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Review Article

# Fatty Liver: A Pragmatic Approach to its Diagnosis and Staging: A Review

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**Abstract:**
Patients with fatty livers have higher death rates from the liver and cardiovascular disease. Recognizing people at risk is the first step because many patients with fatty liver go untreated. With substantial liver illness often being undetected by doctors who rely on abnormal liver enzymes, there is a risk of missing opportunities for intervention. While liver biopsy is the most accurate way to identify and stage fatty liver, the majority of patients may be successfully identified non-invasively using assays that are frequently accessible in the clinic today. Ultrasonography, magnetic resonance imaging, computed tomography, and, most crucially, Fibroscan, which precisely assesses the stiffness of the liver, are additional procedures that are helpful for fatty liver diagnosis in the early and late stages.

**Keywords:** Fatty Liver, Cardiovascular Disease, Liver Biopsy, Fibroscan, Ultrasonography.



## Introduction

A prominent cause of chronic disease that can result in cirrhosis, hepatocellular carcinoma, and end-stage liver disease as well as higher cardiovascular and cancer-related morbidity and death is fatty liver disease [1] The primary pathogenic trigger that, in conjunction with unfavourable genetic, lifestyle, and other variables, precipitates the development of fatty liver is insulin resistance associated with metabolic syndrome. The disease's diagnosis and prognostication are aided by biochemical indicators, radiographic imaging, liver biopsy, and, in certain cases, a fibroscan [2]. The major treatment for fatty liver disease is weight loss; however, because it is challenging to attain and maintain, medication was created. The tremendous advancement in our understanding of illness aetiology has prompted the creation of brand-new medical treatments as well as changes to those that already exist. The aetiology, diagnosis, and therapy of fatty liver disease have recently seen significant advancements, which are summarised in this review [3]. After ruling out all other potential causes of hepatic steatosis, such as liver disorders brought on only by other factors, excessive alcohol use, and other situations that may result in hepatic steatosis, fatty liver disease is the condition in which hepatic fat buildup is evident. Widespread clinical manifestations of fatty liver may eventually overtake other liver conditions as the leading cause of liver transplantation [4]. Due to increased rates of obesity and diabetes, there is an increase in the incidence and prevalence of fatty liver worldwide. In a recent spate of investigations, it was shown that people with fatty liver might acquire liver malignancies even in the absence of cirrhosis. The burden of sickness on both the individual and society as a whole is greatly increased by these results. The diagnosis and treatment of this illness is thus of public interest. This is an overview of current developments in fat liver management and knowledge [5]. Due to the modest damage, liver regeneration is not necessary in either alcoholic or non-alcoholic fatty liver disease, when inflammation brought on by low bacterial infection damages the liver. Interleukin-22, another inflammatory cytokine, encourages liver regeneration while interleukin-17 causes liver damage [6]. In response, antagonistic cytokine expression patterns change to favour IL-17 in the

advanced stage. The growth of fatty liver is significantly influenced by cytokines as well. TNF alpha is an inflammatory cytokine that is produced by a number of different cells, including macrophages and kupffer cells in the liver. Inflammation and insulin resistance both arise as a result of TNF alpha [7]

**Diagnosis**

**Current Diagnostic Flow to Assess the Severity of Fatty Liver**

Screening prospective patients in general populations is essential due to the high frequency and gradual development of fatty liver. Current recommendations from the American Association for the Study of Liver Diseases (AASLD), National Institute for Health and Care Excellence (NICE), and European Associations for the Study of the Liver, Diabetes, and Obesity suggest that systematic screening programmes be established and that patients may benefit from population screening for early assessment and lifestyle intervention [8]. The diagnostic criteria first demand that (a) there be no excessive alcohol intake and (b) there be no subsequent chronic liver disease present. However, current recommendations primarily target patients with high-risk conditions for the development of fatty liver, such as obesity, metabolic syndrome, type 2 diabetes, overnutrition, insulin resistance, dyslipidemia, age, sex, and ethnicity. The cost of sensitive testing should be reasonable and the natural history should be understood while undertaking screening for fatty liver. Because it is inexpensive and readily available, ultrasound is recommended as the initial test to identify steatosis. Ultrasonography, however, lacks the sensitivity to identify steatosis with a fat content less than 20% and is unable to distinguish steatosis from fibrosis [9]. In addition to proton magnetic resonance spectroscopy (H-MRS), fibroscan, and the controlled attenuation parameter (CAP), which appears to be more sensitive than ultrasound for steatosis diagnosis [10] In order to evaluate the amount of fat buildup and scarring in your liver, also known as fatty change, a new method called fibroscan is used to diagnose fatty liver disease. like other ultrasound examinations. Since a fibroscan is non-invasive, it carries none of the hazards associated with an invasive biopsy while being painless, simple, and rapid.

**Serum Biomarker Panels:**

**Serum Cytokeratin (CK-18)**

Since it distinguishes between steatosis and steatohepatitis with the greatest consistency, it is the most frequently studied marker of hepatocyte apoptosis for the diagnosis of fatty liver. The cutoff value for the diagnosis of steatohepatitis is CK-18 > 240U/L, which has a sensitivity of 77% and a specificity of above 95%.

**Serum Aminotransferases**

Most frequently employed as a stand-in for a marker of liver inflammation in clinical practice but has poor prognostic value for the diagnosis of steatohepatitis. The identification of steatohepatitis is 50% sensitive and 60% specific when the serum alanine aminotransferase (ALT) value is > 2 times the upper limit of normal (>70 U/L), although 80% of individuals with fatty liver have ALT levels that are within normal ranges.

**Serum Adinopectin**

The metabolism of lipids and glucose is aided by adiponectin, which is only produced by adipose tissue. In those with fatty livers, it has a cutoff value 29.16μ/L which is a poor predictor of steatohepatitis.[11]

**Fibroblast Growth Factor 21**

Individuals with steatohepatitis have serum FGF21 levels that correspond with the severity of their condition, and knowing these levels may assist identify individuals who are more likely to experience the development of their disease.[12]

**Imaging Techniques**

**Ultrasonography**

Routine ultrasonography is widely applied for the prognosis of fatty liver and steatosis, which offers as a regular hyperechoic liver. Ultrasound is typically implemented clinically due to its simplicity, cost-effectiveness and simplicity of operation, and steatosis can be for my part categorised as mild, moderate and severe, via way of means of ultrasound evaluation. A current meta-evaluation confirmed that in comparison to histology (gold standard), ultrasonography is correct and dependable in detecting fatty liver, with a pooled sensitivity and specificity of 85% and 94% respectively [13]. Although steatosis instances beginning at 5% liver fat are excluded, standard ultrasonography is only able to identify >20% liver fat. Additionally, it became less accurate in detecting liver fat in patients who were very fibrotic and were obese. In order to overcome these restrictions, various ultrasound-based scoring systems with a greater sensitivity and specificity in diagnosing steatosis 20% liver fat have been created [14].

Additionally, ultrasonography can be used in conjunction with the non-invasive algorithm fatty liver index (FLI), which has strong correlates with histology indices in populations, to precisely identify mild to moderate hepatic steatosis. The interpretation of ultrasound pictures based on deep learning algorithms has also been the subject of recent investigations, which have revealed a number of unique diagnostic tools that have shown promise in fatty liver evaluations.

As a result, in clinical settings, ultrasonography is regarded as the preferable diagnostic method for patients who have fatty liver disease or who have a strong suspicion that they do. This method may assist to more accurately identify the causes of fatty liver disease and to take immediate action to lessen its clinical effects [15].

**Fibroscan**

In fatty liver disease, an accumulation of fat cells results in fibrosis, or scarring. The amount of liver fibrosis is one indicator of the severity of fatty liver disease. The liver tissue becomes stiff due to fibrosis. Transient elastography, another name for fibroscan, gauges how quickly ultrasound waves travel through healthy liver tissue and fibrotic areas.[16]

**About your Liver Stiffness Results**

Kilopascals (kPa) are used to express your liver stiffness result. Typically, results fall between 2 and 7 kPa. If you have liver disease, your result might be higher than the normal range. The maximum result is 7.5 kPa. To determine your fibrosis score, your healthcare provider will use the results of your liver stiffness test and your medical background. Results can range from average to sophisticated [17].

**Cap (Controlled Attenuation Parameter) Score**

Your medical professional will determine your level of steatosis based on your CAP score. Decibels per meter (dB/m) is the unit used to express your CAP score. This rating will be in the 100 to 400 dB/m range. Your steatosis grade and CAP score may change over time. The ranges of CAP scores and corresponding steatosis grades are displayed in the table below. It reveals the extent to which fat accumulation has an impact on your liver. Up to 5% of fatty changes are possible in normal livers. If you receive a result that is less than 238 dB/m, your liver does not have more fatty changes than is typical.[18]

**Table 1: controlled attenuation parameter (CAP) score**

| CAP score | steatosis grade | portion of liver affected |
|---|---|---|
| 238-260 dB/m | S1 | less than 1/3 (11-30%) |
| 260-290 dB/m | S2 | between1/3 to 2/3 (34-60%) |
| 290-400 dB/m | S3 | more than 2/3 (67-99%) |

**Computed Tomography(CT)**

Computed Tomography is widely available, simple to use, and extremely accurate in identifying steatosis, much like ultrasonography. Its applicability is unfortunately also constrained by poor clinical grading of mild- to moderate steatosis. Furthermore, exposure to radiation renders CT problematic for the longitudinal assessment of fatty liver in early screening and diagnosis; yet accidental CT examination of hepatic steatosis in other causes is prevalent. According to the most recent clinical practise recommendations from the European Association for the Study of the Liver (EASL), CT is still advised as a regular test for incidental hepatic steatosis even if it is not a key diagnostic tool [19].

**Magnetic Resonance-Based Techniques**

MRI has been advocated as a substitute for liver biopsy in the diagnosis of fatty liver in clinical settings since it is a non-invasive procedure that quantitates liver fat contents with high spatial resolution and no ionising radiation. A more sophisticated MRI-based diagnostic technique known as the MRI Proton Density Fat Fraction (MRI-PDFF) may objectively, quantitatively, and repeatedly identify the presence of liver fat throughout the whole liver [20]. The fundamental idea behind MRI-PDFF is to quantify steatosis by splitting up all the protons in the liver. It has been verified against liver histology and allows for several locations of the liver to examined. As a result, MRI-PDFF has seen widespread use as an approved endpoint in steatohepatitis and fatty liver studies when compared to other imaging modalities. In comparison to ultrasound-based devices, MRI-PDFF currently has less availability due to factors including high cost, complex algorithms, and the need for MRI apparatus and experienced operators. So, at the moment, only clinical research use MRI-PDFF [21].

**Liver Biopsy**

The ultimate study for fatty liver disease—which is usually not necessary for diagnosis—involves a liver biopsy, which assesses hepatic steatosis, hepatocellular damage, inflammation, and fibrosis [22]. The primary histological characteristic that separates hepatic steatosis from fatty liver is the presence of hepatocyte ballooning degeneration in conjunction with steatosis. The most popular method for grading and staging fatty liver histologically is the fatty liver activity score. More recently, the SAF score, which includes an evaluation of steatosis (S), activity (A), and fibrosis (F), was created. This score can be more precise in diagnosing hepatic steatosis. When non-invasive staging is inconclusive or there is diagnostic uncertainty, liver biopsy should be utilised[23].

**Table 2: Fatty liver activity score (FAS)**

| Histological characteristic | Score | Explanation |
|---|---|---|
| **Steatosis** | **0** | **<5%** |
| | 1 | 5-33% |
| | 2 | 34-66% |
| | 3 | >66% |
| **Fibrosis** | 0 | none |
| | 1 | mild to moderate perisinusoidal fibrosis |
| | 2 | periportal/portal fibrosis |
| | 3 | bridging fibrosis |
| | 4 | cirrhosis |
| | 5 | liver failure |
| **Fibrosis score 0-5** | | |
| Although individuals might still have hepatic steatosis with lower fibrosis scores, a score of more than 5 with steatosis and hepatocyte ballooning is typically deemed diagnostic. | | |

## Conclusions

The prevalence of fatty liver disease is on the rise, and it could soon become a leading chronic liver condition worldwide. Despite significant advances in comprehending the natural course and underlying biology of the disease over the last 40 years, there are still numerous obstacles to overcome. Unfortunately, fatty liver disease has not received the attention it deserves from healthcare professionals and society as a whole [24]. This analysis highlights several factors that hinder the development of highly effective treatments in this area. One major obstacle is the ongoing reliance on liver biopsy as a diagnostic tool. There is a lack of reliable biomarkers that can accurately diagnose and stage fatty liver disease across its entire spectrum. Ideally, a combination of diagnostic and prognostic biomarkers could be used to identify high-risk cases and determine the effectiveness of treatments. Another significant challenge is the heterogeneity and complex pathogenesis of fatty liver disease, which has led to a limited understanding of its various phenotypes. Truly, characteristics are improved objectives to enable a suitable medical decision and precise prognosis [18]. Ongoing research on efficient medical solutions in hepatic steatosis are currently focused on different potential facets, such as regulating dietary intake, enhancing energy expenditure, reducing liver fat accumulation, and averting its impact on the liver. After successful attainment, remedies for hepatic steatosis will be more specific and personalized [25].

Collectively, it is becoming more evident that irrespective of present or forthcoming advancements in identifying ailments and medicinal remedies, preserving a wholesome way of life and shedding extra pounds continue to be crucial in the preventive and curative strategies employed for hepatic steatosis.

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## References


1. Powell, E. E., Wong, V. W., & Rinella, M. Non-alcoholic fatty liver disease. Lancet (London, England), 2021; 397(10290): 2212–2224.
2. Ting, Y. W., Wong, S. W., AnuarZaini, A., Mohamed, R., & Jalaludin, M. Y. Metabolic Syndrome Is Associated with Advanced Liver Fibrosis Among Pediatric Patients with Non-alcoholic Fatty Liver Disease. Frontiers in pediatrics, 2019;7: 491-510.
3. Federico, A., Zulli, C., de Sio, I., Del Prete, A., Dallio, M., Masarone, M., & Loguercio, C. Focus on emerging drugs for the treatment of patients with non-alcoholic fatty liver disease. World journal of gastroenterology, 2014;20(45): 16841–16857.
4. Cleveland, E., Bandy, A., & Van Wagner, L. B. Diagnostic challenges of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Clinical liver disease, 2018; 11(4): 98–104.
5. Aras, M., Tchang, B. G., & Pape, J. Obesity and Diabetes. The Nursing clinics of North America, 2021;56(4): 527–541.
6. Janeway, C. A., Jr, & Medzhitov, R. Innate immune recognition. Annual review of immunology, 2002;20: 197–216.
7. Dixon, L. J., Barnes, M., Tang, H., Pritchard, M. T., & Nagy, L. E. Kupffer cells in the liver. Comprehensive Physiology, 2013; 3(2): 785–797
8. Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., & Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 2017;9(6): 7204–7218.
9. Lv, Y., So, K. F., & Xiao, J. Liver regeneration and alcoholic liver disease. Annals of translational medicine, 2020;8(8): 567-578.
10. Toomer, K. H., &Malek, T. R. Cytokine Signaling in the Development and Homeostasis of

Regulatory T cells. Cold Spring Harbor perspectives in biology, 2018;10(3): a028597.
11. Zhai, M., Liu, Z., Long, J. et al. The incidence trends of liver cirrhosis caused by nonalcoholic steatohepatitis via the GBD study 2017. Sci Rep. 2021;11: 5195.
12. Lirussi, F., Azzalini, L., Orando, S., Orlando, R., & Angelico, F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. The Cochrane database of systematic reviews, 2007;(1): CD004996.
13. Freeman, A. M., & Pennings, N. Insulin Resistance. In Stat Pearls. Stat Pearls Publishing. 2022.
14. Ameer, F., Scandiuzzi, L., Hasnain, S., Kalbacher, H., & Zaidi, N. De novo lipogenesis in health and disease. Metabolism: clinical and experimental, 2014;63(7): 895–902.
15. Olzmann, J.A., Carvalho, P. Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol. 2019;20: 137–155.
16. Eming, S. A., Wynn, T. A., & Martin, P. Inflammation and metabolism in tissue repair and regeneration. Science (New York, N.Y.), 2017;356(6342): 1026–1030.
17. Almeida, M., Ranisch, R. Beyond safety: mapping the ethical debate on heritable genome editing interventions. Humanit Soc Sci Commun. 2022; 9: 139.
18. Dietrich, C. G., Rau, M., &Geier, A. Screening for nonalcoholic fatty liver disease-when, who and how? World journal of gastroenterology, 2021;27(35): 5803–5821.
19. Osna, N. A., Donohue, T. M., Jr, &Kharbanda, K. K. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol research: current reviews, 2017;38(2): 147–161.
20. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. Frontiers in public health, 2017;5: 307.
21. Cecil K. M. Proton magnetic resonance spectroscopy: technique for the neuroradiologist. Neuroimaging clinics of North America, 2013;23(3): 381–392.
22. Piazzolla, V. A., & Mangia, A. Noninvasive Diagnosis of NAFLD and NASH. Cells, 2020;9(4): 1005.
23. Fielding, C. M., &Angulo, P. Hepatic steatosis and steatohepatitis: Are they really two distinct entities? Current hepatology reports, 2014;13(2): 151–158.
24. Liu, T., Wang, X., Karsdal, M. A., Leeming, D. J., & Genovese, F. Molecular serum markers of liver fibrosis. Biomarker insights, 2012;7: 105–117.
25. Yanai, H., & Yoshida, H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. International journal of molecular sciences, 2019;20(5): 1190.