferred tool to diagnose hepatic steatosis in clinical practice.[20,21,94] Hepatic steatosis is usually graded as mild, moderate, and severe or grade 1–3 based on the presence of hepatic steatosis, blurring of intra-hepatic vessels, and posterior attenuation seen as blurring of the diaphragm (Table 2). With the increasing availability of vibration controlled transient elastography [VCTE, FibroScan$^{(R)}$] across the country, more clinicians are relying on controlled attenuation parameter (CAP) for the presence and grading of hepatic steatosis. In contrast to USG which is subjective, CAP has the advantage of being more objective for the assessment of hepatic steatosis. Based on the studies showing a sensitivity of >90%, the European Association for the Study of the Liver (EASL) has recently recommended a CAP cut-off of >275 dB/m for the detection of hepatic steatosis.[66] Population-specific cut-offs from

Table 2 Grades of Fatty Liver on USG.

Grade of fatty liver	USG findings
Grade 1 (Mild)	Increased echogenicity of the liver in comparison to spleen and right kidney.
Grade 2 (Moderate)	Blurring of intravascular structures
Grade 3 (Severe)	Deep attenuation of ultrasound signal; diaphragm cannot be readily discerned from posterior surface of liver

USG, ultrasound.

India to grade hepatic steatosis on CAP are almost the same as from other parts of the world (Table 3).[95–104] As such, CAP is excellent for the detection of steatosis but its accuracy for grading the severity of steatosis is comparatively limited.[101–103] Even though more accurate than USG and CAP, magnetic resonance – proton density fat fraction (MR-PDFF) is not recommended for routine detection of hepatic steatosis because of the cost, limited availability, and inconvenience of the procedure.[105] Hepatic steatosis can also be inferred on CT scan when the attenuation of the liver is lower than that of the spleen. This can be quantified using the liver attenuation index (LAI) which refers to the difference in attenuation between liver and spleen on noncontrast CT. LAI < −10 HU is highly specific for moderate to severe macrovesicular steatosis, while a LAI > +5 HU suggests the absence of significant steatosis.[106] Although LAI has been used for the assessment of steatosis in living donors for liver transplantation, CT scan for detecting steatosis

Table 3 Controlled Attenuation Parameter (CAP) Cut-Offs for Detecting and Assessing Severity of Steatosis on FibroScan in Published Meta-Analysis and Indian Studies.

Study	Study details	CAP cut-offs
Karlas *et al.*, 2017[81]	Individual patient data meta-analysis of 2735 including 547 patients with NAFLD	S0: <248 dB/m S1: 248 to <268 dB/m S2: 268 to <280 dB/m S3: ≥280 dB/m
Petroff *et al.*, 2021[89]	Individual patient data meta-analysis of 2346 including 1277 patients with NAFLD	S0: <297 dB/m S1: 297 to <317 dB/m S2: 317 to <333 dB/m S3: ≥333 dB/m
Rout *et al.*, 2019[83]	Prospectively maintained database of 462 Indian patients including 89 patients with NAFLD who underwent liver biopsy and CAP estimation	S0: <263 dB/m S1: 263 to <324 dB/m S2: 324 to <348 dB/m S3: ≥348 dB/m
Shalimar *et al.*, 2020[84]	Prospective study of 219 Indian adults with NAFLD [100 nonobese (45.7%) and 119 (54.3%) obese, respectively] with CAP values who underwent liver biopsy	Nonobese S0: <275 dB/m S1: 275 to <319 dB/m S2: 319 to <337 dB/m S3: ≥337 dB/m Obese S0: <285 dB/m S1: 285 to <340 dB/m S2: 340 to <355 dB/m S3: ≥355 dB/m
Kuchay *et al.*, 2021[86]	Analysis of 137 Indian adults to assess the diagnostic performance of CAP for detecting steatosis with MRI-PDFF as the reference standard	S0: <262 dB/m S1: 262 to <295 dB/m S2: 295 to <324 dB/m S3: ≥324 dB/m
Garg *et al.*, 2017[90]	Assessed the utility of CAP for detecting steatosis in 76 morbidly obese Indian patients	S0: <323 dB/m S1: 323 to <336 dB/m S2: 336 to <357 dB/m S3: ≥357 dB/m

CAP, controlled attenuation parameter; NAFLD, non-alcoholic fatty liver disease.
In the absence of consensus cut-offs, the European Association for the Study of the Liver (EASL) guidelines recommends CAP>275 dB/m for detecting steatosis as it is associated with a high sensitivity and positive predictive value (>90%) for detecting steatosis in NAFLD (59).

Table 4 Cut-Offs of FAST Score for Detecting NASH With SFibrosis (NASH + NAS ≥4 + F ≥ 2) in Patients With NAFLD.

Study	Study details	Rule-out cut-off	Gray zone	Rule-in cut-off
Newsome *et al.*, 2020[88]	Multicentric study comprising of a derivation cohort of 350 patients in England followed by validation in multiple international cohorts	≤0.35	0.35 to 0.67	≥0.67
De *et al.*[89]	Validation of FAST score in 60 Indian patients with biopsy proven NAFLD with derivation of optimal cut-offs validated using internal bootstrapping	≤0.55	0.55–0.78	≥0.78

FAST, FibroScan-AST; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score.

Table 5 Commonly Used Cut-Offs of Noninvasive Scores for Detecting Advanced Fibrosis.[66]

Noninvasive score	Rule-out cut-off	Gray zone	Rule-in cut-off
APRI	0.5	0.5 to 2.0	2.0
FIB-4	<1.3	1.3 to 2.67	>2.67
NFS	<–1.455	−1.455 to 0.675	≥0.676

APRI, AST platelet ratio index; FIB-4, fibrosis-4; NFS, NAFLD fibrosis score.

cannot be recommended routinely in day-to-day clinical practice because of the entailed radiation risk and cost.

Assessment of Hepatic Inflammation

As mentioned earlier, there is an unmet need for good noninvasive markers to detect hepatic inflammation in patients with NAFLD. Serum liver enzymes [aspartate and alanine transaminases (AST, ALT)] do not correlate well with the hepatic inflammation and are not recommended to diagnose or exclude histological NASH.[107,108] Cytokeratin-18 (CK 18) a marker of apoptosis which has been shown to be useful for the diagnosis of NASH is limited by its inaccessibility.[109] Recently, FibroScan-AST (FAST) score (a score based on median liver stiffness on transient elastography, CAP and AST) has been used to identify patients with a histological NAFLD activity score (NAS) ≥ 4 and significant fibrosis (F ≥ 2) and has been validated in Indian patients (Table 4).[110–112] Similarly, a combination of magnetic resonance elastography (MRE) and fibrosis-4 (FIB-4) called MEFIB score has been suggested for the noninvasive diagnosis of NASH but requires validation in Indian population.[113]

Assessment of Hepatic Fibrosis

Like all chronic liver diseases, hepatic fibrosis is the most important parameter for prognosis, treatment, and outcome in patients with NAFLD. NITs to assess hepatic fibrosis include blood-based tests or the use of various types of elastography.[91,114] A number of blood parameters either used alone or in combination have been evaluated for the assessment of hepatic fibrosis in patients with NAFLD.[115] Simple nonpatented parameters include platelet count, AST/ALT ratio, or more specific scores that have been validated across different populations like AST to platelet ratio index (APRI), Fibrosis-4 (FIB-4 comprising of AST, ALT, age, and platelets), NAFLD fibrosis scores (NFS comprising of BMI, AST, ALT, Albumin, and presence of insulin resistance and diabetes), and BARD score (BMI, Age, AST/ALT ratio, and presence of diabetes) (Appendix 3). The advantages of these scores include their free availability and the ease of using them at the bedside on mobile phones or laptops. As shown in Table 5, these cut-offs are commonly being used for ruling-in or ruling-out advanced fibrosis with a rule-in cut-off which has high specificity and a rule-out cut-off which has high sensitivity with an intervening gray zone. Of all the bedside blood-based tests, FIB-4 has been shown to be the most accurate.[116,117] The data on the applicability and cut-offs of these nonpatented, noninvasive scores in Indian patients with NAFLD are scanty and mainly involve APRI and FIB-4[118,119]). In addition, a lot of patented tests like Fibrotest, Fibrometer, Hepascore, enhanced liver fibrosis (ELF) panel, and so on, with higher sensitivity and specificity are commercially available but are limited by their availability and cost.

Other than the blood-based tests, liver elastography has evolved over the years and is an accurate tool for the noninvasive assessment of hepatic fibrosis. The new-generation USG machines with added facility of shear wave elastography are helpful in the simultaneous assessment of hepatic fibrosis. But, of all the forms of elastography, maximum

Table 6 Liver Stiffness Measurement Cut-Offs on Vibration-Controlled Transient Elastography.[116]

Significant fibrosis (F2) unlikely	<6.0 kPa
≥F2	≥8.2 kPa
≥F3	≥9.7 kPa
F4	≥13.6 kPa

LSM ≥20 might suggest clinically significant portal hypertension, particularly in those patients with platelet count <150 × 10^6/L.

data in patients with NAFLD are available with VCTE (Fibroscan(R)) with disease-specific cut-offs available for NAFLD (Table 6).[66,104,116,120–123] Recent data suggest that similar cut-offs may be used in nonobese and obese individuals with correct probe selection. M and XL probes should be selected as per the automatic probe selection tool in the FibroScan machine if the probe to liver capsule distance displayed in real time is < 25 mm and 25–35 mm, respectively. Data are still evolving for other forms of ultrasound elastography like 2D shear wave elastography (2D-SWE) or point SWE.[120,124,125] Even though most accurate and also having the advantage of assessing larger area of the liver, MR elastography (MRE) is limited by its cost and availability.[126,127]

Risk Stratification Based on NonInvasive Assessment

The biggest advantage of NITs is their ability to rule-in or rule-out significant fibrosis (≥F2 fibrosis), advanced fibrosis (F3-4 fibrosis), and cirrhosis (F4 fibrosis). Because of the huge burden of NAFLD globally and in India, this stratification is very important in deciding the referral of patients from primary and secondary healthcare levels to tertiary care level. Patients in whom significant fibrosis or advanced fibrosis/NASH can be confidently ruled out can be managed at the primary and secondary health care levels. In contrast, those patients predicted to have significant/advanced fibrosis/NASH on noninvasive assessment need to be referred to tertiary care level for further evaluation and treatment (Figure 1).[24,66,128] The patients falling in the gray zone or with discordant results at primary and secondary healthcare levels would also need a referral to tertiary care centers (Figure 1).

Stratification of patients with NAFLD at primary and secondary healthcare levels can be done with simple scores like APRI and FIB-4. If required, further evaluation at the tertiary healthcare level can be done with elastography or liver biopsy (Figure 1).[66] The National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) in India has recently integrated NAFLD into this national program and also suggests similar stratification and referral of patients to tertiary care centers.[129]

Risk stratification in most Western guidelines is based on the exclusion of advanced fibrosis by noninvasive tests.[66,116] Ruling-in or ruling-out advanced fibrosis is important when it comes to inclusion in clinical trials and for liver-related morbidity or mortality, but significant fibrosis is equally important when it comes to overall mortality in patients with NAFLD in comparison to general population. Moreover, majority of guidelines would favor use of pharmacotherapy in patients with significant fibrosis. It was thus felt by the members of the task force that significant fibrosis (≥F2) is more suited as an entry point into a referral pathway rather than advanced fibrosis (≥F3) (Figure 1). Indeed, the time to development of advanced liver disease is 22–26 years in F0-1, 9.3 years in F2 and 2.3 years in F3. Further, there is a progressive increase in mortality with the increasing stages of fibrosis, with stage F2 having an intermediate hazard ratio of 1.36 between F0–F1 (0.88) and F3 (2.54) and F4 (5.19).[130] Thus, in the setting of primary care, using a cut-off for advanced fibrosis for referral would result in the exclusion of patients with significant fibrosis who are at risk of developing clinically significant liver disease, CVD and may potentially benefit from consultation at a tertiary center with addition of pharmacotherapeutic agent in addition to lifestyle interventions (Figure 1).

Many Western guidelines suggest the use of certain patented NITs (ELF, Fibrotest, Fibrometer) for the stepwise approach in stratification of liver disease in patients with NAFLD. These patented tests are however limited by their cost and availability; hence, nonpatented tests are more relevant in the Indian setting. As mentioned earlier, most of the data for the nonpatented, noninvasive scores from India are for APRI and FIB-4. Even though FIB-4 may not be accurate at the extremes of the age, both these tests are simple and easily available, and INASL recommends using these tests at the primary healthcare level (Figure 1). The available Indian data suggest that APRI <0.45 or FIB-4<1 can rule out significant fibrosis with very high sensitivity.[118,119] In a recent study of 129 Indian patients with biopsy-proven NAFLD, NFS demonstrated a poor discriminatory ability for detecting the presence of either significant or advanced fibrosis on histology.[131] At the tertiary care level, INASL suggests using transient elastography as the next step for confirming the degree of hepatic fibrosis (Figure 1). Over the years, transient elastography has become widely available in India especially at the tertiary care levels; is noninvasive; relatively cheap with reasonable accuracy. Even though the data are scant, the validation of transient elastography in Indian patients with NAFLD suggests similar cut-offs as in Western patients.[132,133] Based on a systematic review and individual participant meta-analysis of biopsy-proven NAFLD patients, an expert panel review by the American College of Gastroenterology has recently endorsed cut-offs of <6.0 kPa and ≥8.2 kPa on VCTE for ruling-out and ruling-in significant fibrosis, respectively.[116,134] Liver biopsy is an invasive procedure and may be associated with complications. A large real-life data from India suggest poor acceptability of liver biopsy in patients with NAFLD (19); hence, INASL suggests using it only in specific clinical situations (detailed in the section on liver biopsy) (Figure 1).

Diagnosis of NASH-Related Cirrhosis and HCC

The modalities used for the diagnosis of cirrhosis and HCC in patients with NASH are same as for other modalities. NASH has emerged as the most important cause for cryptogenic cirrhosis/HCC. Ideally, the diagnosis of NASH

cirrhosis would require a histological documentation of NASH either in the past or at present but is usually difficult due to reluctance of liver biopsy and reduction of hepatic fat with increasing hepatic fibrosis. Hence, a noninvasive diagnosis of NASH cirrhosis/NASH HCC can be made by excluding other etiologies and the presence or history of metabolic risk factors. Since, patients identified for the first time at the stage of cirrhosis/HCC may have lost the MeS components after the development of liver disease (body weight, blood pressure, and lipids decrease) or some may develop hepatogenous diabetes due to cirrhosis which in true sense is not component of MeS, the history of these MetS risk factors may be equally important in making the diagnosis of NASH-cirrhosis/HCC.[25]

An LSM cut-off of ≥13.6 kPa suggests the presence of cirrhosis, while LSM ≥20 kPa might suggest clinically significant portal hypertension, particularly in patients with platelet count <150 × 10^6/L.[116] As in other etiologies, most patients with NASH-HCC have underlying cirrhosis and those with NASH-cirrhosis should be screened every 6 months for HCC using USG abdomen with or without alphafetoprotein (AFP). However, USG is often suboptimal in obese patients with poor quality of imaged liver due to attenuation of the USG beam by subcutaneous fat. It is now being increasingly recognized that in comparison to other etiologies, more patients with NASH have HCC without cirrhosis.[18,135,136] However, screening all noncirrhotic patients with NAFLD for HCC is unlikely to be cost-effective, given the extremely high prevalence of NAFLD in the community.

Consensus Statements

- INASL recommends using USG (abdomen) or controlled parameter (CAP) on transient elastography as the noninvasive tests for the detection of hepatic steatosis (I, Strong).
- INASL recommends that serum transaminases should not be used for differentiating NAFL from NASH (II, Strong).
- INASL recommends using APRI, FIB-4 as the initial screening tools for the assessment of hepatic fibrosis at the primary and secondary healthcare levels (II, Strong).
- INASL suggests that patients with high or intermediate results of APRI and FIB-4 or those with discordant results may be referred to tertiary health care levels (III, Weak).
- INASL recommends using VCTE at tertiary care levels to corroborate the results of APRI and FIB-4 (II, Strong).
- INASL suggests that an LSM cut-off of ≥8.2 kPa and ≥13.6 kPa may be used for detecting the presence of significant fibrosis and cirrhosis, respectively, in clinical practice (II, Weak).

Liver Biopsy in the Diagnosis of NAFLD/NASH

Liver biopsy is still considered as the gold standard for the diagnosis of NASH. In clinical situations, where noninvasive assessment is inconclusive, liver biopsy remains the only reliable modality for differentiating NAFL from NASH. It is also helpful in evaluating patients with competing etiologies for hepatic steatosis and raised transaminases and remains a short-term treatment end-point for most clinical trials.[92] However, liver biopsy is an invasive procedure and is not free from complications and may not be required routinely for the clinical management of all patients with NAFLD (Figure 1).

Evaluation of Hepatic Histology in NAFLD/NASH

The diagnosis of NAFLD by definition requires the presence of hepatic steatosis in 5% or more of hepatocytes. Histologically, the diagnosis of NASH can be made by a semiquantitative grading using a combination of steatosis, lobular and portal inflammation, and hepatocyte ballooning. In contrast to viral and autoimmune hepatitis, inflammatory activity in NASH has predominantly zone 3 localization. Fibrosis stage assessment can be done according to progressive involvement of the lobules.[109] The scoring systems provided by NASH Clinical Research Network (CRN) as the NAFLD activity score (NAS) and SAF score (steatosis, activity, and fibrosis) proposed by the Fatty Liver Inhibition of Progression (FLIP) algorithm are the two most commonly used scoring systems in clinical trials (Appendix 4–6).[137–141] Subtle histological differences exist between adults and pediatric NAFLD/NASH, children having more of portal disease (zone 1) in contrast to centri-zonal (zone 3) disease seen in adults [142,143] (Details in the section on NAFLD in children and adolescents).

Correlation of noninvasive tests with liver histology: Noninvasive serum-based tests such as APRI, BARD score, NFS, and FIB-4 have been found to correlate with NASH and significant fibrosis and adverse clinical outcomes in follow-up studies.118,144–149 CAP assessed using VCTE and MRI-PDFF has been reliably shown to diagnose hepatic steatosis.[150,151] The CAP cut-offs described for various grades of hepatic steatosis vary across studies. Possible factors affecting these include etiology, body mass index, diabetes, aspartate aminotransferase level, and gender of the patient.[95,97,98,150,152–154] FAST score identifies patients accurately with a NAS ≥4 and significant fibrosis (F ≥ 2) with AUROC of 0.79.[110–112] Overall, noninvasive modalities provide useful information similar to that

provided by a liver biopsy with the added benefit of ease and safety to repeat the assessment if required.

Limitations of liver biopsy: Even though considered as the gold standard for the diagnosis of NAFLD and NASH, liver biopsy is an imperfect tool due to sampling variability and a small but significant risk of complications, including pain, bleeding, and death.[93,155,156] Moreover, it is difficult and impractical to repeat liver biopsy for monitoring the progression of the disease. Apart from patient-related issues, other limitations include the limited expertise available to interpret the liver histology, interobserver, and intraobserver variability and requirement of a referral to a tertiary care center.[157,158]

Moreover, in clinical practice, the acceptance rate of liver biopsy in patients with NAFLD is not very high, and the diagnosis of NAFLD and significant/advanced fibrosis can be made in majority of patients based on noninvasive assessment with avoidance of liver biopsy.[19,67] However, in clinical situations where noninvasive assessment is inconclusive or falls in the gray zone or where patients may have confounding etiologies, a liver biopsy may still be required for the definite diagnosis of NAFLD/NASH (Figure 1).

Consensus Statements

- Liver biopsy remains the gold standard for the diagnosis of NASH (I).
- Liver biopsy is not routinely required for the management of NAFLD in day-to-day clinical practice (III, Weak).
- INASL recommends using noninvasive tests for the assessment of hepatic steatosis and fibrosis in clinical practice (I, Strong).
- Liver biopsy should be considered in patients where the noninvasive assessment for hepatic fibrosis is discordant (I, Strong).
- Liver biopsy should be considered in NAFLD patients in whom other competing etiologies of hepatic steatosis/liver disease cannot be ruled out (I, Strong).

TREATMENT

Being a lifestyle disease, the treatment of patients with NAFLD revolves around controlling the risk factors with lifestyle modifications or medications if required.[20,21,23,159] Pharmacological therapy for the treatment of liver disease in NAFLD is still evolving with only a few drugs recommended by various societies with many drugs still being in phase II or III clinical trials.[160]

Control of Risk Factors

The major risk factors for NAFLD include overweight or obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia. Of these, overweight or obesity is the most common risk factor present in up to 90% of patients with NAFLD in India.[19] Around 50% of Indian patients with NAFLD have MetS, with central obesity being the most common component.[8,15,19]

Weight Reduction – Lifestyle Interventions

Lifestyle interventions including dietary calorie restriction and exercise constitute the central pillar of NAFLD management.[161–165] There is a dose–response relationship between the magnitude of weight loss and the degree of histological improvement in NAFLD with weight loss of 3–5%, ≥7% and ≥10% being associated with improvement in steatosis, steatohepatitis, and fibrosis, respectively.[162,166] As such, a weight loss target of 7–10% is recommended in overweight or obese patients with NAFLD.[20,21,23] With respect to diet, daily caloric restriction by 30% or 500–1000 kcal appears to be more important than the type of diet *per se*. Although some evidence suggests that a Mediterranean diet may have some benefit,[167,168] this is difficult to recommend and practice for Indian patients who should be counseled to cut down on both carbohydrates and fats in their staple diet. A healthy diet sourced from locally available food products that are suited to local culinary tastes is more likely to be adhered to on a long term, which is crucial for sustainable benefits. Intermittent fasting may be a promising approach, but further data need to be generated in NAFLD before it can be recommended routinely.[169] It should also be noted that there is substantial heterogeneity in the various approaches of intermittent fasting that have been employed in studies [e.g., alternate day fasting, 5:2 fasting (severely reduced caloric intake for 2 days followed by 5 days of normal consumption), daily intermittent fasting of 18 h], and there is a need to standardize approaches to intermittent fasting.[169,170]

Exercise usually consists of moderate-intensity aerobic exercises, such as brisk walking, jogging, running, swimming, or cycling for 30–45 min/day at least 5 days in a week (at least 200 min per week) to achieve a target heart rate of 60–70% of maximal heart rate.[171] Resistance exercises can supplement aerobic exercises and may be particularly useful for patients who cannot otherwise do aerobic exercises.[172–175] Further, there is evidence that exercise may improve insulin resistance and hepatic steatosis even without weight loss.[173,176] This is reassuring for patients with lean NAFLD who have normal BMI. Key lifestyle interventions for NAFLD are summarized in Table 7.

Patients with cirrhosis should be encouraged to exercise as per their limits of tolerance. One of the vexing issues in NAFLD-cirrhosis is that while many of these patients are overweight or obese, they have underlying muscle loss (sarcopenia) with the muscles being partially replaced by fat deposition (myosteatosis).[177] As such, diet in patients with cirrhosis should be individualized and restriction of carbohydrates should be supplemented with adequate

Table 7 Lifestyle Interventions in Patients With NAFLD.

Weight loss	- There is a dose–response relationship between the magnitude of weight loss and the degree of histological improvement in NAFLD. - Targeting a weight loss of 7–10% is recommended in overweight or obese patients with NAFLD.
Diet	- A healthy diet protects against not only NAFLD but numerous noncommunicable diseases including diabetes mellitus, hypertension, obesity, cardiovascular disease and stroke. - In overweight or obese patients with NAFLD, daily calorie intake should be restricted by 30% or 500–1000 kcal by cutting down on carbohydrates and fats in the staple diet. In lean individuals, energy intake (calories) should be balanced with energy expenditure. - Total fat should not exceed 30% of total energy intake. Intake of saturated fats should be <10% of total energy intake, and intake of trans-fats <1% of total energy intake, with a shift in fat consumption away from saturated fats and trans-fats to unsaturated fats - Limit intake of free sugars to less than 10% of total energy intake; a further reduction to less than 5% of total energy intake may have additional health benefits. Fructose and sweetened beverages should be curtailed - There is some evidence of the benefit of >2 cups of caffeinated coffee per day in NAFLD. However, the standard Indian habit of sweetening and coloring their coffee with sugar and milk or cream may be counterproductive and more evidence is required. - Overall, calorie restriction appears to be more important than the specific type of diet *per se*. Although there is some evidence suggesting that a Mediterranean diet may have some benefit, this may be difficult to incorporate in daily life for the average Indian patients. Indeed, a healthy diet consisting of the standard constituents of the local staple diet is more likely to be adhered to in the long term.
Exercise	- INASL recommends moderate intensity aerobic or resistance exercises 30–45 min/day at least 5 days in a week (at least 200 min per week) in all patients with NAFLD irrespective of body weight - Moderate intensity aerobic exercises include brisk walking, jogging, running, swimming, cycling etc. - Resistance exercises can supplement aerobic exercises and may be particularly useful for patients with who cannot otherwise partake in aerobic exercises like patients with arthritis, morbid obesity, poor cardiorespiratory fitness etc - The role of yoga in NAFLD is under explored. Asanas that involve physical exertion and the maintenance of certain body postures (akin to isometric resistance exercises) may certainly be beneficial although this needs to be further studied

NAFLD, non-alcoholic fatty liver disease.

amounts of protein (1.5 g/day). Protein restriction is not required even in patients with history of hepatic encephalopathy although it may be prudent to replace meat protein with plant, dairy, or fish proteins.[178,179]

Weight Reduction – Pharmacological Interventions

Even though weight reduction by lifestyle interventions is effective in improving NAFLD/NASH, only a proportion attain this target weight loss with life-style interventions alone, and only a minority of them are able to sustain this weight loss over meaningful periods.[171] Several drugs are available for weight loss (orlistat, liraglutide, phentermine–topiramate combination, and naltrexone–bupropion), but none of these drugs targeting weight loss are recommended for NAFLD.[20,21,23,25,171,180]

Weight Reduction- Bariatric Surgery and Endoscopic Bariatric and Metabolic Therapy (EBMT)

The general indications for bariatric surgery for obesity in the West are BMI ≥40 kg/m^2 or a BMI between 35 and 39.9 kg/m^2 with one or more obesity-related comorbidities.[181] Endoscopic bariatric metabolic therapy (EBMT) is usually indicated in patients who do not fit the BMI criteria for surgery, are not fit for surgery, who fail to lose weight or are not able to maintain weight loss on life-style interventions. The guidelines by the Obesity and Metabolic Surgery Society of India however state that bariatric/metabolic surgery should be considered in the following situations: BMI ≥35 kg/m^2 or BMI ≥30 kg/m^2 in the presence of two or more obesity-related comorbidities or as a nonprimary treatment option for BMI ≥27.5 kg/m^2 with uncontrolled T2DM despite optimum medical management.[182] Various bariatric surgery and EBMT procedure done for obesity are shown in Appendices 7 and 8.

In spite of the efficacy of these procedures for weight reduction, both bariatric surgery and EBMT are not recommended as a primary treatment for patients with NAFLD/NASH; the primary reasons being the associated morbidity and mortality and absence of randomized clinical trials.[183–193] However, if the patient otherwise requires bariatric surgery or EBMT for his/her obesity and or associated comorbidities, then the presence of noncirrhotic NAFLD/NASH is not a contraindication and may help in NASH resolution and fibrosis regression.[184] Caution and risk assessment needs to be exercised in those with compensated cirrhosis prior to surgery or if cirrhosis is detected during bariatric surgery.[194–196] There is limited experience with intragastric balloon placement in patients with morbid obesity and decompensated cirrhosis before liver transplantation.[197] In a small number of patients, use of intragastric balloon in cirrhotic patients with obesity prior to living donor liver transplantation showed it to be an effective modality in a select group of patients to improve their graft to recipient weight ratio.[197]

Pharmacological Management of Metabolic CoMorbidities

Timely diagnosis and appropriate management of metabolic comorbidities like T2DM, hypertension and dyslipidemia are the mainstay of the holistic management of NAFLD. Statins, even though not found to be useful in

improving the liver histology, if indicated, are safe even in the presence of elevated transaminases.[198] However, it is prudent to be cautious in patients with cirrhosis, particularly in those with decompensated disease. Given the close link between T2DM and NAFLD, it is not surprising that several anti-diabetic drugs have been evaluated in NAFLD.[199,200] Pioglitazone, which is recommended by various society guidelines in patients with biopsy-proven NASH is discussed in detail below. Metformin improves liver biochemistry but not liver histology.[201,202] There is much excitement with glucagon-like peptide-1 (GLP-1) analogs, with two molecules, Liraglutide and Semaglutide which have beneficial effects on the resolution of NASH in phase 2 clinical trials.[203,204] Preliminary data with the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in NASH are also promising and need further evaluation.[205–208] An added advantage of both GLP-1 analogs and SGLT-2 inhibitors is the associated reduction in body weight, which may have further putative benefits in NAFLD. However, as of now, barring pioglitazone, none of the anti-diabetic agents are recommended as NASH-specific pharmacotherapy.[20,23,25] As such, in patients with NAFLD, T2 DM and other metabolic comorbidities should be managed along similar lines as in the general population.

Consensus Statements

- INASL recommends weight loss (7–10% of baseline) induced by diet and exercise as the primary treatment in overweight/obese patients with NAFLD for the improvement in hepatic steatosis, inflammation, and fibrosis (I, Strong).
- INASL recommends daily calorie restriction by 30% or 500–1000 kcal to achieve the target weight loss (I, Strong).
- INASL recommends moderate intensity aerobic or resistance exercises 30–45 min/day at least 5 days in a week (at least 200 min per week) in all patients with NAFLD irrespective of body weight (I, Strong).
- In the absence of randomized clinical trials, bariatric surgery cannot be recommended as a primary treatment for NAFLD/NASH (II, Strong).
- Bariatric surgery, if otherwise indicated in obese patients, can be done in the presence of noncirrhotic NAFLD/NASH and may help in NASH resolution and fibrosis regression (II, Strong).
- Bariatric surgery should be done with caution in patients with compensated NASH cirrhosis and should be avoided in decompensated NASH cirrhosis even if it is otherwise indicated (II, Strong).
- In the absence of randomized clinical trials, bariatric endoscopic therapy cannot be currently recommended as a primary treatment for NAFLD/NASH (III, Weak).
- INASL suggests managing type 2 diabetes mellitus, hypertension, and dyslipidemia in NAFLD patients as per the standard recommendations applicable to non-NAFLD patients (III, Weak).
- Statins if indicated can be used safely in patients with NAFLD even in the presence of elevated transaminases (I, Strong).

Pharmacologic Treatment for NAFLD/NASH

Who Needs Pharmacological Treatment in NAFLD/NASH?

The histology-based studies on the natural history of NAFLD have clearly shown faster disease progression in those with NASH in comparison to NAFL.[209] Current evidence also suggests that the key determinant of histological and clinical outcomes in NAFLD is the degree of underlying hepatic fibrosis.[16,209–215] Hence, pharmacotherapy in patients with NAFLD is directed toward patients with biopsy-proven NASH with or without hepatic fibrosis.

Even though liver biopsy is still the gold standard for the diagnosis of NASH/fibrosis, it has its own limitations, including sampling error and a small but definite risk of complications, as discussed previously in the section on liver biopsy. Because of these limitations, liver biopsy is not a feasible option in the vast majority of patients in routine clinical practice and the decision to treat patients with pharmacotherapy may have to be taken based on the noninvasive assessment.

As mentioned previously, NITs have reasonably good performance for the diagnosis of hepatic steatosis and fibrosis. Therefore, INASL suggests that in the absence of liver biopsy, an individualized decision may be taken to treat such patients with NASH-specific pharmacotherapy if they have significant fibrosis without cirrhosis on noninvasive assessment (Figure 1) (see section on noninvasive assessment for the definition of significant fibrosis and cirrhosis).

In addition, noninvasive tools have reasonable correlation with liver histology and response in ALT, hepatic steatosis, and fibrosis can also be used in monitoring the treatment response.[216]

Choice of Drugs

Current drugs: Of the various drugs used in the treatment of patients with NASH, only vitamin E, pioglitazone, and saroglitazar are currently recommended by either scientific societies or a regulatory agency.[20,21,23] Vitamin E has antioxidant properties, pioglitazone is a peroxisome proliferator activated receptor (PPAR) γ agonist, and saroglitazar is a dual PPAR α/γ agonist, and these drugs target different

pathways involved in the pathogenesis of NASH.[217–219] In the landmark PIVENS trial, 247 patients with biopsy-proven NASH without DM were randomized to either pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 96 weeks.[220] Compared to placebo, vitamin E significantly decreased hepatic steatosis, lobular inflammation, and ballooning with an improvement in NAS.[220] Multiple other studies including meta-analyses have also shown that vitamin E improves biochemistry and liver histology including steatosis, inflammation, and ballooning but not fibrosis in adult and pediatric patients with NASH.[221–223] In the PIVENS trial, patients on pioglitazone did not achieve the primary end-point of "improvement in NAS by 2 points with at least 1-point improvement inhepatocellular ballooning and 1-point improvement in either the lobular inflammation or steatosis score, and no increase in the fibrosis score." However, significantly more patients in the pioglitazone group attained a resolution of NASH as compared to placebo, and pioglitazone was also associated with a decrease in steatosis and lobular inflammation. No improvement in fibrosis was observed with either Vitamin E or pioglitazone.[220] In a randomized, placebo-controlled, double-blind phase IV study of patients with NASH with prediabetes or type 2 diabetes (n = 101), therapy with pioglitazone for 18 months was associated with a significantly greater proportion of patients attaining a ≥ two-point reduction in NAS without worsening of fibrosis. Resolution of NASH was also significantly more frequent in the pioglitazone arm.[224] However, since pioglitazone has not been evaluated in pediatric NASH, it is not recommended in this population.

In a phase II randomized-controlled trial (EVIDENCES IV), saroglitazar (4 mg/day) significantly improved serum transaminases, hepatic steatosis, insulin resistance, and dyslipidemia in NAFLD patients.[225] In the multicentric, EVIDENCES II study from India, 102 patients with biopsy-proven noncirrhotic NASH were randomized in a 2:1 ratio to receive either saroglitazar or placebo for 52 weeks. Significantly more patients in the saroglitazar group (52.3%) attained the primary end-point of decrease in NAS by ≥ 2 points without worsening of fibrosis as compared to those in the placebo group (23.5%; p = 0.04).[226] Based on these data and other real-life data, saroglitazar in a dose of 4 mg/day was approved by the Drug Controller General of India (DGCI) for use in patients with NASH and F1-3 fibrosis in March 2020.[227,228]

Landmark studies showing the dose, duration, side-effects, and limitations of these three drugs are shown in Tables 8 and 9.

How to choose a drug?: In addition to the efficacy and safety of the drugs, other factors that may help in choosing a drug for patients with NASH with or without significant fibrosis include age and gender of the patient, presence or absence of diabetes mellitus, and dyslipidemia. There is a

Table 8 Dose, Duration and Benefit of NASH-Specific Pharmacotherapy.

Drug	Phase III study	Dose	Clinical effect	Level of evidence for clinical benefit	Suggested minimum duration
Vitamin E[a]	PIVENS	800 IU/day[a] in two divided doses	- Decrease in ALT - Decrease in hepatic steatosis, lobular inflammation, ballooning and NAS - No effect on fibrosis - No effect on body weight	I	2 years
Pioglitazone	PIVENS	30 mg/day	- Decrease in ALT - Improved insulin resistance - Decrease in hepatic steatosis and lobular inflammation - Increased resolution of NASH - No effect on fibrosis - Body weight may increase	I	2 years
Saroglitazar	EVIDENCES II	4 mg/day	- Decrease in ALT - Improved insulin resistance - Decrease in triglycerides with improved lipoprotein particle composition and size and reduced lipotoxic lipid species - Decrease in hepatic steatosis - Decrease in NAS - No significant effect on body weight	III	1 year

ALT, alanine aminotransferase; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis.
[a]Dose conversion in vitamin E (α-tocopherol): to convert from IU to mg, divide by 1.5.

Table 9 Choosing NASH Pharmacotherapy.

Drug	Factors to consider
Vitamin E	- Widely available, low cost - Recommended by various international societies in biopsy-proven NASH in patients without diabetes - Debatable effect on fibrosis - Adverse effects on long term use include increased risk of prostate cancer and hemorrhagic stroke; no increased risk of all-cause mortality
Pioglitazone	- Recommended by various international societies in biopsy-proven NASH - Can be used in patients with or without diabetes mellitus - Debatable effect on fibrosis - Adverse effects include propensity to weight gain, osteoporosis (in females). Increased risk of bladder carcinoma has been suggested but most of the evidence is to the contrary
Saroglitazar	- Approved by DCGI for use in NASH with F1–F3 fibrosis and NAFLD with co-morbidities (obesity, diabetes mellitus, dyslipidemia or metabolic syndrome) - Although approved for use in patients with or without diabetic dyslipidemia, the majority of the published literature is in patients with diabetic dyslipidemia - Only phase II study (EVIDENCES IV) available as a full paper. - Debatable effect on fibrosis - Cost of drug needs to be considered - Available only in India

DCGI, drug controller general of India; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

possible increased risk of prostate cancer with long-term use of vitamin E. Pioglitazone has been associated with osteoporosis particularly in postmenopausal females. Table 9 lists some of the factors that should be considered while choosing a drug for NASH pharmacotherapy.

Future drugs: Based on encouraging phase II data, various drugs like farnesoid X receptor (F x R) agonist, obeticholic acid (OCA) (REGENERATE trial in NASH with F2-3 fibrosis and REVERSE trial in NASH patients with compensated cirrhosis), chemokine 2 and 5 inhibitor, thyroid hormone receptor beta agonist, resmetirom (MAESTRO-NASH in NASH with F1–F3 fibrosis) semaglutide (GLP-1 agonist), synthetic fatty acid/bile acid conjugate, aramchol (ARMOR in NASH with F2-3 fibrosis), and lanfibranor (NATiV3 in NASH with F2–F3 fibrosis) are being evaluated in phase III studies.[160,229] An interim analysis of the REGENERATE study at 18 months showed that the primary outcome of ≥1 stage improvement in fibrosis without worsening of NASH was significantly more common in patients treated with 25 mg (23.1%, p = 0.0002) of obeticholic acid as compared to placebo (11.9%). However, almost half of the patients who received 25 mg of OCA complained of pruritus, while 13% patients discontinued treatment.[230] Besides, elevated LDL was also seen in 17% of patients receiving 10 mg and 25 mg of obeticholic acid. This side-effect of OCA appears to be a class effect of F x R agonists and responds well to statins.[230,231] Pending further evidence, INASL suggests not using obeticholic acid as pharmacotherapy for treating NASH.

NASH pharmacotherapy in patients with cirrhosis: Recent retrospective, single-center data on patients with biopsy-proven NASH and bridging fibrosis or cirrhosis have shown the efficacy of vitamin E and metformin in lowering the risk of HCC, hepatic decompensation, transplant, and death.[232,233] However, in the absence of prospective RCTs, these drugs are still not recommended for the treatment of NASH-cirrhosis. Results of OCA and other future drugs in patients with cirrhosis are still awaited.

End-points of pharmacological treatment: Being a metabolic and lifestyle disease, it is reasonable to presume that prolonged treatment would be required for patients with NASH. In this context, the pharmacological treatment with the available drugs would not be a viable option for long-term therapy and lifestyle modifications would continue to remain the backbone of treatment. Based on the duration of treatment in the registration trials, INASL suggests treatment duration of 2 years for vitamin E or pioglitazone, and 1 year for Saroglitazar (Table 8).[220,225,226] Assessing response to treatment is another vexing clinical problem in these patients. Evidence suggests that

reduction in the liver fat fraction by MR-PDFF may be used as a surrogate marker for predicting histological improvement.[234] However, MR-PDFF is largely confined to research settings and is not suitable for routine clinical use. A secondary data analysis of the phase 2 FLINT trial showed that decrease in serum ALT by 17 U/L at 24 weeks of therapy was significantly associated with histological response of improvement in NAS≥2 without worsening of fibrosis.[216] Hence, INASL suggests that serum ALT may be used for monitoring patients on NASH-specific pharmacotherapy. Depending upon the availability, CAP and LSM on transient elastography can also be used on an individual basis for monitoring these patients while on treatment.[225,227,235]

Consensus Statements

- Pharmacotherapy should be considered in patients with liver biopsy-proven NASH with or without hepatic fibrosis (F1–F3) (I, Strong).
- The choice of drugs for NASH pharmacotherapy should be individualized on the basis of age, gender and the presence/absence of diabetes/dyslipidemia (III, Weak).
- INASL recommends vitamin E as pharmacotherapy for NASH with or without hepatic fibrosis (F1–F3) in nondiabetic adult and pediatric patients (I, Strong).
- INASL recommends pioglitazone as pharmacotherapy for NASH with or without hepatic fibrosis (F1–F3) in both diabetic and nondiabetic adult patients (I, Strong).
- INASL recommends saroglitazar as pharmacotherapy for NASH with or without hepatic fibrosis (F1–F3) in both diabetic and nondiabetic adult patients (III, Weak).
- In patients in whom liver biopsy is not available, NASH-specific pharmacotherapy can be used in noncirrhotic patients found to have significant fibrosis on noninvasive assessment (III, Weak).
- Pending further evidence, INASL suggests not using obeticholic acid as pharmacotherapy for NASH (III, Weak).
- Pending further evidence, INASL suggests not using NASH-specific pharmacotherapy in patients with NASH cirrhosis (III, Weak).

LIVER TRANSPLANTATION

Over the years, NASH has become an important indication for liver transplantation both for end-stage liver disease and HCC. Recent data from India also suggest rising numbers of patients undergoing liver transplantation for NASH cirrhosis and HCC.[236] The indications and outcome of liver transplantation in NASH largely remains the same as for other indications.[237] However, special attention is required for the associated metabolic comorbidities that may affect the selection, and operative and postoperative course in patients with NASH undergoing liver transplantation. Even though patients with NASH cirrhosis and NASH-HCC are more likely to be associated with metabolic risk factors, the assessment, work-up, and evaluation for these metabolic comorbidities like obesity, diabetes mellitus, hypertension, and dyslipidemia would remain the same as done in other etiologies of liver disease undergoing liver transplantation.

Detailed management of obesity in patients with decompensated cirrhosis listed for transplantation is beyond the scope of these consensus guidelines and can be read in the recent INASL consensus on nutrition in liver disease.[178] A single report from India on the use of intragastric balloon in cirrhotic patients with obesity prior to liver transplantation showed it to be an effective modality in a select group of patients specially to improve their graft to recipient weight ratio in the setting of living donor liver transplantation.[197] Morbidity and mortality in patients with cirrhosis undergoing bariatric surgery is higher than patients without cirrhosis, with a further increase in patients with decompensated cirrhosis and should be avoided in this clinical situation unless it is being scheduled during or after liver transplantation.[180,195,238,239] Patients with NASH-cirrhosis and HCC are also at a higher risk of having cardiovascular (CVD) and CKD but the assessment and evaluation for associated CVD and CKD in these patients would be the same as for other etiologies. Even though patients with NASH-cirrhosis and HCC may be complicated more often with the post-operative occurrence of CVD and CKD, the overall outcome of liver transplantation in these patients is the same as for other etiologies.[237,240]

The choice of immunosuppression in NASH patients is also the same as for other etiologies except that corticosteroids may be tapered early after transplantation to reduce the risk of metabolic complications. However, of all the immunosuppressive agents, mycophenolate mofetil may be the preferred drug because of the lowest risk of metabolic complications.[241]

Recurrent NAFLD/NASH after liver transplantation in patients undergoing transplant for NASH is common and may in fact be universal.[240] *De novo* occurrence of NAFLD/NASH in patients undergoing liver transplantation for other indications is also a major issue.[242] The reasons for both recurrent and *de novo* NAFLD/NASH are multifactorial but are predominantly related to the post-transplant metabolic syndrome (PTMS) due to lifestyle and dietary changes and immunosuppressive drugs.[243,244] The treatment of both recurrent and *de novo* NAFLD/NASH is adherence to lifestyle interventions and control of metabolic risk factors.[245] None of the drugs (vitamin E, pioglitazone, saroglitazar) which are recommended for treatment in NASH prior to liver transplant have been evaluated in the postliver transplant patients; hence, they are not recommended in this population.

Consensus Statements

- INASL recommends that screening and assessment for co-morbidities in NASH transplant recipients should be done in the same manner as for other etiologies (II, Strong).
- INASL suggests that obesity in decompensated NASH cirrhosis be managed with lifestyle interventions with avoidance of bariatric surgery (II, Strong).
- INASL suggests that the algorithm for cardiovascular (CV) risk assessment be determined by local expertise as there is insufficient evidence to recommend a specific CV risk algorithm for NASH patients undergoing LT evaluation (II, Weak).
- INASL recommends appropriate screening and management of renal dysfunction before and after liver transplantation (I, Strong).
- The postliver transplant survival in patients with NASH-related cirrhosis is similar to that in other etiologies (I).
- INASL suggests that corticosteroids should be tapered early after liver transplant (depending on center experience) in patients with NASH undergoing liver transplantation (II, Weak).
- INASL suggests mycophenolate as the safest immunosuppressant in patients with NASH undergoing liver transplantation (II, Weak).
- Postliver transplant recurrent or *de novo* NAFLD/NASH should be managed with lifestyle interventions without any specific drugs till further data are available for the use of pharmacotherapy in this setting (I, Strong).

NAFLD in Children and Adolescents

With the rise in obesity among children, it is not surprising that NAFLD, which was once considered to be a disease of adults, is being increasingly recognized in children and adolescents. Indeed, a recent meta-analysis that included eight studies and almost 2900 children reported a pooled NAFLD prevalence of 12.4% and 63.4% among nonobese and obese Indian children, respectively.[11] However, a detailed discussion of pediatric NAFLD is beyond the scope of the current guidance document, and it will only be discussed in brief.

Most children are asymptomatic and are diagnosed incidentally. It is important to consider genetic causes of fatty liver including defects of fatty acid or carnitine metabolism, peroxisomal disorders, lysosomal storage disorders, and Wolman's disease, particularly in children who are nonobese or very young.[20] The role of USG for screening of NAFLD in children remains debated given its low sensitivity for milder degrees of steatosis.[246] While the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines advocate against the use of USG, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines identify USG as an inexpensive screening tool for detecting steatosis.[247,248] Most of the guidelines of international expert societies recommend screening with ALT in obese children above 9 years of age and overweight children with family history of NAFLD or other risk factors. Search for other etiologies is recommended particularly in those with ALT levels more than twice of the upper limit of normal.[20,246–248] Although liver biopsy remains the gold standard for diagnosis, it is not feasible in most cases. As in adults, liver biopsy in clinical practice is mainly restricted to children in whom there is a diagnostic confusion.[92,249] There are subtle differences in the histology of NAFLD observed in children compared to adults. In a nutshell, NAFLD in adults shows a zone 3 centered injury, while in children, there is a preponderance of zone 1 centered steatosis, inflammation, and fibrosis.[249] This is possibly related because the SONIC hedgehog pathway is relatively preserved in the portal regions in children.[250] Further, hepatocyte ballooning is often absent in children with NASH.

Lifestyle modifications is the mainstay of management of pediatric NAFLD and weight reduction has been shown to improve liver biochemical parameters and possibly histology although the evidence is less robust than in adults.[20,246,251] Among pharmacotherapeutic agents, metformin, and vitamin E were compared in the multicentric TONIC trial in children. Vitamin E but not metformin was associated with a significant improvement in NAS and NASH resolution (daily dosing of 800 IU of vitamin E (58 patients), 1000 mg of metformin (57 patients), or placebo (58 patients) for 96 weeks).[252] However, it should be noted that the long-term safety of vitamin E in children is unknown. A detailed discussion of anticipated risks and benefits with the parents should be done if vitamin E is used for the treatment of NASH in children on an individualized basis, as recommended in the AASLD guidelines.[20]

EPILOGUE

NAFLD has emerged as a major health problem in India, and recognizing its importance, the government of India has taken the bold initiative of integrating NAFLD into the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS), an endeavor toward addressing India's noncommunicable diseases. In view of the burgeoning pandemic, the need for an updated guidance for management of NAFLD in Indians was the need of the hour. With this purpose, INASL decided to initiate steps to formulate this guidance on the nomenclature, diagnosis, and treatment of NAFLD. These recommendations provide an evidence-based approach to different important

and contentious issues related to NAFLD including nomenclature, diagnosis, and management of NAFLD in Indians. These recommendations are based on a comprehensive review and analyses of global and Indian literature on NAFLD and the opinion of experts with years of experience in managing NAFLD patients. These recommendations are not intended to be a substitute for clinical judgment but are intended to provide general guidance to physicians and healthcare providers for managing NAFLD patients. However, merely publishing these guidelines for the management of NAFLD patients cannot be the be-all and end-all in the management of NAFLD. It's essential that we should initiate programs not only to implement guidance-based care by standardizing care but also to educate the masses and prevent NAFLD.

SUGGESTIONS FOR FUTURE RESEARCH

In spite of all the progress made in the field of NAFLD, the following areas require more research to address many unmet needs in NAFLD.

- The controversy of NAFLD nomenclature should be resolved by a global democratic process taking into account all the stakeholders. An attempt has recently been made by EASL and AASLD by starting the Global NAFLD Nomenclature Development effort involving multiple hepatology and gastroenterology societies, patients and patient advocacy organizations, regulators, and industry representatives. There was a consensus conference in the first week of July, 2022 in Chicago, USA, and three rounds of voting. As of now, nomenclature of NAFLD is being followed. Another survey is planned; the outcome of which would be communicated at the Annual Liver Meeting of AASLD in November, 2022. However, even if the new name is proposed in the next survey, the new name will only be taken forward if there are reassurances from stakeholders including FDA/EMA and industry partners that it will not negatively impact the drug/biomarker development.
- The incorporation of the additional criteria of normal waist circumference in addition to BMI for defining lean NAFLD will lead to exclusion of patients with normal BMI but increased waist circumference from the category of lean NAFLD. The clinical impact of such a change in definition needs to be evaluated in future studies.
- More research is needed for the noninvasive diagnosis of NASH, specifically to improve the accuracy of noninvasive tests for hepatic fibrosis. Appropriate cut-offs for nonproprietary, easy to use, blood-based scores like APRI and FIB-4 should be derived and validated in the Indian population.
- Upper limit of normal for AST and ALT needs to be derived in Indian males and females.
- Better algorithms need to be developed to manage patients at the primary and secondary health care levels.
- Lifestyle interventions as the treatment for NAFLD need to be emphasized.
- Efficacy of future drugs in NASH should be evaluated based on noninvasive assessment.
- Preventive strategies to improve the lifestyle need to be implemented in the early years of life as a public health policy.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ajay Duseja: conceptualization, supervision methodology, data curation, writing of original draft; SP Singh: conceptualization, supervision, methodology, data curation, writing, critical revision; Arka De: data curation, writing, visualization, critical revision; Kaushal Madan: data curation, writing, critical revision; PN Rao: data curation, writing, critical revision; Akash Shukla: data curation, writing, critical revision; GC Choudhuri: data curation, writing, critical revision; Sanjiv Saigal: data curation, writing, critical revision; Shalimar: data curation, writing, critical revision; Anil Arora: data curation, writing, critical revision; Anil C Anand: data curation, writing, critical revision; Ashim Das: data curation, writing, critical revision; Ashish Kumar: data curation, writing, critical revision; CE Eapen: data curation, writing, critical revision; Krishnadas Devadas: data curation, writing, critical revision; KT Shenoy: data curation, writing, critical revision; Manas Panigrahi: data curation, writing, critical revision; Manav Wadhawan: data curation, writing, critical revision; Manish Rathi: data curation, writing, critical revision; Manoj Kumar: data curation, writing, critical revision; Narendra S Choudhary: data curation, writing, critical revision; Neeraj Saraf: data curation, writing, critical revision; Preetam Nath: data curation, writing, critical revision; Sanjib Kar: data curation, writing, critical revision; Seema Alam: data curation, writing, critical revision; Samir Shah: data curation, writing, critical revision; Sandeep Nijhawan: data curation, writing, critical revision; Subrat K Acharya: data curation, writing, critical revision; Vinayak Aggarwal: data curation, writing, critical revision; Vivek A Saraswat: data curation, writing, critical revision; Yogesh K Chawla: data curation, writing, critical revision.

CONFLICTS OF INTEREST

The authors have none to declare.

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Appendix 1. Common Causes of Hepatic Steatosis.

Macrovesicular steatosis	Microvesicular steatosis
- Nonalcoholic fatty liver disease	- Reye's syndrome
- Excessive alcohol	- Medications (valproate, anti-HIV)
- Hepatitis C (genotype 3)	- Acute fatty liver of pregnancy
- Wilsons Disease	- HELLP syndrome
- Lipodystrophy	- Inborn errors of metabolism
- Starvation	
- Parenteral nutrition	
- Abetalipoproteinemia	
- Medications (methotrexate, steroids)	

Appendix 2. Metabolic Syndrome Risk Factors as er the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Criteria Modified for Indians.

Abdominal Obesity	Waist circumference >90 cm in males and >80 cm in females
Impaired fasting glucose	Fasting glucose ≥110 mg/dl or on pharmacological treatment
Hypertension	Blood pressure ≥130/85 mm of Hg or on antihypertensives
Hypertriglyceridemia	Serum triglycerides ≥150 mg/dl or on pharmacological treatment that lowers triglycerides
Decreased HDL	Serum HDL <40 mg/dl in males and <50 mg/dl in females

Metabolic syndrome is defined as the presence of three or more risk factors.

Appendix 3. Commonly Used Non-proprietary Non-Invasive Scores for Discriminating Fibrosis in nonalcoholic fatty liver disease (NAFLD).

Score	Formula
AST platelet ratio index (APRI)	[(AST/upper limit of the normal AST range) X 100]/Platelet Count
FIB-4	(Age × AST)/(Platelet count × $ALT^{1/2}$)
NAFLD fibrosis score (NFS)	−1.675 + (0.037 × age) + (0.094 × BMI) + (1.13 × presence of IFG or diabetes) + (0.99 × AST/ALT) – (0.013 × Platelet count) – (0.66*albumin)
BARD score	AST/ALT ratio ≥0.8: 2 points BMI ≥28: 1 point Presence of diabetes mellitus: 1 point Total: 0–4 points

AST, aspartate amino transferase in U/L; ALT, alanine transferase; platelet count in 10^9/L; age in years; BMI, body mass index in kg/m^2; albumin in g/dL; IFG, impaired fasting glucose.

Appendix 4. Nonalcoholic fatty liver disease (NAFLD) Activity Score (NAS) as per the nonalcoholic steatohepatitis Clinical Research Network (NASH-CRN) System.

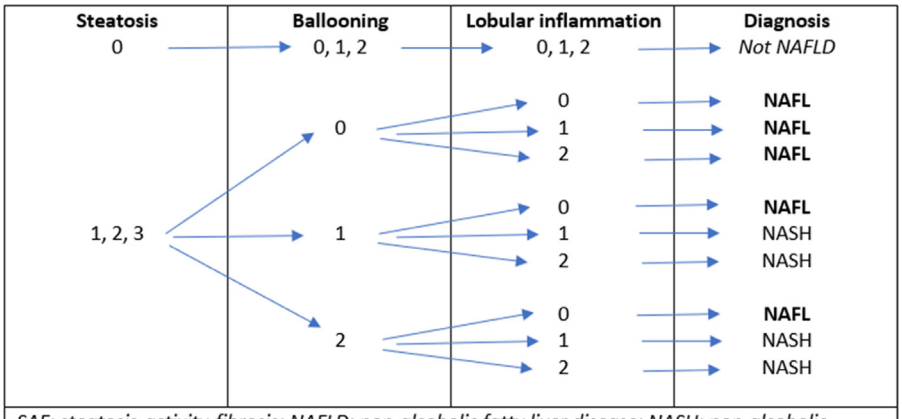
Histologic Feature	Score	Definition
Steatosis	0	<5%
	1	5–33%
	2	34–66%
	3	>66%
+		
Hepatocyte ballooning	0	None
	1	Few
	2	Many
+		
Lobular Inflammation	0	None
	1	1-2 foci per 20 X field
	2	2-4 foci per 20 X field
	3	>4 foci per 20 X field
= NAFLD activity score (NAS); range 0–8		
Fibrosis Stage	0	No fibrosis
	1a	Zone 3 mild perisinusoidal fibrosis
	1b	Zone 3 moderate perisinusoidal fibrosis
	1c	Portal or portal fibrosis only
	2	Zone 3 + portal/periportal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic fatty liver disease; CRN, clinical research network.

Appendix 5. Steatosis-Activity-Fibrosis (SAF) Score for nonalcoholic fatty liver disease (NAFLD).

Histologic Feature	Score	Definition
Steatosis	0	<5%
	1	5–33%
	2	34–66%
	3	>66%
= Steatosis score (S 0–3)		
Hepatocyte ballooning	0	None
	1	Clusters of round hepatocytes with pale cytoplasm
	2	Same as above with enlarge hepatocytes (>2 times than normal)
+		
Lobular Inflammation	0	None
	1	<2 foci per 20 X field
	2	>2 foci per 20 X field
= Activity score (A 0–4)		
Fibrosis	0	No fibrosis
	1a	Zone 3 mild perisinusoidal fibrosis
	1b	Zone 3 moderate perisinusoidal fibrosis
	1c	Portal or portal fibrosis only
	2	Zone 3 + portal/periportal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis
= Fibrosis score (F 0–4)		

Appendix 6. Fatty liver inhibition of progression (FLIP) Algorithm Based on the Steatosis-Activity-Fibrosis (SAF) Score for Diagnosis of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH).



SAF: steatosis-activity-fibrosis; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis

Appendix 7. Bariatric Surgery Procedures for Obesity.

Main mechanism of weight loss	Procedures	Comments
Restrictive and malabsorption	Biliopancreatic diversion with a duodenal switch	Studies have shown improvement in NASH and fibrosis No RCTs in NASH
	Roux-en-Y gastric bypass	Bariatric surgery has not been done for NASH alone without other indications
Restrictive	Sleeve gastrectomy	Type of bariatric surgery depends on patient's characteristics
	Adjustable gastric band	Limited data in patients with cirrhosis

Appendix 8. Endoscopic Bariatric and Metabolic Procedures.

Main mechanism of weight loss	Procedures	Comments
Gastric restriction	Intragastric balloons	Limited data with intragastric balloons, duodenal mucosal resurfacing and endobarrier in NASH
	Transpyloric shuttle	
	Satisphere	
	Gelessi 100	
	Stapling devices	
Malabsorption	Duodenal mucosal resurfacing	
	Endobarrier	
	REVITA	
	Incision-less anastomosis system	
	Gastroduodnojejunal bypass sleeve	
Others	Aspire assist	
	Botulinum toxin injection	