Diagnostic Modalities for Non-alcoholic Fatty Liver Disease (NAFLD), Non-alcoholic Steatohepatitis (NASH) and Associated Fibrosis

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What Are the Best Diagnostic Modalities for Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis and Associated Fibrosis? A Summary of AALSD Trend Conference in NASH (154/120)

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Abbreviations:

AFL: alcoholic fatty liver
NAFL: non-alcoholic fatty liver
NAFLD: non-alcoholic fatty liver disease
NASH: non-alcoholic steatohepatitis
AUROC: area under the curve
AASLD: American Association for the Study of Liver Diseases
ELF: enhanced liver fibrosis
HCC: hepatocellular carcinoma
PRO's: patient reported outcomes
NIH NASH CRN: National Institute of Health non-alcoholic steatohepatitis Clinical Research Network
Abstract (284/275)

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum that ranges from isolated steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis. The majority of subject with NAFLD don’t have underlying NASH without significant risk for adverse liver-related outcomes. The prevalence of NAFLD is about 24% with a gradient of high to low rates from Urban areas to rural of some of the Asian countries. Although relatively dynamic, patients with NASH are at risk for progressive liver disease and those with significant fibrosis are at the highest risk of mortality. Given the enormous prevalence of NAFLD, the clinical, economic and patient experience related burden of NAFLD and NASH can be enormous. The diagnosis of NASH is plagued with suboptimal modalities. Although liver biopsy is the most accurate modality to establish the diagnosis and stage of NASH, it suffers from being invasive and from observer variability in the pathologic interpretation of pathologic features of NASH. A number of approaches have been undertaken to non-invasively diagnose and establish the stage of NASH. These include predictive models such as NAFLD fibrosis score as well as “wet and dry biomarkers”. Serum based biomarkers such ELF have been utilized to establish stage of fibrosis in NASH. Radiologic-based technologies such as transient elastography or MR elastography have been used to estimate significant fibrosis in NASH. Although quite dynamic field research, it seems that most modalities have AUROC between 0.76 to 0.90 %. In this context, MRE may have the best predictive performance for NASH. The issue of accurate diagnostic modalities in NAFLD is of utmost importance. Not only are these modalities important to risk stratify subjects for progressive liver disease but also to be used as endpoints of therapeutic clinical trials.

Key words: predictive models, noninvasive, biomarkers, imaging
Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Based on a recent meta-analysis, 25% of the general adult population in the world are potentially affected by NAFLD. [1] NAFLD seems to be more prevalent among males and Hispanics. [1]. Although very common in adults, the prevalence of NAFLD in children is also high and estimated to be around 10%. Similar to adults, NAFLD is most common in highest rates in Hispanic boys [2,3]. The data on the incidence of NAFLD are quite sparse. In fact, studies conducted in Israel and Asia have estimated NAFLD incidence to be between 28 to 52/1000 person-years, respectively [1]. These rates are probably higher, given the rising incidence of obesity and diabetes in adult population. Long long-term studies have suggested that most patients with NAFLD die primarily of cardiovascular complications [4-6]. Nevertheless, there is subgroup of subjects with NAFLD, primarily those with histologic NASH, and those with significant fibrosis who were at risk of developing advanced liver disease, hepatocellular carcinoma (HCC) and excess liver-mortality, and candidacy for liver transplantation (7-14). In addition to the clinical burden, NASH places significant burden on patient reported outcomes (PROs) and the economy [15-19]. A recent Decision Analytic Morkov Model estimated tremendous economic burden of NAFLD and NASH to the US and European economies (20). These data provide strong evidence that the progressive form of NAFLD or NASH, especially those with significant fibrosis pose tremendous clinical, PRO and economic burden to the subjects and the society. In this context, two steps are important to deal with this important cause of liver disease. First, development of accurate, non-invasive, simple and inexpensive modalities to diagnose the potentially progressive form of NAFLD and enable clinicians to risk stratify these patients. Second, effective prevention strategies, or treatment regimens must be developed to manage the most progressive form of NAFLD. In this manuscripts, we will present the review of the literature and expert opinion about the state of diagnostic modality for NASH and fibrosis presented at a recent AASLD Trend Conference on NASH.
Role of Histopathology in the Clinical Research and Management of Patients With NAFLD (Figures 1-4)

The liver biopsy is the definitive technique for the diagnosis and classification of NAFLD in which the role of histopathology is to establish a diagnosis, characterize the lesions, and correlate the lesions with clinical outcome in the context of the natural history of the disease. (21-26) Historically, the terminology and concepts of the histopathologic features of NAFLD were derived from alcoholic liver disease. Thus, alcoholic fatty liver (AFL) is analogous to simple steatosis (NAFL), alcoholic hepatitis to nonalcoholic steatohepatitis (NASH), and alcoholic cirrhosis to the cirrhotic stage of NAFLD. Although there may be differences in degree, the features are sufficiently similar to preclude an etiologic diagnosis based on histology alone. Therefore, the characteristic histopathologic features which are investigated when diagnosing AFL or NAFL include: 1). Fat – hepatocellular triglyceride accumulation, 2). Hepatocellular injury in the centrilobular location which is most severe in the acinar zone, 3). Cytoskeletal damage shown as hepatocellular ballooning with or without Mallory-Denk bodies, 4). Parenchymal inflammation where lymphocytes and macrophages predominate, though neutrophils may be present in severe cases, and 5). Perisinusoidal fibrosis seen as collagen deposition in the space of Disse. (Figure 1)

As an aid to help characterize these lesions and allow for statistical analysis in clinical trials, the pathologists of the National Institute of Health NASH Committee (NIH NASH CRN) devised a grading system called the NAFLD Activity Score (NAS). (27) (Figures 2 and 3) After studying the inter- and intra-observer variability of a variety of histologic features, the features with the greatest reproducibility (severity of steatosis, hepatocellular ballooning, and lobular inflammation) were chosen to formulate the NAS score. The NAS system then assigns a numerical grade to each feature such that the severity of steatosis is graded from zero to three (0 to 3), hepatocellular ballooning is graded from zero to two (0 to 2), and lobular inflammation is
graded from zero to three (0 to 3). The NAS score is the unweighted sum of these three numbers with a range from zero to eight (0 to 8). Improvement in histologic severity is accompanied by a decrease in the NAS. (27)

However, the histologic feature with the greatest reproducibility was found to be fibrosis, a feature which is not part of the NAS score because fibrosis is considered a sign of the stage of disease rather than a grade of injury. Fibrosis staging is, therefore, scored separately. Accordingly, the NASH CRN system is used to grade fibrosis where stage 0 = no fibrosis; stage 1 = centrilobular pericellular fibrosis; stage 2 = centrilobular and periportal fibrosis; stage 3 = bridging fibrosis; and stage 4 = cirrhosis. (5,11) (Figure 4)

As a result of this histologic work done on NAFLD, the natural history of the various lesions associated with NAFLD are gradually being elucidated. For example, fatty liver, alone or with some lobular inflammation but without evidence of cytoskeletal damage (ballooning or Mallory-Denk bodies) or fibrosis, has long been considered a benign, non-progressive disease; however, recent follow-up studies, have found that some patients do, in fact, eventually develop fibrosis and even cirrhosis. (28) Another example, NASH with ballooning ± Mallory-Denk bodies, was long thought to be the progressive form of NAFLD; however, recent long-term follow-up studies have found that the single histologic feature that predicted mortality was not NASH but fibrosis in the liver biopsy. (5,11,28) Furthermore, studies of NAFLD patients with paired biopsies found that spontaneous regression of fibrosis may be as common as fibrosis progression, both in the long-term and short-term.

Liver biopsies are considered the gold standard for diagnosing NAFLD and its progression. Through a collaborative effort with NIH NASH CRN, two scoring systems were developed to grade the level of liver injury associated with NAFLD (NAS) and stage the level of disease associated with NAFLD- fibrosis score. As such, the use of histology in diagnosing NAFLD has
allowed a more in-depth understanding of the natural history of the various NAFLD histologic lesions, but more information is still needed on the mechanisms of fibrosis progression and development of cirrhosis in patients with NAFLD.

**The Role Radiologic Modalities for Diagnosing, Staging and Monitoring NASH (figure 5-8)**

Though, liver biopsy is the gold standard to diagnose NASH and assess the stage of fibrosis in patients with NAFLD, it has many limitations including cost, sampling error, complications leading to morbidity, and though rare, death. [29] However, when a clinician sees a patient for the first time with suspected NAFLD he/she would like to know the following: 1) Whether the patient has NAFLD, 2) Whether the patient is likely to have underlying NASH, 3) Whether the patient has any fibrosis, 4) Whether the patient has any advanced fibrosis? As a result there is an urgent need for an accurate non-invasive diagnostic modalities for the diagnosis and staging of NAFLD and NASH. [30]

In the context of NAFLD, the first challenge is to accurately show presence of fat in the liver which 33% of fat is thought to be the optimal level for detecting hepatic steatosis (11,29-34). In fact, fat is thought to have its own chemical signature which can be detected directly by magnetic resonance spectroscopy (MRS). When performed properly, MRS quantifies the proton density fat fraction (PDFF), a standardized measure of liver tissue [TG]. However, the limitations of MRS include: restricted coverage, need for expertise in protocol prescription, data collection and spectral analysis is required, while MRS is not available on routine scanners. (11-32-35). Like conventional in-phase and opposed-phase, MRI- Proton Density Fat Fraction (PDFF), addresses confounding factors and is not affected by scanner field strength, patient factors ( age, sex, BMI, etiology of liver disease) and concomitant liver abnormalities such as iron overload or necroinflammation. (11,32-35) (**Figure 8**)
In contrast, fibrosis has no molecular signature that can be detected by current imaging techniques so all imaging tests for fibrosis attempt to detect fibrosis indirectly using proposed biomarkers which include: stiffness, diffusion, perfusion, metabolites, and image texture. However, the leading biomarker is liver “stiffness” (or “elasticity”) and its family of related parameters. The rationale for using “stiffness” or “elasticity” is that the collagen deposition associated with fibrosis imparts parenchymal rigidity which on imaging tests is considered assessing “stiffness” or “elastography”. (36-40)

The most accurate noninvasive methods which assess the stiffness of the liver and dichotomizes the patient into advanced versus non-advanced fibrosis include Fibroscan, Magnetic Resonance Elastography (MRE) and emerging techniques such as Shear Wave Elastography and Acoustic Radiation Force Imaging. [35-43] (Figures 5,6,7)

MRE sensitivity has been shown when using a “stiffness” cutoff of 3.63 kPa had a sensitivity of 0.86 (95% confidence interval [CI]: 0.65-0.97), a specificity of 0.91 (95% CI: 0.83-0.96), a positive predictive value of 0.68 (95% CI: 0.48-0.84), and a negative predictive value of 0.97 (95% CI: 0.91-0.99) with an area under the curve (AUC) of advanced of 0.924 for diagnosing advanced fibrosis. (Figure) (44) In addition, the use of 3D MRE has shown that at 40Hz and a “stiffness” cutoff of 2.43 an AUC of 0.962 for diagnosing advanced fibrosis. (17) In fact, in a recent study comparing ultrasound based versus MRE-based NAFLD fibrosis assessment, MRE was significantly better (43) (Figure) Further, MRE was significantly better than TE when diagnosing advanced fibrosis.[43]

Though transient elastography or other ultrasound-based tests are more accessible and easier to use, they are limited when used in patients with obesity, ascites, acute inflammation, or cirrhosis. However, even though, the 3D MRE is able to overcome all these issues except for iron overload or acute inflammation, it is limited by the having restricted accessibility at many
centers and the required expertise needed to obtain adequate tests. So, as of now, accurate imaging is a trade off between specificity, accessibility, and ease of use such that as specificity goes up accessibility and ease go down. Further research is needed to quantify the exact trade off that occurs when one imaging technique is traded off for the other.

**Noninvasive Biomarkers in NASH**

In addition to the non-invasive tests based on the imaging modalities, there is an attempt to define non-invasive biomarkers using predictive models or serum biomarkers. These non-invasive markers include those that are based on alanine aminotransferase levels, those that include components of metabolic syndrome, measuring circulating keratin18 fragment levels as well as tests based on soluble markers such as Fibrometer, microRNA panels, and lipidomic panels. [30,31,42-45]

Using these non-invasive tests to diagnose for NASH current studies have found that the frequency of NASH in individuals with normal ALT (<35 U/L) was 11% whereas the frequency was 29% in those with elevated ALT (≥35 U/L) and if the ALT was two times the upper limit of normal (>70 U/L), predicting NASH was found to have a 50% sensitivity and 61% specificity for NASH. Another study found that individuals with NAFLD can have normal ALT levels as the disease progresses (30)

Feldstein et al., in their seminal work, found that circulating levels of keratin-18 fragments were predictors of NASH in patients with NAFLD.[46] Since the release of their observations, there has been intense investigations which have unequivocally found that increased circulating levels of keratin 18 fragments are associated with NASH. However, at the same time, there are a number of issues with this diagnostic method (lack of a commercially available clinical test, the ability for the results to be reproducible and a lack of a clear cut-off point) which limit its clinical utility at the present time.
Other have looked into combining these different measures to diagnose NASH. The NASH Test, combines demographic characteristics (age, gender, and BMI) with serum parameters (aminotransferases and lipids), and with alpha-2 macroglobulin, ApoA1, and haptoglobin. The NASH Test sensitivity is 33 %, and its specificity is 94% indicating it has a good negative predictive value (NPV) for NASH (81%) [47]. Another combined test, The NASH Diagnostics Panel, which uses the presence of CK-18 fragments, adiponectin, and resistin initially performed well but in a larger study was not found to be as effective. [48]. The NAFLD Diagnostic Panel, used CK-18 fragments in combination with the presence of type II diabetes mellitus, triglycerides, and gender, but it did not perform any better than the NASH Diagnostics Panel [49]. Several prognostic scores (Palekar score, Shimada index, Nice model, Gholam’s model), have also been develop with all performed somewhat similarly with AUROC ranging from 0.76 to 0.90 [50-52].

Metabolic syndrome is another commonly used index to identify individuals with NAFLD at risk for NASH. Several studies have found a significant relationship between the increasing number of metabolic syndrome components and the likelihood of NASH in patients with NASH.(13) Yet, what has not been explored is the combination of metabolic syndrome, levels of ALT and age to predict NASH in NAFLD leaving another area of further exploration.

With these continuing challenges in correctly diagnosing NASH, the NAFLD scientific community needs to reevaluate the need for predicting NASH in patients with NAFLD. Should we instead focus on NASH with stage ≥2 fibrosis as it is the sub-phenotype that is primarily targeted in Phase 2B and Phase 3 clinical trials?

Serum Fibrosis Markers in Non-alcoholic Steatohepatitis (9-14)

Since stage of fibrosis is the most important predictor of outcome, a great deal of effort has focused on determining presence of fibrosis. In this context, NAFLD biomarkers have been
codified within three FDA BEST biomarker target domains: 1) Diagnostic Markers reflect current stage of fibrosis; 2) Prognostic Markers stratify individuals by fibrosis progression risk, discriminating fast vs. slow progressors and/or predicting long-term outcomes and hard endpoints; and 3) Monitoring Markers used to track disease progression or treatment response. Such biomarkers may be at one of four qualification levels: 1) Exploration (early-phase experimental biomarkers), 2) Demonstration (“probable valid” biomarkers), 3) Characterisation (“known valid” biomarkers), and 4) Surrogacy (registerable “surrogate endpoint”). (Figure 9)

Although there has been some progress in biomarker development for detection of advanced fibrosis, existing biomarkers are generally at the first two qualification levels and need validation. Therefore, serological markers for the evaluation of liver fibrosis are divided into ‘indirect’ markers (that reflect alterations in hepatic function but not collagen turnover, e.g. platelet levels) and ‘direct’ markers [associated with extracellular matrix (ECM)] deposition and turnover).

[53,54]

Indirect Markers and ‘Simple Panels’

Significant hepatic fibrosis can lead to hepatocellular dysfunction and portal hypertension, which are reflected by changes in standard biochemical and haematological parameters. These tests, alone or combined as ‘simple panels’, are potentially attractive clinical tools as they are inexpensive and many indices are already routinely measured in patients with liver disease. [54] The results of a head-to-head comparison in a large cohort with biopsy-proven NAFLD patients have been published 4. In general, simple panels have relatively robust NPV and so can reliably exclude advanced fibrosis but have poor positive predictive value (PPV) (ranging from 27-79%). [55] Although, these tests are unreliable at diagnosing advanced fibrosis they do have the potential to help with the triage of patients by reliably excluding advanced fibrosis. Using such tests may help to mitigate the healthcare burden such a large ‘at risk’ population places on
resources by not allowing those considered ‘low-risk’ scores to not have to undergo further investigation. (Figure 11)

In some cases, advancing fibrosis serum ALT falls whereas AST remains stable or increases. The consequent increase in the AST/ALT ratio is a component of many of the simple panels. The NAFLD Fibrosis Score (NFS) is calculated using six routinely measured parameters found to be independently associated with advanced fibrosis on multivariate analysis. By applying a low cut-off (<-1.455), advanced fibrosis can be excluded with high accuracy (NPV 93%) whilst a high cut-off threshold (>0.676) offers accurate detection of advanced fibrosis (PPV 90%). [56] Use of this score has been suggested to reduce the need for liver biopsy by ~75%. This score has been independently validated and although the formula appears daunting, calculation can be performed using a simple online calculator (www.nafldscore.com).

The FIB4 Score is one of the best performing simple non-invasive tests for advanced fibrosis in NAFLD. A score of <1.3 has a 90% NPV for stage 3-4 fibrosis, whilst a score of >2.67 had an 80% PPV with only a quarter of the cohort being unclassified 1.3 or above 2.67. [57] Other studies have also found that the FIB-4 score narrowly outperforms other simple non-invasive tests in predicting advanced fibrosis. [55] The specificity for advanced fibrosis using the FIB-4 and NFS declines with age, becoming unacceptably low however age-adjusted lower cut-offs (NFS <0.12 and FIB4 <2) have been derived to exclude advanced fibrosis in those aged ≥65-years. [58]

**Direct Markers: Collagen Turnover**

As a result of repeated injury to the liver, liver regeneration eventually fails and hepatocytes are replaced by an ECM composed of collagens (I, III, and IV), fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans 3. Candidate biomarkers deriving from these processes are appealing targets and so this is an area of active research.[59,60] (Figure 12)
One such biomarker is Hyaluronic acid (HA). HA production is increased when collagen synthesis is accelerated so is a marker of the increased ECM production. Similarly, liver fibrosis results in the deposition of collagen and release of pro-peptides, predominantly Pro-Collagen III (PIIINP). The terminal peptide of PIIINP correlates with the NAFLD activity score (NAS), and its constituent components (P<0.001). A threshold of 6.6 ng/mL gave a NPV for advanced fibrosis of 95%-97% and 100% for cirrhosis. [59]. The Enhanced Liver Fibrosis (ELF®) test is a commercial panel of markers focusing on matrix turnover that comprises tissue inhibitor of matrix metalloproteinase 1 (TIMP 1), hyaluronic acid (HA), and aminoterminal peptide of procollagen III (P3NP). [61] When compared with the NAFLD fibrosis score this test performed only marginally better for severe fibrosis (AUROC 0.93 vs 0.89) and moderate fibrosis (AUROC 0.90 vs 0.86), but combining the two enhanced efficacy (AUROC 0.98 for severe fibrosis and 0.93 for moderate fibrosis). [62] Fibrotest® 11 is another commercial panel, with a reported AUROC of 0.75-0.86 for F2-F4 and 0.81-0.92 for F3-F4. Other commercial assays in development detect pathologically modified proteins generated by specific proteases. Specific collagen fragments such as Pro-C3 and Pro-C6 may be detected using proprietary Protein Fingerprint™ ELISA assays and have thus far provided promising results. [63]

Other Promising Experimental Markers (Genetics/Epigenetics, Metabolomics, Lipidomics)

Inter-patient variation in NAFLD progression risk is, at least in part, determined by genetic modifiers that influence individual response to environmental (diet, lifestyle) factors. Mounting evidence indicates that epigenetic factors such as differential DNA methylation and circulating cell-free DNA methylation signatures in plasma, may potentially stratify patients with NAFLD into mild versus severe fibrosis. [64,65] (Figure 13) MicroRNA (miRNA) is another genetic marker that appears to be relatively stable and can be detected in plasma following release from injured tissue and may serve as another disease biomarker. [66,67] (Figure 14)
Dysregulation of liver lipid metabolism is central to the development of NAFLD and may also offer the potential for development of novel biomarkers. This is exemplified by a metabolomics/lipidomic approaches that can distinguish between NAFL and NASH. Other plasma-based lipidomic biomarkers that identify and potentially stage hepatic fibrosis have been developed with algorithms to discriminate between F0 vs. F1-4 (AUROC 0.92±0.02) and between early vs. advanced fibrosis (AUROC 0.89±0.03). These, like the majority of the direct markers discussed above, require further validation before they are likely to be widely used in routine clinical practice.

**Summary:**

Over the last forty years, NAFLD has evolved from an unrecognized entity or to a heterogeneous collection of overlapping liver disease with a common phenotype of having hepatic steatosis. Although NAFLD is quite common, nearly affecting about 25% of the world’s adult population, it is increasingly clear that subjects with NASH and especially those with significant fibrosis are at greatest risks for excess mortality and adverse clinical outcomes as well as impairment of PRO and significant economic burden.

However, despite the growing recognition of this important burden, there are significant challenges to accurately and non-invasively diagnose the progressive form of NAFLD. Although liver biopsy is considered the current imperfect “gold” standard for diagnosing NASH and staging fibrosis, it is an invasive procedure with some variability in assessment of key feature of NASH. In fact, in 2017, the regulatory bodies requires histologic endpoints for approval of drugs and diagnostic modalities. Nevertheless, a number of serum markers, radiographic modalities, and noninvasive predictive algorithms have been investigated. Most of these modalities suffer from suboptimal performance. In this context, MRI-PDFF seems to be the most accurate modality for detecting hepatic fat. In contrast, MRE seems to be the most accurate test for
staging liver disease. The combination of MRI-PDFF and MRE can provide a relatively accurate method to risk stratify subjects with NAFLD. On the other hand, availability of these modalities present a major challenge to most clinical practices.
References


52. Younossi 2017


