# Fatty Liver Syndrome

Subjects: Gastroenterology & Hepatology
Contributor: Ma Ai Thanda Han

Fatty liver syndrome is an emerging health problem in the world, due to the high prevalence of obesity and alcohol use disorder. Given the nature of the disease's advancement to cirrhosis and liver-related complications, it is important to assess the severity of the disease, which is typically done via a liver biopsy. Due to the limitations and risks of liver biopsy, the role of noninvasive tests is essential and evolving to stratify the stage of the liver disease, predict the outcomes, and/or monitor the treatment response. This review is focused on noninvasive tests, including the use of serum-based biomarkers, ultrasound-based shear wave elastography, transient elastography, and magnetic resonance elastography in both clinical and research settings

Keywords: non-alcoholic fatty liver disease ; alcoholic liver disease ; hepatic fibrosis ; hepatic steatosis

## 1. Introduction

Hepatic steatosis is found in both non-alcoholic fatty liver (NAFLD) and alcoholic liver disease (ALD), both of which can coexist. The manifestations of both non-alcoholic fatty liver (NAFLD) and alcoholic liver disease (ALD) are the same, including simple steatosis to steatohepatitis with or without fibrosis, cirrhosis, and hepatocellular carcinoma. Therefore, we use the term "Fatty Liver Syndrome" to cover both NAFLD and ALD. The health burden of fatty liver syndrome is increasing globally along with the emerging prevalence of obesity and alcohol use disorder. Fatty liver syndrome is becoming one of the most common etiologies of chronic liver disease and liver transplantation [1][2][3][4]. Given the natural history of the disease, which can progress to an advanced liver disease and develop complications, it is essential to assess the severity of the disease. The degree of hepatic fibrosis, regardless of other histologic features (such as steatohepatitis), is the most important variable to stratify the risk, as this factor can predict the mortality and long-term outcomes of patients with fatty liver syndrome [5][6][7][8].

Liver biopsy is the gold standard to evaluate hepatic fibrosis. Since it is an invasive procedure and has limitations, including a risk of complications, sampling errors, low acceptance by patients, and inconvenience [9][10], non-invasive tests have been investigated to stratify the stage of hepatic fibrosis. The histologic staging of hepatic fibrosis has been used in phase 3 clinical trials, but magnetic resonance elastography (MRE)-based staging of hepatic fibrosis is used currently in phase 2 clinical trials [2][11]. In this article, we review non-invasive fibrosis tests (NITs), which are mainly categorized into tests of serum-based biomarkers and imaging tests. Serum-based biomarkers include both simple and complex serum-based biomarkers. The imaging tests include shear wave elastography (SWE), transient elastography (TE), and magnetic resonance elastography (MRE).

## 2. Prediction of Mortality and Liver-Related Outcomes

The evidence in the literature suggests that histologic hepatic fibrosis assessed by liver biopsy can predict mortality and liver-related outcomes. Liver-related outcomes include hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy, hepato–renal syndrome, hepato–pulmonary syndrome, hepatic hydrothorax, etc.), liver failure, and hepatocellular carcinoma [5][6][7][8]. These predictions were also explored for non-invasive biomarkers and imaging tests.

### 2.1. Prediction with Serum-Based Biomarkers

A retrospective multi-center international study of 320 biopsy-proven NALD patients revealed that the NFS, APRI, FIB4-index, and BARD score were able to estimate liver-related events, mortality, and liver transplantation with a high hazard ratio (HR). Among those scores, the best predictor was NFS, as its HR values for liver-related events were 7.7 and 34.2, while the HR for mortality and liver transplantation was 4.2 and 9.8 among intermediate-risk and high-risk groups, respectively [12]. Another retrospective analysis from Sweden investigated the accuracy of non-invasive serum biomarkers to predict mortality and liver-related outcomes in 646 biopsy-proven NAFLD patients. The AUROCs of NFS (0.72) and the FIB-4 index (0.72) were better in predicting mortality than those of BARD (0.62) and APRI (0.52). Similarly, better

AUROCs of NFS (0.72) and the FIB-4 index (0.72) were found compared to those of BARD (0.62) and APRI (0.69) to predict severe liver-related outcomes, including decompensated liver disease, liver failure, and hepatocellular carcinoma [13]. The accuracy of all-cause and liver-related mortality or liver transplantation, as well as liver-related outcomes including cirrhosis, hepatic decompensation, and hepatocellular carcinoma, were compared between NAFLD patients with and without diabetes mellitus using APRI and FIB-4. Compared to the NAFLD patients without diabetes mellitus, APRI and FIB-4 in patients with diabetes mellitus were less accurate in predicting overall mortality/liver transplantation, liver-related outcomes, and liver-related mortality [14]. The enhanced liver fibrosis score (ELF) is also useful for predicting liver-related outcomes in patients with NASH and decompensated cirrhosis based on data extrapolated from a phase 2 randomized controlled trial of Belapectin (NCT02462967). Liver related outcomes in this study included the incidence or worsening of gastroesophageal varices, variceal hemorrhaging, the occurrence of new ascites, hepatic encephalopathy, an increase in the Child–Turcotte–Pugh (CTP) score of ≥2 points from baseline or a rise in the MELD score to >15. Patients with ELF ≥11.3 were more likely to develop liver-related events with a cox proportional hazard ratio (HR) of 4.81 compared to patients with an ELF <9.8. The AUROC of baseline ELF was 0.67, and that after increasing ELF overtime was 0.68 for predicting liver-related outcomes [15]. Similarly, the AUROCs for the serum biomarkers of FibroTest, FIB4, APRI, and Forns index were 0.79, 0.65, 0.60, and 0.40, respectively, for predicting non-liver-related mortality and 0.69, 0.64, 0.57, and 0.43, respectively, for predicting overall mortality in patients with ALD [16].

### 2.2. Predictions with Imaging Tests

The liver stiffness measured by transient elastography provided similar accuracy to the portal pressure measurement (Hepatic Venous Portal Gradient, HVPG), which is the gold standard to predict portal hypertension at a cut-off of 21.1 kPa, as shown in a prospective study by Robic et al. [17]. Patients higher in transient elastography based liver stiffness, especially F4 defined by TE, were found to have lower survival in another prospective study of 360 patients with NAFLD [18]. In a retrospective analysis of NAFLD patients, high baseline TE-based liver stiffness and a change in liver stiffness within 6 months were associated with hepatic decompensation, hepatocellular carcinoma, liver-related mortality, and overall mortality (HRs of 1.56, 1.72, 1.96, 1.73, respectively) [19].

Studies have shown that liver stiffness measured by MRE can accurately diagnose portal hypertension defined by HVPG in chronic liver disease patients [20][21]. The baseline liver stiffness value measured by MRE also predicts hepatic decompensation. Patients with compensated liver disease with baseline liver stiffness value ≥5.8 kPa had an HR of 4.96 for hepatic decompensation when compared to those with a low baseline value [22]. A recent multi-center NAFLD cohort study demonstrated that the baseline MRE based liver stiffness can predict hepatic decompensation, including ascites, hepatic encephalopathy, esophageal variceal bleeding, and mortality. The odds of hepatic decompensation increased 3.28-fold with an increase of 1 kPa in liver stiffness over time. The cut-off for the liver stiffness value to predict hepatic decompensation was 6.48 kPa, with an AUROC of 0.707, 66.7% sensitivity, 80.8% specificity, and 73.7% accuracy. This study also defined the median cut-offs for individual decompensation events: 7.1 kPa for the occurrence of ascites, 8.85 kPa for hepatic encephalopathy, and 10.1 kPa for esophageal variceal bleeding and mortality [23].

## 3. Non-Invasive Tests to Monitor Treatment Response

Finally, the role of non-invasive tests (both serum biomarkers and imaging tests) in the monitoring of treatment response is integral in phase 2 clinical trials. A reduction of 10 U/L in alanine aminotransferase (ALT) was shown to be associated with histologic improvements and NASH resolution [24]. Moreover, a reduction of ≥17 IU/L in ALT was able to predict histologic response with an AUROC of 0.83 [25]. The MRI-proton density fat fraction (MRI-PDFF) non-invasively measures the percentage of fat in the liver. An absolute reduction of ≥5% in the MRI-PDFF value was found to be associated with regression in steatosis with 90% specificity and 58% sensitivity [26]. A relative reduction of ≥30% in the MRI-PDFF value was associated with improvement in the NAFLD activity score without the worsening of fibrosis [27]. When liver stiffness measured by MRE was evaluated for treatment response among 54 NAFLD patients, a reduction in liver stiffness of at least 2.3% was associated with fibrosis improvement. Any percentage of relative reduction (≥0%) in liver stiffness measured by MRE can predict fibrosis improvement with 67% sensitivity, 64% specificity, 48% PPV, 79% NPV, and AUROC of 0.79. Similarly, fibrosis progression can be also detected by MRE-liver stiffness [28]. Other complex non-invasive serum biomarkers, such as ELF, Pro-C3, and liver stiffness measured by TE, were proposed for use in the monitoring of treatment response [29]. When the treatment response assessed by histology was compared with percent change in NIT tests, AUROC of MRE (0.617) was superior compared to that of MRI-PDFF (0.515), NFS (0.561), FIB-4 (0.585), TE (0.578), and ELF score (0.581) [28]. Further investigations into the non-invasive tests for monitoring treatment response are warranted.

## 4. Conclusions

In summary, the staging of hepatic fibrosis in fatty liver syndrome is essential. The utilization of non-invasive tests to assess the staging of liver disease has become an acceptable alternative to liver biopsy. Among the simple non-invasive biomarkers, the FIB4-index and NFS provide the best accuracy in identifying advanced fibrosis or cirrhosis. New complex serum biomarkers are presently evolving with promising accuracy. Moreover, the performance of MRE is superior to that of TE and SWE in assessing hepatic fibrosis. The roles of non-invasive tests are emerging but are not limited to risk stratification, the prediction of disease outcomes, and the monitoring of treatment response.

## References


1. Barritt, A.S.; Jiang, Y.; Schmidt, M.; Hayashi, P.H.; Bataller, R. Charges for Alcoholic Cirrhosis Exceed All Other Etiologies of Cirrhosis Combined: A National and State Inpatient Survey Analysis. Dig. Dis. Sci. 2019, 64, 1460–1469.
2. Chalasani, N.P.; Younossi, Z.M.; LaVine, J.E.; Charlton, M.; Cusi, K.; Rinella, M.; Harrison, S.A.; Brunt, E.M.; Sanyal, A.J. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2017, 67, 328–357.
3. Parikh, N.; Marrero, W.J.; Wang, J.; Steuer, J.; Tapper, E.B.; Konerman, M.A.; Singal, A.G.; Hutton, D.W.; Byon, E.; Lavieri, M.S. Projected increase in obesity and non-alcoholic-steatohepatitis-related liver transplantation waitlist additions in the United States. Hepatology 2018, 70, 487–495.
4. Singal, A.K.; Bataller, R.; Ahn, J.; Kamath, P.S.; Shah, V.H. ACG Clinical Guideline: Alcoholic Liver Disease. Am. J. Gastroenterol. 2018, 113, 175–194.
5. Angulo, P.; Kleiner, D.E.; Dam-Larsen, S.; Adams, L.A.; Björnsson, E.S.; Charatcharoenwitthaya, P.; Mills, P.R.; Keach, J.C.; Lafferty, H.D.; Stahler, A.; et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015, 149, 389–397.e10.
6. Hagström, H.; Nasr, P.; Ekstedt, M.; Hammar, U.; Stål, P.; Hultcrantz, R.; Kechagias, S. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J. Hepatol. 2017, 67, 1265–1273.
7. Ekstedt, M.; Hagström, H.; Nasr, P.; Fredrikson, M.; Stål, P.; Kechagias, S.; Hultcrantz, R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015, 61, 1547–1554.
8. Vilar-Gomez, E.; Bertot, L.C.; Wong, V.W.-S.; Castellanos, M.; La Fuente, R.A.-D.; Metwally, M.; Eslam, M.; Gonzalez-Fabian, L.; Sanz, M.A.-Q.; Conde-Martín, A.F.; et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology 2018, 155, 443–457.e17.
9. Bedossa, P.; Dargere, D.; Paradis, V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003, 38, 1449–1457.
10. Takyar, V.; Etzion, O.; Heller, T.; Kleiner, D.E.; Rotman, Y.; Ghany, M.G.; Fryzek, N.; Williams, V.H.; Rivera, E.; Auh, S.; et al. Complications of percutaneous liver biopsy with Klatskin needles: A 36-year single-centre experience. Aliment. Pharmacol. Ther. 2017, 45, 744–753.
11. Han, M.A.T.; Saouaf, R.; Ayoub, W.; Todo, T.; Mena, E.; Noureddin, M. Magnetic resonance imaging and transient elastography in the management of Nonalcoholic Fatty Liver Disease (NAFLD). Expert Rev. Clin. Pharmacol. 2017, 10, 379–390.
12. Angulo, P.; Bugianesi, E.; Björnsson, E.S.; Charatcharoenwitthaya, P.; Mills, P.R.; Barrera, F.; Haflidadottir, S.; Day, C.P.; George, J. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013, 145, 782–789.e4.
13. Hagström, H.; Nasr, P.; Ekstedt, M.; Stål, P.; Hultcrantz, R.; Kechagias, S. Accuracy of Noninvasive Scoring Systems in Assessing Risk of Death and Liver-Related Endpoints in Patients With Nonalcoholic Fatty Liver Disease. Clin. Gastroenterol. Hepatol. 2019, 17, 1148–1156.e4.
14. Bertot, L.C.; Jeffrey, G.P.; De Boer, B.; MacQuillan, G.; Garas, G.; Chin, J.; Huang, Y.; Adams, L.A. Diabetes impacts prediction of cirrhosis and prognosis by non-invasive fibrosis models in non-alcoholic fatty liver disease. Liver Int. 2018, 38, 1793–1802.
15. Are, V.S.; Vuppalanchi, R.; Vilar-Gomez, E.; Chalasani, N.P. Enhanced Liver Fibrosis Score Can Be Used to Predict Liver-Related Events in Patients With Nonalcoholic Steatohepatitis and Compensated Cirrhosis. Clin. Gastroenterol. Hepatol. 2020.

16. Naveau, S.; Gaudé, G.; Asnacios, A.; Agostini, H.; Abella, A.; Barri-Ova, N.; Dauvois, B.; Prévot, S.; Ngo, Y.; Munteanu, M.; et al. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. Hepatology 2008, 49, 97–105.
17. Robic, M.A.; Procopet, B.; Métivier, S.; Péron, J.M.; Selves, J.; Vinel, J.P.; Bureau, C. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: A prospective study. J. Hepatol. 2011, 55, 1017–1024.
18. Boursier, J.; Vergniol, J.; Guillet, A.; Hiriart, J.-B.; Lannes, A.; Le Bail, B.; Michalak, S.; Chermak, F.; Bertrais, S.; Foucher, J.; et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J. Hepatol. 2016, 65, 570–578.
19. Petta, S.; Sebastiani, G.; Viganò, M.; Ampuero, J.; Wong, V.W.-S.; Boursier, J.; Berzigotti, A.; Bugianesi, E.; Fracanzani, A.L.; Cammà, C.; et al. Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver disease. Clin. Gastroenterol. Hepatol. 2020.
20. Gharib, A.M.; Han, M.A.T.; Meissner, E.G.; Kleiner, D.E.; Zhao, X.; McLaughlin, M.; Matthews, L.; Rizvi, B.; Abd-Elmoniem, K.Z.; Sinkus, R.; et al. Magnetic Resonance Elastography Shear Wave Velocity Correlates with Liver Fibrosis and Hepatic Venous Pressure Gradient in Adults with Advanced Liver Disease. BioMed Res. Int. 2017, 2017, 1–8.
21. Wagner, M.; Hectors, S.; Bane, O.; Gordic, S.; Kennedy, P.; Besa, C.; Schiano, T.D.; Thung, S.; Fischman, A.; Taouli, B. Noninvasive prediction of portal pressure with MR elastography and DCE-MRI of the liver and spleen: Preliminary results. J. Magn. Reson. Imaging 2018, 48, 1091–1103.
22. Asrani, S.K.; Talwalkar, J.A.; Kamath, P.S.; Shah, V.H.; Saracino, G.; Jennings, L.; Gross, J.B.; Venkatesh, S.K.; Ehman, R.L. Role of magnetic resonance elastography in compensated and decompensated liver disease. J. Hepatol. 2014, 60, 934–939.
23. Han, M.A.T.; Vipani, A.; Noureddin, N.; Ramirez, K.; Gornbein, J.; Saouaf, R.; Baniesh, N.; Cummings-John, O.; Okubote, T.; Setiawan, V.W.; et al. MR Elastography-Based Liver Fibrosis Correlates with Liver Events in Nonalcoholic Fatty Liver Patients: A Multi-Center Study. Liver Int. 2020, 40, 2242–2251.
24. Vuppalanchi, R.; Jain, A.K.; Deppe, R.; Yates, K.; Comerford, M.; Masuoka, H.C.; Neuschwander-Tetri, B.A.; Loomba, R.; Brunt, E.M.; Kleiner, D.E.; et al. Relationship Between Changes in Serum Levels of Keratin 18 and Changes in Liver Histology in Children and Adults With Nonalcoholic Fatty Liver Disease. Clin. Gastroenterol. Hepatol. 2014, 12, 2121–2130.e2.
25. Loomba, R.; Sanyal, A.J.; Kowdley, K.V.; Terrault, N.; Chalasani, N.P.; Abdelmalek, M.F.; McCullough, A.J.; Shringarpure, R.; Ferguson, B.; Lee, L.; et al. Factors Associated With Histologic Response in Adult Patients With Nonalcoholic Steatohepatitis. Gastroenterology 2019, 156, 88–95.e5.
26. Middleton, M.S.; Heba, E.R.; Hooker, C.A.; Bashir, M.R.; Fowler, K.J.; Sandrasegaran, K.; Brunt, E.M.; Kleiner, D.E.; Doo, E.; Van Natta, M.L.; et al. Agreement Between Magnetic Resonance Imaging Proton Density Fat Fraction Measurements and Pathologist-Assigned Steatosis Grades of Liver Biopsies From Adults With Nonalcoholic Steatohepatitis. Gastroenterology 2017, 153, 753–761.
27. Patel, J.; Bettencourt, R.; Cui, J.; Salotti, J.; Hooker, J.; Bhatt, A.; Hernandez, C.; Nguyen, P.; Aryafar, H.; Valasek, M.; et al. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Ther. Adv. Gastroenterol. 2016, 9, 692–701.
28. Jayakumar, S.; Middleton, M.S.; Lawitz, E.J.; Mantry, P.S.; Caldwell, S.H.; Arnold, H.; Diehl, A.M.; Ghalib, R.; Elkhashab, M.; Abdelmalek, M.F.; et al. Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib. J. Hepatol. 2019, 70, 133–141.
29. Alkhouri, N.; Lawitz, E.; Noureddin, M. Looking Into the Crystal Ball: Predicting the Future Challenges of Fibrotic NASH Treatment. Hepatol. Commun. 2019, 3, 605–613.