

Review Article

Non-alcoholic steatohepatitis: diagnosis, management and challenges in clinical trials: an Indian perspective

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Received: 24 September 2020

Accepted: 05 December 2020

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide and non-alcoholic steatohepatitis (NASH), its progressive form, is rapidly becoming the leading cause of end-stage liver disease and liver transplantation. There is a huge unmet need in the management of NAFLD and NASH. The key challenge is that NAFLD/NASH remains to be an under recognized disease despite its increasing prevalence, and early diagnosis is crucial to reduce the risk of progression and its consequent complications. In India, cases of NAFLD/NASH may go undetected due to lack of awareness and absence of a structured patient referral pathway. Efforts to increase patient and physician awareness along with standardization of local management guidelines for NAFLD and NASH can help improve patient care in India. Another major concern is the lack of approved NASH therapy; in order to address this issue, there has been a global surge in clinical trials. However, many countries, including India, have encountered challenges in the conduct of these trials related to patient recruitment and retention, lack of validated less invasive diagnostic tests, and the effect of placebo response on trial outcomes. Measures to improve the NAFLD and NASH clinical trial environment can help accelerate the approval and availability of better treatment options for NASH.

Keywords: Clinical trial, NAFLD, NASH

INTRODUCTION

Global urbanization and the associated changes in lifestyle have led to innumerable lifestyle-related diseases, such as diabetes mellitus (DM), cardiovascular diseases (CVD), and dyslipidemia. The increasing prevalence of these diseases parallels the increasing prevalence of nonalcoholic fatty liver disease (NAFLD), which is the most common chronic liver disease worldwide.¹ Worldwide prevalence of NAFLD is around 24% and it is known to develop through a multifactorial process starting with insulin resistance and excessive fatty acids.² Nonalcoholic steatohepatitis (NASH), the aggressive form of NAFLD, can progress to cirrhosis and hepatocellular cancer (HCC); and is rapidly becoming the leading cause

of end-stage liver disease and liver transplantation.³ There is a need to create awareness and improve the level of care of NAFLD/NASH. It is estimated that the prevalence of NAFLD will increase by 21% by 2030, from 83.1 million in 2015 to 100.9 million, while prevalence of fibrotic NASH will increase by 63% from 16.52 million to 27.00 million cases and there would be around 178% rise in liver-related mortality in the same time period.⁴ NAFLD and NASH, commonly considered a liver disease of Western countries, appears to have exponentially increased in South America, Asia, and the Middle East. It is considered as a hepatic manifestation of metabolic syndrome (MetS), which includes DM, dyslipidemia, hypertension, and obesity. A recent meta-analysis including 85 studies with a study population of 8.5 million

patients showed that 82% of NASH patients were obese, 72% had dyslipidemia, and 44% had type 2 DM.²

The incidence and prevalence of NAFLD in India is comparable to global figures; seen commonly in ages 30 to 50 years; and around 5% of the patients diagnosed with NAFLD would probably have NASH. The common predisposing factor is central obesity and DM; hence, the risk is always higher in people with these co-morbid conditions.⁵ Based on a report by the India state-level disease burden initiative diabetes collaborators, there were 65 million Indians with DM in 2016 and the number is constantly growing, which adds to the burden of liver disease and its morbidity.⁶ So does obesity, a major concern today, which is also on the rise in the Indian population.⁷ Almost 30 to 65% of adult urban Indians are either overweight/obese or have abdominal obesity.⁵

In India, NAFLD is not only a concern for obese or patients with DM, it has been observed that NAFLD can develop in the absence of obesity, which is termed as “lean” NAFLD (i.e. body mass index [BMI] within the ethnic-specific cutoff of 25 kg/m² in Caucasian and 23 kg/m² in Asian subjects).⁸ Lean NAFLD comprises a heterogeneous spectrum of different causes, ranging from environmental causes (such as high fructose and high fat intake), body fat distribution (visceral obesity as opposed to general obesity), body composition (acquired or congenital lipodystrophy, sarcopenia) and genetic risk factors, including rare congenital defects of metabolism such as lysosomal acid lipase deficiency (LAL-D) and familial hypobetalipoprotein B (FHLB). Lean NASH is seen in Asians and more often in Indians due to poverty and malnutrition.^{8,9} In a cohort of subjects with biopsy-proven NAFLD, free of diabetes, obesity, and MetS, the metabolic pattern of insulin resistance in the main target tissues (muscle, liver, and adipose tissue) was similar to that observed in obesity, with adipose tissue insulin resistance playing an important role despite a low BMI and normal subcutaneous fat.⁸ This early finding was further supported by more recent studies, showing higher circulating concentration of free fatty acids (FFA) in lean NAFLD patients compared with healthy controls and a higher portal FFA flow, which may induce intrahepatic fat accumulation.⁸

In a prospective epidemiological study carried out in a rural area of West Bengal, India, NAFLD was identified in 8.7% of the overall population, but 75% of NAFLD subjects belonged to the non-obese group, with an average BMI <18 and fasting blood glucose that is slightly above 100 mg/dl.^{9,10} The non-obese and lean individuals with NAFLD had more visceral fat, higher fasting blood glucose, and higher levels of triglycerides. However, this population also included 47% with malnutrition, which can be associated with NAFLD by a different mechanism (choline deficiency).⁸ This is alarming because NASH can develop in individuals with a low to normal BMI and mild elevations of fasting blood glucose in a population which is seeing a rise in obesity. Indians are also prone to insulin

resistance, which further puts them at risk to develop NAFLD and NASH. Thus, a steep rise in the incidence of these diseases is expected in the future.

NASH DIAGNOSIS AND TREATMENT - AN UNMET NEED

It is evident that there is a huge unmet need in the diagnosis and management of NAFLD and NASH. Despite increasing prevalence rates, NASH is still an under-recognized disease. Increasing awareness of this disease in the general population and among primary care physicians (PCPs) is essential to allow for a structured referral pathway and early detection.

Currently, there are no standard screening recommendations for NAFLD and NASH globally. Routine screening for NAFLD in high-risk patients attending primary care, diabetes or obesity clinics is not recommended by the American association for the study of liver diseases (AASLD) guidelines due to uncertainties surrounding diagnostic tests and treatment options; while the European guidelines allows screening for NAFLD in the population at risk with context of the available resources.^{11,12} In India too, there are no established screening guidelines for NAFLD. As the majority of non-cirrhotic NAFLD and NASH patients are asymptomatic, the diagnosis of fatty liver is usually made based on an incidental finding on ultrasound and/or elevated liver enzymes. Further investigation may reveal the presence of metabolic syndrome such as central obesity, dyslipidemia and diabetes. Mild hepatomegaly can also be an important initial sign on ultrasound. Patients may have normal liver enzymes and remain undiagnosed. Diagnostic modalities are directed to confirm the presence of fatty liver and determine the severity of liver disease.¹³

Conventional ultrasonography is often used as the first modality of choice for screening and detection of hepatic steatosis. Its sensitivity is dependent on the degree of steatosis in the hepatocytes; more than 20% of the liver should be laden with fat to be detectable by ultrasound with a reported sensitivity of 79.7% and specificity of 86.2%.¹⁴ Its accuracy decreases with increasing BMI and being a qualitative exam is considered subjective. Other conventional imaging such as computed tomography (CT) scan and magnetic resonance imaging (MRI) are also used in the diagnosis of liver steatosis. CT scan is more specific than ultrasound and although more sensitive in detecting moderate to advanced steatosis, it cannot provide reliable assessment of mild steatosis. MRI has a better accuracy than ultrasound, as it can detect histologically confirmed steatosis with at least 5% fat content, having a sensitivity and specificity of 76.7-90.0% and 87.1% respectively.¹⁴ MRI-proton density fat fraction (MRI-PDFF) is a more advanced type of MRI which is considered to be the most accurate diagnostic tool in the quantitative assessment of hepatic steatosis.¹⁵ However, these conventional modalities cannot be used in the evaluation of inflammation and fibrosis in NASH.^{14,16} Despite the

limitations of ultrasound, it remains to be the preferred initial imaging modality in India to diagnose fatty liver in clinical practice due to its lack of invasiveness, wider availability and relatively low cost.^{13,14}

Newer technologies such as transient elastography (TE) and Magnetic resonance elastography are non-invasive modalities that provide a quantitative measure of liver stiffness and are useful in the evaluation of liver fibrosis in NASH.¹⁴ However, the accuracy of TE is reduced in obesity and severe steatosis may lead to false positives, and it is also operator dependent.¹⁷ Despite these limitations, based on a study involving patients from Western India, liver stiffness measurement with fibroscan is an effective method for screening patients with NAFLD.¹⁸ magnetic resonance elastography (MRE) has a high diagnostic accuracy in detecting hepatic fibrosis and the results are not dependent on patient demographics. It has also been shown to be able to differentiate NASH from simple steatosis. However, ultrasound-based elastography are preferred due to relative inexpensiveness and ease of use in clinical practice while MRE represents a potentially important non-invasive tool in the accurate identification and quantification of the severity of fibrosis in clinical trials.¹⁵ Table 1 summarizes the non-invasive imaging modalities used in the diagnosis of steatosis, steatohepatitis and presence of fibrosis.

Since TE is available only at specialized private centers in India owing to its high costs, non-invasive scoring systems such as NAFLD fibrosis score (NFS); aspartate aminotransferase (AST) to platelet ratio index (APRI); AST/alanine aminotransferase (ALT) ratio (AAR); and fibrosis-4 (FIB-4) index are used as alternative options.^{18,19} AAR, NFS and FIB-4 are simple noninvasive markers of fibrosis which can be used as screening tools in patients with high risk for fibrosis to determine the need for biopsy while APRI index has a low sensitivity and specificity.^{18,19} Scoring systems using a combination of laboratory tests have the advantage of being readily available and cost-effective. Table 2 summarizes the clinical scores and markers that are being utilized in clinical practice. They are useful in ruling out the presence of advanced fibrosis with negative predictive values >90%. Values greater than the upper cutoff require liver biopsy for confirmation of fibrosis, whereas a score less than the cutoff is likely sufficient to rule out advanced fibrosis and may reduce the need for liver biopsy by 75%.¹⁷ However, these scoring systems are less accurate at detecting early fibrosis and would need further validation particularly in the Asian population.

While liver biopsy remains the gold standard in the diagnosis of NASH, its utility is limited by its invasive nature, procedure-related risks, sampling error, intra and inter-observer variability and cost.¹⁷ Hence it is used mainly in a clinical trial setting. Therefore, a combination of non-invasive diagnostic methods are utilized in clinical practice such as imaging and scoring systems to identify patients with high risk of NASH and advanced fibrosis

where liver biopsy is indicated.²⁰ However, there is no consensus on strategies for use in clinical practice on when liver biopsy can be avoided.¹² Also, repeated liver biopsy is not suitable to monitor disease progression and response to treatment. Hence the need for reliable and validated non-invasive modalities for screening, risk stratification and disease monitoring.²¹

Currently in India there is no established patient pathway for NAFLD. Most patients seen by specialists are generally walk-in patients as patients may have tests done upon request and seek hepatology consult directly only for incidental finding of elevated liver enzymes or fatty liver on ultrasound. Doctor referrals are few and far between as NAFLD is managed in the primary healthcare setting generally with advice on management of weight and diabetes. There is general lack of awareness of NASH and its complications or its long-term consequences among patients and PCPs alike and recommendations given by treating physicians regarding weight loss and healthy lifestyle are interpreted by patients as relatively unimportant since the same advice is being given for other co-morbidities.²²

In a survey done among 250 primary care physicians (PCP), although the association of NAFLD with metabolic syndrome was identified by 91% of PCPs, only 46% screened diabetic obese patients for NAFLD and only 27% of PCPs referred NAFLD patients to a hepatologist for evaluation.²³ Another survey involving 152 PCPs, revealed that almost half of the responding primary care physicians were unfamiliar with the differences between NAFLD and NASH, yet 58% of them were treating these patients.²⁴ PCPs are the primary point of consultation for patients with or at risk of NAFLD and the gap in awareness has a negative impact on optimizing patient care.²⁵

The management of NAFLD and NASH entails an interdisciplinary approach involving PCPs and specialists to facilitate patient identification and ensure appropriate work-up and management. There is currently no established consensus on the optimal management of NASH and no approved pharmacologic therapy; however, being a metabolic disorder, patients are monitored and managed holistically for other abnormalities including obesity, diabetes and dyslipidemia. Targeted treatment options in India consist of the use of either pioglitazone, vitamin E, metformin or ursodeoxycholic acid (UDCA) in patients with histological evidence of NASH.¹³ Thus, there is a huge unmet need for effective treatment options for NASH patients with advanced fibrosis who have the highest rates of liver-related morbidity and mortality.²⁶ In addition, the optimal duration of therapy is unknown and there is no clear evidence to support the frequency of follow-up. It is essential that physicians follow an individualized approach to management of NAFLD and NASH, taking in consideration the patient's co-morbidities, disease severity, availability and costs of diagnostic modalities and treatment options in the local setting as well as patient preference.

CHALLENGES IN THE CONDUCT OF NASH CLINICAL TRIALS IN INDIA

Approximately 5% of NAFLD patients develop end stage liver disease i.e. cirrhosis. Merely 2% decompensate and 98% die due to causes other than liver disease per se.²⁷ Since there is no approved therapy, there is a global surge of clinical trials with drugs targeting lipid metabolism, inflammation and fibrosis.²⁸ Majority of these are large global multicenter trials involving patients from various countries in Europe, North America, South America, Middle East and Asia-Pacific. India has participated in trials on a PPAR agonist and ASK1-inhibitor for NASH. However, India, along with many other countries, has encountered challenges in the conduct of clinical trials in NASH, ranging from the selection of the appropriate patient population and clinically meaningful trial endpoints that will help reduce the placebo response rate to issues related to patient recruitment and retention.^{29,30}

Patient recruitment is a major hurdle in NASH trials. Despite a high prevalence of NAFLD, identifying and recruiting patients with confirmed NASH is a challenge. Most patients with NAFLD are usually asymptomatic, or may present with fatigability, heaviness, and discomfort on the right side of the upper abdomen.⁵ Many may not even be aware of their condition until the later stages of the disease when they develop complications like cirrhosis and HCC.¹⁰ It is, therefore, a challenge to convince asymptomatic patients who feel healthy to participate in a clinical trial that may involve invasive diagnostic procedures for a disease that does not cause any signs and symptoms at the onset. This is a dilemma faced by most countries involved in NASH trials, including India.

Identifying appropriate clinical trial sites is paramount for the successful execution of any clinical trial. For NASH trials, it is important for sites to have a database of patients with NAFLD/NASH as well as dedicated and experienced site staff. It is important to identify sites that have a multidisciplinary approach to management of NAFLD and a robust referral system from PCPs, endocrinologists and gastroenterologists/hepatologists, including other relevant specialties. With referrals and conduct of patient awareness programs, more patients can be identified and referred to specialists for further evaluation, potentially increasing the patient pool. Like in many countries, there is a lack of disease awareness even among PCPs. The initial stages of this condition are usually missed, as one or two laboratory parameters slightly out of range in an asymptomatic patient may be considered as non-significant by the PCP, without further follow up. Since there is no established referral pathway in India to identify these patients, this has resulted in a large number of unrecognized fatty liver patients who are not referred for further specialist management, leading to the underdiagnosis of the disease.^{23,31}

Currently, most trials are designed to identify patients with fibrosis, without cirrhosis. Fibrosis follows a heterogeneous course which makes the identification of

patients that fall into the criteria of fibrosis who may progress and would be the main beneficiaries of efficacious therapy, difficult. As such, therapeutic trials in NASH require liver biopsy to establish the diagnosis of NASH and fibrosis stage at baseline, as well as to confirm treatment response.^{16,32} A second or even a third biopsy is required during and at the end of a trial to assess disease progression and trial endpoints. It may be unreasonable to use only liver biopsy to assess NAFLD and NASH activity since multiple procedures are required during follow-up.³³ Convincing patients to undergo a liver biopsy is challenging, due to the inherent risks associated with an invasive procedure. Moreover, the results from the biopsy will not alter disease management due to lack of specific treatment.¹⁰ This is a major reason for patients' refusal to undergo the procedure in India as in other countries. In addition, the procedure has a risk of sampling errors where required histological parameters may not be present in the sample leading to rejection. In global multicentric clinical trials, investigators, including those from India, have experienced issues with discordance between local and central reader in the interpretations of the primary biopsy and between pre and post biopsy samples resulting in screen failures.³³ This many have a negative impact on site engagement and, consequently, enrolment rates. The effect of intra- and inter-rater variability in the assessment of liver biopsies is quite considerable. In a study comparing pioglitazone, vitamin E and placebo on histologic improvement in NASH patients, 17-26% of subjects failed to meet entry criteria based on central review of independent sections from the baseline biopsy used for the final analysis.³²

Non-invasive biomarkers are available such as APRI, FIB-4 and NFS and used widely. These biomarkers can be leveraged to potentially reduce the high percentage of screen failures due to liver biopsy by selecting patients who would likely yield positive biopsy results. However, these biomarkers have their own limitations. Further analysis is needed to evaluate whether its diagnostic performance may be affected by some clinical factors and concomitant drugs.³⁴ A strategy is to combine at least 2 non-invasive biomarkers (one imaging method such as transient elastography) to pre-screen subjects to better predict those that are likely suitable for a NASH clinical study.

Ultrasound is routinely used for the diagnosis and monitoring of fatty liver and is widely used in India where large populations can be screened easily. Recent advances in technology have produced newer and better imaging modalities for assessing fatty liver and fibrosis such as magnetic resonance imaging derived proton density fat fraction (MRI-PDFF) and MR elastography, respectively. These non-invasive modalities provide a quantitative and accurate measure of liver fat content and fibrosis stage to assess treatment response in early-phase NASH trials.^{15,16} However, in both developed and developing nations, sites struggle to adopt new technologies primarily due to its prohibitive cost and lack of reimbursements for these procedures. Due to these limitations, the newer diagnostic

modalities have not been incorporated fully in India in the clinical practice setting but are available at specialized centers for use in clinical trials.

The heterogeneous course of NAFLD/NASH affects trial outcomes where the true effect of the drug may not be apparent due to a spontaneous regression in the placebo arm. This placebo response is approximately 19% and likely related to the effect of lifestyle intervention in the control arms.³⁵ A patient-related factor known as the “Hawthorne effect”, where the knowledge that one is being observed, or simply participating in a clinical trial alters behavior. This effect is especially relevant in NAFLD where lifestyle change can significantly affect the underlying disease.²⁹ The placebo response can also be significantly affected by study design. This relates to trial entry criteria, particularly the histological severity threshold for enrolment, and the stringency of the efficacy endpoint adopted. Most studies specify a minimum NASH grade and fibrosis stage for trial entry. Past trials provide valuable lessons demonstrating that the permissiveness of inclusion criteria can influence trial outcomes, largely by increasing the placebo response rate. Adopting a more stringent endpoint definition for NASH resolution may reduce the placebo response rate.²⁹ Although most trials have focused on monotherapy, combination therapies may be the way forward as various drugs use different pathways. The current treatment regimens in clinical trials are using monotherapy, however, combination therapy may be the future to treat NASH that may be directed toward improving hepatic steatosis, inflammation, liver cell injury, and fibrosis.³⁶

Based on prior experience in NASH clinical trials, targeting the correct patient population as well as selecting meaningful study endpoints for each clinical trial phase may help address the issues. A clinical trial may be designed to include NASH subjects with F2/F3 fibrosis to demonstrate no worsening/regression of steatohepatitis and fibrosis. Currently, an improvement in fibrosis by one stage is considered an acceptable endpoint, However, as more evidence accumulates, this may need to be revised,

and a more rigorous standard such as improvement in fibrosis by at least two stages would increase specificity and minimize the placebo effect.²⁹ Patients with compensated cirrhosis may also be targeted with liver-related outcome endpoints to demonstrate no progression to decompensation, HCC or death with the use of the study drug. Other meaningful endpoints include rates of hospitalization, unscheduled clinic and emergency room visits, tests performed, and lost work days, and together with an endpoint measuring a clinically meaningful change in health status, it may provide a more comprehensive picture of an intervention’s potential benefit.³⁰ In addition, studies of longer duration may help to assess long term safety, durability, and benefits of various interventions on not just liver-related but cardiovascular and metabolic outcomes, which strongly contribute to the disease burden of NASH.³⁵ However, in the cirrhotic population, large sample sizes or long trials will be required to demonstrate statistically significant differences in rates of development of the events of interest in a reasonable timeframe. These timeframes may be potentially reduced if the treatment effect is large or by limiting the patient population to include patients with a hepatic venous pressure gradient (HVPG) >10 mm Hg or a MELD score >10.³⁷ In the context of pivotal trials for NASH, safety-related endpoints in the form of measures of cardiovascular health, such as the fasting lipid profile including small density LDL and HDL subclass, carotid intimal thickness and markers of systemic and vascular inflammation e.g. c reactive protein, can be measured to provide reassurance that there are no potential safety issues.³² Different trial endpoints can also be utilized in early phase studies; regulatory authorities recognize this option and have allowed the utilization of non-invasive tools for diagnosis and outcomes. Based on evidence confirming the association of surrogate histologic and clinical endpoints and clinical outcomes, the US food and drug administration has established regulatory pathways which incorporate non-invasive, clinical and histologic endpoints, for phase 2 and 3 clinical development, with the expectation for post-marketing clinical outcome evaluation in phase 4 studies.²⁸

Table 1: Non-invasive imaging modalities in the diagnosis of NAFLD.

| Diagnosis of steatosis | Sensitivity (%) | Specificity (%) | Comments |
|--|--------------------|--------------------|---|
| Conventional ultrasonography | 79.7 ¹⁴ | 86.2 ¹⁴ | Sensitivity is dependent on the degree of steatosis [$>20\%$ of the liver should be laden with fat to be detectable] ¹⁴ Limitations: qualitative/subjective, accuracy decrease with increasing BMI, cannot differentiate steatosis and steatohepatitis or stage of fibrosis ¹⁴ |
| Unenhanced computed tomography (CT) | 73 ¹⁴ | 100 ¹⁴ | In the presence of $\geq 30\%$ macrovesicular steatosis at a cutoff attenuation value of 42 HU ¹⁴ It is sensitive for detecting moderate to advanced steatosis and limited accuracy for mild steatosis ¹⁴ Unenhanced CT scans are usually preferred to avoid the potential errors in contrast-enhanced CT caused by variations in liver attenuation related to contrast injection methods and scan timing ³⁸ |

Continued.

| Diagnosis of steatosis | Sensitivity (%) | Specificity (%) | Comments |
|--|---|---|---|
| Contrast-enhanced CT | 54-93 ¹⁴ | 87-93 ¹⁴ | Accuracy is confounded by variability in contrast-enhanced CT protocols and timing differences related to peripheral injection site variation ¹⁴ |
| Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) | 76.7-90.0 ¹⁴ | 87.1-91 ¹⁴ | Most definitive imaging tool to qualitatively and quantitatively evaluate hepatic steatosis ¹⁴ It can detect histologically confirmed steatosis with at least 5% fat content ¹⁴ MRI based PDFF assessments had a high diagnostic accuracy for differentiating between the presence (≥1 NASH-CRN grade) or absence (0 NASH-CRN grade) of hepatic steatosis ¹⁵ |
| Magnetic resonance spectroscopy (MRS) | 80.0-91.0 ³⁸ | 80.2-87.0 ³⁸ | MRS and MRI can evaluate hepatic steatosis in an objective manner using the quantitative index (i.e. PDFF) ³⁸ |
| Diagnosis of steatosis and fibrosis | | | |
| Transient elastography | Steatosis: 82 Fibrosis: 91 (for F≥3 at a cut-off value of 7.9 kPa) ¹⁴ | Steatosis: 91 Fibrosis: 75 (for F≥3 at a cut-off value of 7.9 kPa) ¹⁴ | Obesity is a significant cause of technical failure and unreliable measurements ¹⁴ |
| Magnetic resonance elastography | Steatosis | Steatosis | MRE has a higher diagnostic accuracy compared to ultrasound-based techniques |
| | 94 (cut-off of 2.74 kPa, AUROC 0.93) | 73 (at a cut-off of 2.74 kPa, AUROC 0.93) | It may have a high diagnostic accuracy for differentiating NASH from simple steatosis |
| | Fibrosis | Fibrosis | It has a high diagnostic accuracy for identifying advanced fibrosis ¹⁵ |
| | 92 (cut-off of 3.64, AUROC 0.957) ¹⁵ | 90 (cut-off of 3.64 kPa, AUROC 0.957) ¹⁵ | |

Table 2: Clinical scores for detecting advanced fibrosis in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

| NAFLD score | Sensitivity (%) | Specificity (%) | Positive predictive value (PPV) | Negative predictive value (NPV) | Components | Comments |
|--|------------------|------------------|---------------------------------|---------------------------------|---|--|
| FIB4 index | Low cutoff | Low cutoff | Low cutoff | Low cutoff | Age, platelet count, AST and ALT levels ³⁹ | Highest AUROC for predicting advanced fibrosis (0.80-0.86) compared to AST/ALT ratio, BARD score and NFS ³⁹ |
| | 85, high cutoff | 65, high cutoff | 36, high cutoff | 95, high cutoff | | Appears to be one of the most useful non-invasive test for diagnosing advanced fibrosis in NAFLD ⁴⁰ |
| | 26 ¹⁷ | 98 ¹⁷ | 75 ¹⁷ | 85 ¹⁷ | | Low cutoff of <1.30; high cutoff >3.25 ¹⁷ |
| Nonalcoholic fatty liver disease fibrosis score (NFS) | Low cutoff | Low cutoff | Low cutoff | Low cutoff | Age, hyperglycemia, BMI, platelet count, albumin level, AST/ALT ratio ³⁹ | Score less than -1.455 predicts absence of fibrosis, while score greater than 0.675 predicts the presence of advanced fibrosis ³⁹ |
| | 78, high cutoff | 58, high cutoff | 30, high cutoff | 92, high cutoff | | |
| | 33 ¹⁷ | 98 ¹⁷ | 79 ¹⁷ | 86 ¹⁷ | | High AUROC of 0.85 (95% CI, 0.81-0.90) ³⁹ |

Continued.

| NAFLD score | Sensitivity (%) | Specificity (%) | Positive predictive value (PPV) | Negative predictive value (NPV) | Components | Comments |
|---|--|--|--|--|---|---|
| | | | | | | Disadvantage: large percentage of patients fall in the indeterminate category ³⁹ low cut off less than -1.455; high cut off >0.676 ¹⁷ |
| Enhanced liver fibrosis panel (ELF) | Low cutoff 89, high cutoff 78 ¹⁷ | Low cutoff 96, high cutoff 98 ¹⁷ | Low cutoff 80, high cutoff 87 ¹⁷ | Low cutoff 98, high cutoff 96 ¹⁷ | Hyaluronic acid, tissue inhibitor of metalloproteinase 1, and amino-terminal propeptide of type III procollagen ¹⁷ | Good predictor of clinical outcomes (liver-related morbidity and mortality) in a group of patients with CLD ³⁹ Excellent at detecting advanced fibrosis with an AUROC of 0.90 (95% CI, 0.84-0.96) ³⁹ In combination with NFS results in an AUROC of 0.93 for moderate fibrosis and 0.98 for severe fibrosis ⁴⁰ Low cutoff 0.375; high cutoff >0.462 ¹⁷ |
| Fibro test | Low cutoff 77, high cutoff 15 ¹⁷ | Low cutoff 77, high cutoff 98 ¹⁷ | Low cutoff 54, high cutoff 73 ¹⁷ | Low cutoff 90, high cutoff 76 ¹⁷ | Haptoglobin, α2-macroglobulin, apolipoprotein A1, total bilirubin, GGT ³⁹ | Can reliably predict advanced fibrosis with an AUROC of 0.88 (95% CI, 0.82-0.92) ³⁹ Low cutoff 30; high cutoff 70 ¹⁷ |
| BMI, AST/ALT ratio and diabetes score (BARD) | 89 ¹⁷ | 44 ¹⁷ | 27-42 ¹⁷ | 96 ¹⁷ | BMI, AST:ALT, diabetes ⁴⁰ | AUROC ranging from 0.70-0.77 ³⁹ High negative predictive value ³⁹ |
| Steato test | 90 ¹⁷ | 90 ¹⁷ | 63 ¹⁷ | 93 ¹⁷ | Age, sex, BMI, fasting glucose, cholesterol, triglycerides, ALT, bilirubin, GGT, haptoglobin, α2 macroglobulin, apolipoprotein A1 ¹⁷ | Low cutoff <0.30; high cutoff >0.72 ¹⁷ |
| AST:ALT ratio (AAR) | Low cutoff 74, high cutoff 52 ^{17,40} | Low cutoff 78, high cutoff 90 ^{17,40} | Low cutoff 44, high cutoff 55 ^{17,40} | Low cutoff 93, high cutoff 89 ^{17,40} | AST:ALT ¹⁷ | AUROC of 0.83 (CI, 0.74-0.91) ^{17,40} Reasonably accurate alone but its accuracy is enhanced when combined with other clinical and biochemical features and as a result incorporated into other non-invasive scores ⁴⁰ Low cutoff <0.80; high cutoff >1.0 ¹⁷ |
| APRI | 27 ¹⁷ | 89 ¹⁷ | 37 ¹⁷ | 84 ¹⁷ | AST: platelets ¹⁷ | AUROC of 0.67 (CI, 0.58-0.8) ¹⁷ |

CONCLUSION

The rise in obesity and other lifestyle-related diseases has resulted in a significant increase in the number of NAFLD/NASH patients; however, physicians still face

many challenges in managing the disease, the most basic of which is the lack of awareness of the disease and its sequelae. The lack of established guidelines in the diagnosis and management of NAFLD/NASH is likewise a critical issue that needs to be addressed, as well as the limited treatment options with no approved medications

for this disease. Conducting well designed clinical trials with meaningful endpoints and less invasive procedures will accelerate the development of potentially efficacious treatments for NASH. Measures to improve the NAFLD/NASH clinical trial environment are imperative in order to respond to the need for more available approved therapeutic options to manage the disease.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Pooja Hingorani for her assistance and expert advice on the preparation of the paper. The authors would also like to thank Dr. Mark Delegee for his expertise and valuable insights on the NASH clinical trial environment.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Ang ELR, Sison MCM, Ghaisas SM, Cama RC, et al. Nonalcoholic steatohepatitis: diagnosis, management and challenges in clinical trials: an Indian perspective. *Int J Clin Trials* 2021;8(1):92-100.