

Need for a Multiparametric Ultrasound-Based Assessment of MAFLD: The Backbone of Strategic Management

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Received: 08 Sep 2025

Accepted: 29 Sep 2025

Published: 10 Oct 2025

J Short Name: ACMCR

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Citation:

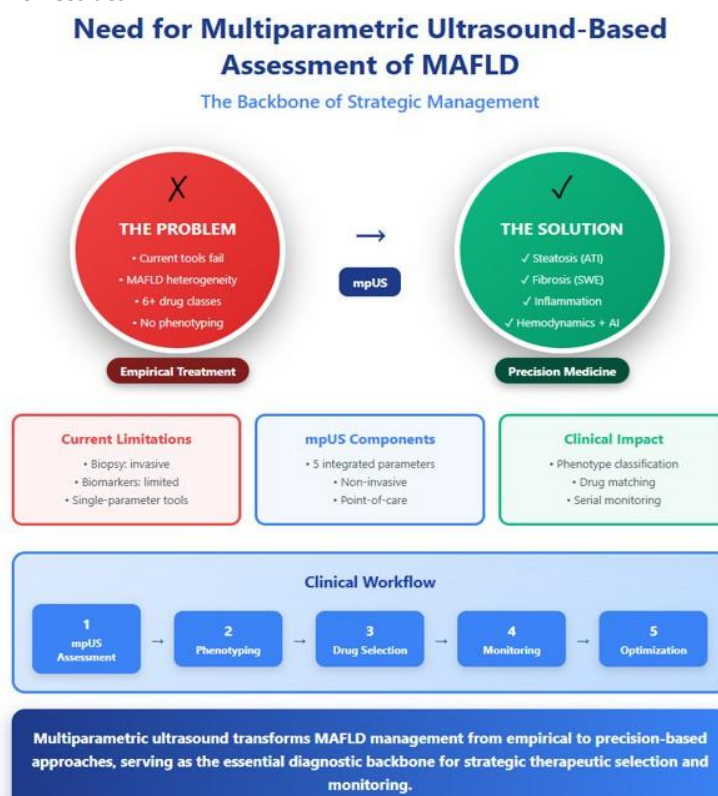
Atul Kapoor, Need for a Multiparametric Ultrasound-Based Assessment of MAFLD: The Backbone of Strategic Management. Japanese Jour of Gastro and Hepatology® 2025; V11(1): 1-14

1. Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is an escalating global health concern, impacting approximately 25-30% of the global population. The heterogeneous nature of MAFLD, which spans a spectrum from simple steatosis to steatohepatitis and fibrosis, necessitates precise phenotyping to optimize therapeutic strategies. Current diagnostic and monitoring methodologies have significant limitations in terms of disease classification, risk stratification, and treatment selection. Although liver biopsy is regarded as the reference standard, it is invasive, costly, and subject to sampling variability. Conventional imaging modalities and serum biomarkers provide an incomplete assessment of the multifaceted pathophysiology of MAFLD. Emerging pharma-

cotherapies targeting various pathogenic pathways require accurate identification of specific disease phenotypes and severity stages. Multiparametric ultrasound (mpUS), which integrates B-mode assessment, elastography techniques, quantitative fat quantification, inflammation markers, and vascular parameters, provides a comprehensive, noninvasive solution for MAFLD characterization. This review examines the critical need for mpUS in addressing current diagnostic limitations, enabling precise disease phenotyping, and guiding personalized treatment selection and monitoring of therapeutic response. We propose that mpUS should serve as the cornerstone of strategic MAFLD management, facilitating the transition from one-size-fits-all approaches to precision medicine for this complex disorder.

Graphic Abstract



2. Introduction

2.1: The Growing Burden of MAFLD

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the most prevalent chronic liver condition worldwide, with its burden closely paralleling the epidemics of obesity, type 2 diabetes, and metabolic syndrome [1,2]. The recent nomenclature shift from non-alcoholic fatty liver disease (NAFLD) to MAFLD reflects a paradigm shift toward positive diagnostic criteria based on metabolic dysfunction rather than exclusion of alcohol consumption [3]. This evolution in terminology underscores the fundamental pathophysiological basis of metabolic dysregulation. MAFLD encompasses a wide spectrum of liver pathologies, ranging from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma [4,5]. Progressive forms of MAFLD, particularly those with significant fibrosis, are associated with increased liver-related morbidity, cardiovascular disease, and all-cause mortality [6,7]. Notably, MAFLD has become a leading indication for liver transplantation in many developed countries, and its prevalence continues to increase globally [8,9]. One of the most significant challenges in MAFLD management is the marked heterogeneity in disease presentation, progression and outcomes [10]. Patients with comparable degrees of steatosis may exhibit vastly different trajectories, with some progressing rapidly to fibrosis, while others remain stable for decades [11]. This heterogeneity reflects the complex interplay between genetic factors, metabolic comorbidities, environmental exposures, and gut microbiome composition [12,13]. The multifactorial pathogenesis of MAFLD involves lipotoxicity, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory cascades, and fibrogenic signaling [14,15]. Different patients may exhibit predominant activation of specific pathogenic pathways, potentially requiring tailored therapeutic approaches for each patient. However, current diagnostic paradigms inadequately capture this pathophysiological complexity, limiting our ability to deliver precision medicine [16].

2.2: The Treatment Landscape Evolution

The therapeutic landscape for MAFLD has evolved dramatically in recent years, with multiple pharmacological agents in various stages of clinical development targeting distinct pathogenic mechanisms [17,18]. These include:

- Metabolic modulators: Peroxisome proliferator-activated receptor (PPAR) agonists, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and thyroid hormone receptor- β agonists addressing insulin resistance and lipid metabolism [19,20]

- Anti-inflammatory agents: Chemokine receptor antagonists and anti-inflammatory compounds targeting hepatic inflammation [21].
- Antifibrotic therapies: Agents targeting fibrogenesis pathways, including FXR agonists and ASK1 inhibitors [22,23].
- Combination therapies: Dual or triple combinations addressing multiple pathogenic pathways simultaneously [24].

Each therapeutic class demonstrates efficacy in specific patient subsets, disease stages or pathophysiological contexts. For instance, GLP-1 receptor agonists are particularly beneficial in patients with concomitant diabetes and obesity [25], whereas antifibrotic agents may be most appropriate for patients with established fibrosis (26). The emerging principle of precision medicine in MAFLD necessitates accurate patient phenotyping to match individuals with the most appropriate therapeutic interventions [27]. Despite advances in therapeutics, a significant gap persists between the need for precise disease characterization and the capabilities of current diagnostic tools (28). This diagnostic gap manifests in several critical areas, which will be explored in detail in this review.

3. Discussion

3.1: Liver Biopsy

has traditionally served as the reference standard for MAFLD diagnosis, grading, and staging (29,30). Histopathological assessment evaluates steatosis, inflammation, hepatocellular ballooning, and fibrosis using standardized scoring systems like the NAFLD Activity Score and fibrosis staging [31]. However, liver biopsy has significant limitations in clinical practice. A) Sampling variability: A liver biopsy samples only 1/50,000 of liver volume [32]. MAFLD shows heterogeneous distribution of pathological features [33], leading to fibrosis stage misclassification in 20-30% of cases [34,35]. B) Invasiveness and complications: Liver biopsy risks include pain (20-30%), bleeding (0.3-0.6%), and death (1 in 10,000) [37,38], limiting its use for screening and monitoring [39]. C) Inter-observer variability: Expert pathologists show moderate agreement (kappa 0.4-0.7) for steatosis grading, inflammation, and ballooning [41,42], with fibrosis staging discordance in 10-30% of cases [43]. D) Cost and accessibility: Biopsy costs \$2,000-5,000 and requires specialized expertise (44,45), limiting availability in resource-limited settings [46]. E) Unsuitability for monitoring: Its invasive nature and cost prevent frequent disease monitoring [47,48]. F) Limited functional information: Histopathology provides static tissue architecture views but minimal insight into metabolic processes and hepatic function (49,50) (Figure 1).

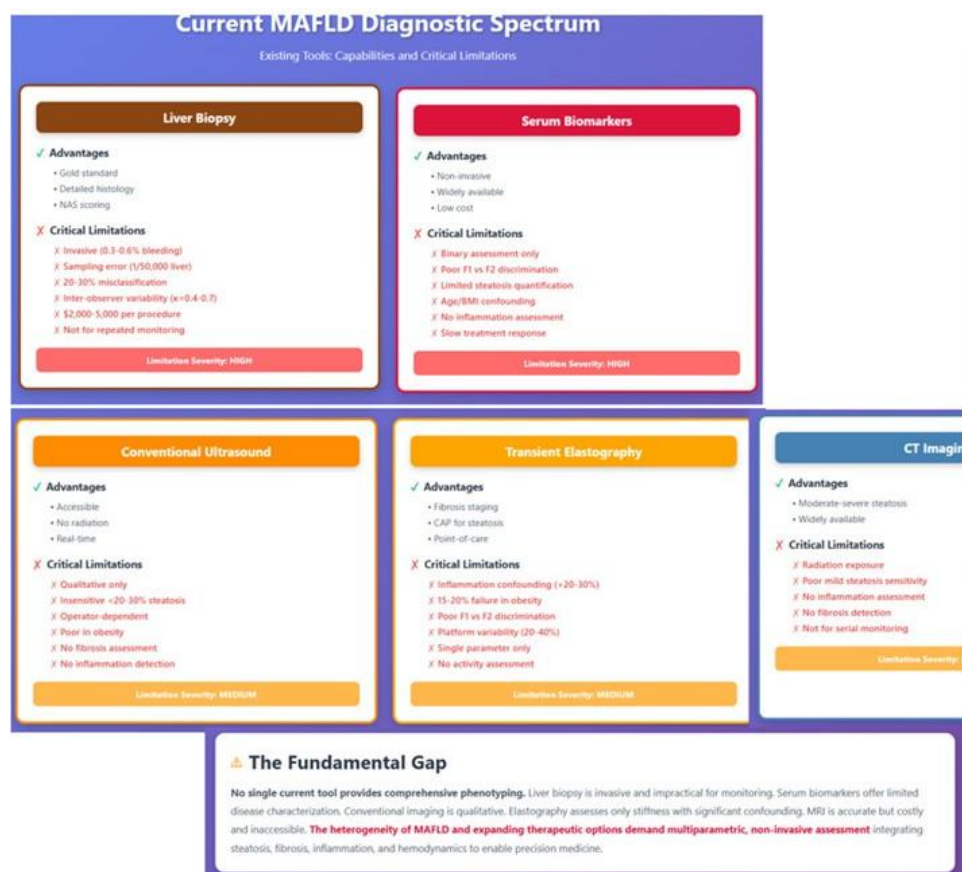


Figure 1: Tools for Evaluation of MAFLD.

3.2. Serum Biomarkers: Incomplete Windows into Disease

Serum biomarkers and scoring systems have been developed to assess MAFLD non-invasively, focusing on fibrosis detection [51]. These include simple indices (FIB-4, NAFLD Fibrosis Score, APRI) and proprietary panels (Enhanced Liver Fibrosis test and Fibro Test) [52,53]. While useful for excluding advanced fibrosis in low-risk populations, these tools have limitations. Most biomarker panels only distinguish advanced fibrosis ($\geq F3$) from earlier stages but cannot differentiate intermediate stages (F1 vs. F2) [54,55], insufficient for precision medicine [56]. Serum biomarkers primarily assess fibrosis, providing minimal information about steatosis, inflammation, and metabolic dysfunction [57], limiting their utility for treatment selection [58]. Additionally, biomarker performance is affected by age, sex, BMI, diabetes, and medications [59,60]. FIB-4 overestimates fibrosis in elderly patients and underestimates it in young individuals [61], reducing diagnostic accuracy across patient populations [62]. D) Inability to accurately assess steatosis: Although the controlled attenuation parameter (CAP) addresses this gap in vibration-controlled transient elastography platforms, pure serum biomarkers do not reliably quantify hepatic fat content [63]. The cytokeratin-18 fragments show promise for detecting hepatocyte apoptosis and inflammation but lack widespread validation and standardization [64,65]. E) Poor monitoring of treatment response: Serum biomarkers often show discordance with histological changes during therapeutic interventions [66]. Their slow response to treatment and significant biological variability limits their utility in monitoring disease modification [67,68].

3.3 : Conventional Imaging: Qualitative and Limited

Traditional ultrasound, CT, and MRI have distinct limitations for MAFLD assessment. B-mode ultrasound detects hepatic steatosis through echogenicity but is qualitative, operator-dependent, and insensitive to steatosis <20-30% [69,70]. It cannot differentiate steatosis grades or assess inflammation without elastography [71]. Its performance deteriorates in obese patients, who have highest MAFLD risk [72]. Unenhanced CT identifies moderate to severe steatosis through liver-to-spleen attenuation ratios but uses ionizing radiation [73,74]. CT shows poor sensitivity for mild steatosis and cannot assess inflammation or early fibrosis [75]. While MRI-PDFF provides accurate steatosis assessment and serves as the non-invasive reference standard [76,77], standard MRI cannot assess inflammation or fibrosis. MRE evaluates fibrosis effectively [78] but requires specialized equipment not widely available [79]. Combined MRI-PDFF and MRE assessment is comprehensive but expensive (\$1,000-3,000), limiting accessibility [80,81]. Conventional imaging typically assesses parameters separately, with patients undergoing multiple tests without integration into a comprehensive profile [82]. This fragmented approach fails to capture MAFLD's multidimensional nature [83].

3.4: Multiparametric Ultrasound: Addressing the Diagnostic and Therapeutic Gaps

Multiparametric ultrasound represents an integrated solution to the limitations outlined above, combining multiple ultrasound-based techniques into a comprehensive disease assessment [136,137]. The mpUS approach typically integrates

3.4.1 : Core Components of Multiparametric Ultrasound

Quantitative steatosis assessment: Advanced ultrasound techniques like attenuation imaging, backscatter coefficient analysis, and speed of sound measurement enable hepatic fat quantification comparable to MRI-PDFF [138,139]. These methods provide continuous fat quantification across the steatosis range [140]. **Elastography for fibrosis staging:** Shear wave elastography (SWE) and transient elastography measure liver stiffness for fibrosis [141,142]. Point and 2D-SWE provide reliable fibrosis staging similar to MRE for advanced fibrosis [143,144]. Meta-analyses show AUROCs >0.85 for significant fibrosis and >0.90 for cirrhosis [145,146]. **Inflammation markers:** Viscosity plane wave ultrasound and viscoelastic parameters may indicate necro-inflammatory activity [147,148]. Dispersion slope parameters help distinguish MASH from simple steatosis [149]. **Vascular assessment:** Doppler ultrasound assesses portal vein velocity and hemodynamics to identify portal hypertension [150,151,152]. Spleen stiffness correlates with portal hypertension and complements liver stiffness assessment [153,154]. **Texture analysis:** Radiomics and machine learning extract features from ultrasound images to identify disease patterns and outcomes [155,156].

3.4.2 : Advantages of Multiparametric Ultrasound for MAFLD Management

Comprehensive phenotyping: mpUS integrates multiple parameters to create patient profiles capturing steatosis severity, fibrosis stage, inflammation, and hemodynamics [157]. This enables precision phenotyping unavailable with single-parameter approaches [158]. **Noninvasive and safe:** Ultrasound has no radiation exposure, allowing safe repeated examinations for disease monitoring [159,160]. **Cost-effective and accessible:** mpUS is less expensive than MRI (\$200-500 vs. \$1,000-3,000) and more widely available in primary care settings [161,162], enabling population screening [163]. **Point-of-care capability:** Unlike MRI or biopsy, ultrasound can be performed during routine visits for immediate clinical decisions [164]. **Dynamic assessment:** Ultrasound provides real-time hepatic hemodynamics evaluation and can incorporate functional challenges to assess metabolic reserve [165,166]. **Treatment monitoring:** mpUS enables frequent assessments of therapeutic interventions [167], with ultrasound parameters correlating to histological improvement during treatment [168,169]. Multiparametric ultrasound addresses drug selection limitations through phenotype identification by integrating steatosis, fibrosis, inflammatory, and hemodynamic parameters to identify distinct phenotypic clusters [170]. For instance:

- High-fat, low-fibrosis, metabolic phenotype → GLP-1 RA or THR- β agonist
- Moderate fat, high inflammation, progressive fibrosis → PPAR agonist or FXR agonist
- Established fibrosis with active fibrogenesis → antifibrotic therapy
- Portal hypertension features → consideration for beta-blockers or novel portal hypertension therapies [171,172].

Risk stratification: Composite scores derived from multiple mpUS parameters could stratify patients according to progression risk more accurately than single biomarkers [173]. Machine learning algorithms trained on multiparametric data may predict which patients will progress to advanced disease, enabling targeted intervention [174,175]. **Response prediction:** Baseline multiparametric profiles may predict treatment response. Early studies suggest that certain elastographic patterns or combinations of parameters are associated with better therapeutic responses to specific drug classes [176,177]. Serial mpUS assessments can detect early changes in multiple disease parameters, providing earlier signals of treatment efficacy than waiting for histological or clinical endpoints [178]. For example, reductions in hepatic fat (weeks), inflammation markers (months), and fibrosis (months to years) can be tracked in parallel [179]. Different parameters can be emphasized for different therapeutic mechanisms, such as fat quantification for metabolic therapies, stiffness for anti-fibrotics, and hemodynamic parameters for portal hypertension-targeted interventions [180].

3.5 : Implementation Challenges and Future Directions

Despite its promise, multiparametric ultrasound faces implementation challenges [181]: Standardization requires minimizing equipment and interpretation variability through protocols and training [182,183]. International guidelines exist but need wider adoption [184]. **Validation:** While individual mpUS components are validated, comprehensive protocols need validation against histological outcomes [185]. Studies correlating mpUS phenotypes with treatment outcomes are needed [186]. **Integration:** Precision medicine requires combining mpUS with biomarkers, genetic scores, and microbiome data [187,188], necessitating multimodal frameworks [189]. Artificial intelligence can enhance mpUS through automated analysis and decision support [190,191], but requires diverse datasets for validation [192]. Clinical trials should incorporate standardized mpUS protocols [193] to accelerate drug development [194]. Healthcare integration requires evidence of clinical utility and cost-effectiveness [195,196] for successful implementation in practice guidelines and workflows.

3.6 : Current Elastography Methods: Single-Parameter Limitations

While elastography advances imaging techniques, current methods like TE and SWE have limitations for MAFLD phenotyping [197,198]. LSM reflects fibrosis, inflammation, steatosis, and vascular congestion [199,200]. In MAFLD patients, steatohepatitis increases LSM values by 20-30% independent of fibrosis stage, affecting F2-F3 distinction [201,202]. LSM decreases may occur without fibrosis regression [203,204]. Elastography cannot differentiate between active fibrogenesis and stable fibrotic tissue [205]. Patients with identical LSM values may have different prognoses—one with active MASH and progressing fibrosis, another with resolved inflammation [206]. TE shows high failure rates in obese patients, the main MAFLD risk group [208,209]. The XL probe reduces failures but may underestimate fibrosis [210]. Central obesity affects signal quality [211]. 2D-SWE shows improved feasibility in obese patients [212,213]. Technical variability exists between

platforms, with LSM values differing by 20-40% across devices [214,215]. Factors like fasting status and operator experience affect measurements [216,217]. Lack of unified cutoffs limits research generalizability [218]. Guidelines recommend different thresholds for TE and 2D-SWE (219). TE provides single measurements assuming homogeneous disease distribution [220]. MAFLD exhibits heterogeneous fibrosis patterns [221]. 2D-SWE enables stiffness visualization but samples limited liver volume [222,223]. Standard elastography provides only stiffness information without assessing other parameters [224]. Patients may have low LSM but severe steatosis requiring intervention [226]. Elastography detects advanced fibrosis but performs poorly in early stages F0-F2 [227,228]. Most MAFLD patients present with early disease [229]. Early F1-F2 fibrosis associates with increased mortality [230,231]. LSM's predictive ability for outcomes remains suboptimal [232,233]. Composite models show better prognostic performance [234,235].

3.7: The Challenge of Mixed Phenotypes and Comorbid Conditions

MAFLD patients present with complex phenotypes involving concurrent processes that affect disease behavior and prognosis [236,237]. Current diagnostics inadequately characterize these phenotypes. A) Concurrent Liver Iron: Hepatic iron accumulation occurs in 30-40% of MAFLD patients (238,239). The coexistence of steatosis and iron creates distinct pathophysiology. B) Synergistic hepatotoxicity: Iron and lipids increase oxidative stress and cell injury [240,241]. Combined steatosis and iron overload cause more severe inflammation than isolated steatosis [242,243]. Iron-catalyzed Fenton reaction generates hydroxyl radicals promoting MASH [244]. C) Altered disease progression: MAFLD patients with iron show 2-3-fold higher risk of advanced fibrosis [245,246]. Iron stimulates collagen synthesis and fibrogenic pathways [247,248,249]. D) Cardiovascular impact: Iron overload increases cardiovascular risk through endothelial dysfunction [250,251,252]. Combined metabolic syndrome, MAFLD, and iron create high cardiac risk [253]. E) Metabolic effects: Iron impairs insulin signaling [254,255] and increases diabetes prevalence [256,257]. F) Treatment implications: Iron overload affects treatment priorities [258]. Phlebotomy may improve insulin sensitivity and slow fibrosis [259,260]. Iron reduction improves metabolic parameters in MAFLD patients [261,262,263]. G) Diagnostic challenges: Standard tests cannot detect hepatic iron [264]. Serum ferritin increases with inflammation, obesity, and metabolic syndrome, reducing specificity in MAFLD [265,266]. Transferrin saturation shows poor sensitivity [267]. Liver biopsy remains reference standard [268]. MRI provides accurate assessment but increases cost [269,270]. H) Iron deposition increases liver stiffness, causing fibrosis overestimation [271,272]. MAFLD patients with iron overload show higher LSM [273]. This confounding remains unaddressed [274]. I) Met-ALD combines metabolic dysfunction and alcohol consumption (275,276). Many patients with metabolic risk factors consume alcohol above MAFLD thresholds [277,278]. These factors accelerate liver injury [279], with faster fibrosis progression than MAFLD

alone [280,281]. Alcohol increases cirrhosis risk in metabolically dysfunctional patients [282]. Current criteria poorly address mixed phenotypes [283,284,285]. MetALD patients need interventions for both conditions (286). MAFLD treatments may be contraindicated with alcohol use [287], while focusing on alcohol cessation ignores metabolic factors [288]. Elastography shows reduced accuracy in MetALD [289,290,291]. J) Other comorbidities include viral hepatitis, autoimmune hepatitis, and genetic immune overlap. HBV/HCV infection in MAFLD accelerates fibrosis and increases cancer risk [294,295]. These patients develop cirrhosis earlier [296,297]. Viral replication and metabolic dysfunction activate fibrogenic pathways [298]. Treated HCV patients with metabolic dysfunction show progression [299,300]. Treatment requires viral and fibrosis assessment [301,302]. Autoimmune conditions can coexist with MAFLD (303). Metabolic syndrome occurs in many AIH/PBC patients [304]. Steatosis may delay immunosuppressive therapy [305,306]. Both conditions share elevated aminotransferase and hypergammaglobulinemia [307]. Corticosteroids worsen metabolic dysfunction (308), while weight gain worsens MAFLD [309,310]. Genetic variants PNPLA3 I148M, TM6SF2 E167K, GCKR, and MBOAT7 create distinct MAFLD phenotypes [311], occurring in 40-50% Hispanic and 20-25% European individuals. These variants increase disease progression and HCC risk [312,313]. PNPLA3 risk alleles predict severity independent of metabolic syndrome [314]. Current methods cannot identify genetic risk phenotypes [318], leading to different prognoses [319]. Genetic information integration with clinical data is essential for risk stratification [320].

3.8. Implications for Multiparametric Assessment

These mixed phenotypes and comorbid conditions highlight the need for comprehensive multiparametric evaluations rather than single-parameter diagnostics [321]. An optimal diagnostic platform should assess multiple pathological processes including steatosis, fibrosis, inflammation, iron content, and hemodynamics in one examination [322], combined with serological markers, genetic risk scores, and metabolic profiling [323]. Machine learning can identify distinct phenotypic subgroups (pure metabolic MAFLD, MetALD, iron-loaded MAFLD, genetic high-risk) based on multiparametric signatures [324]. Patients should receive targeted therapies based on their pathophysiological drivers: phlebotomy for iron-loaded cases, alcohol intervention for MetALD, and metabolic therapy for genetically high-risk individuals [325]. Track relevant parameters for each phenotype, such as iron quantification in iron overload and hepatocellular carcinoma surveillance in PNPLA3 homozygotes [326]. Multiparametric ultrasound with point-of-care iron assessment and integrated genetic and serological data enables comprehensive phenotyping [327]. Advanced ultrasound techniques may enable iron quantification through acoustic quantification [328]. Integration of ultrasound parameters with clinical, laboratory, and genetic data through AI could create phenotypic profiles capturing MAFLD complexity in patients [329,330] (Figure 2).

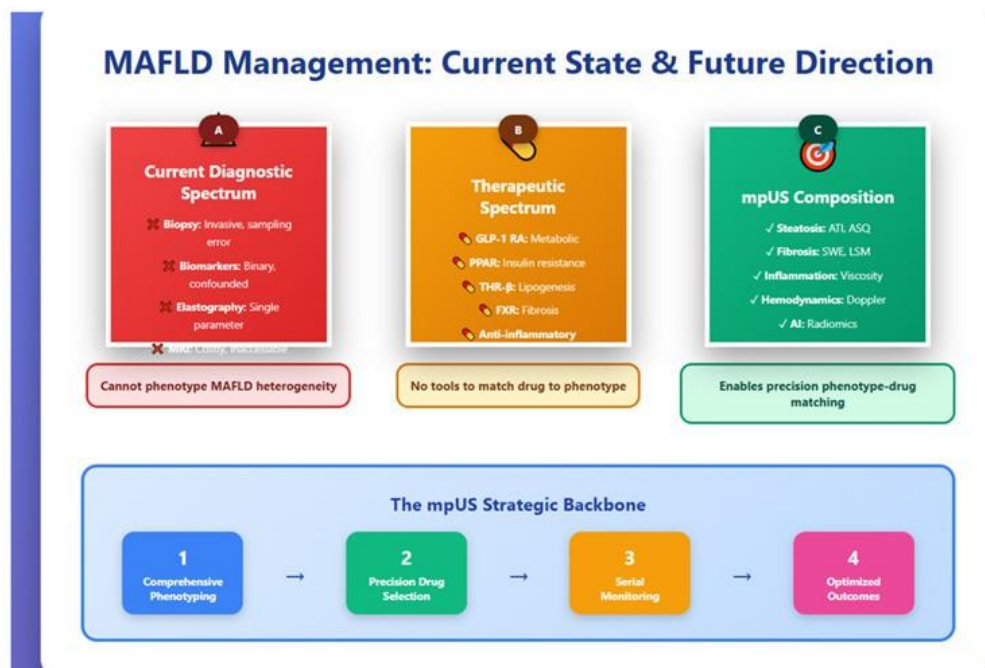


Figure 2: Future Status of MAFLD Management.

3. Conclusion

The complexity of MAFLD and expanding therapeutics create an urgent need for comprehensive non-invasive disease characterization. Current tools, including liver biopsy, biomarkers, and imaging, have limitations in disease classification and progression prediction, impeding precision medicine. Multiparametric ultrasound provides integrated assessment of steatosis, fibrosis, inflammation, and hemodynamics on a single, cost-effective platform. mpUS enables comprehensive phenotyping to identify responsive patients, stratify risks, and monitor treatment efficacy. For mpUS to guide MAFLD management, standardization, validation, and integration with biomarkers and guidelines are essential. These developments will transform MAFLD care from empirical to personalized therapeutic strategies, improving outcomes for millions affected.

References

1. Younossi ZM. Global epidemiology of nonalcoholic fatty liver disease. *Hepatol Commun.* 2016; 1(6): 515-525.
2. Riazi K. The prevalence and incidence of NAFLD worldwide: A systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2022; 7(9): 851-861.
3. Eslam M. A new definition of metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol.* 2020; 73(1): 202-209.
4. Chalasani N. Diagnosis and management of nonalcoholic fatty liver disease. *Hepatology.* 2018; 67(1): 328-357.
5. Rinella ME. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023; 77(5): 1797-1835.
6. Dulai PS. Increased risk of mortality by fibrosis stage in non-alcoholic fatty liver disease. *Hepatology.* 2017; 65(5): 1557-1565.
7. Hagström H. The fibrosis stage, but not NASH, predicts mortality and the time to the development of severe liver disease in biopsy-proven NAFLD. *J Hepatol.* 2017; 67(6): 1265-1273.
8. Wong RJ. Non-alcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015; 148(3): 547-555.
9. Younossi Z. Global burden of NAFLD and NASH. *Hepatology.* 2021; 75(6): 1704-1720.
10. Loomba R. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell.* 2021; 184(10): 2537-2564.
11. Singh S. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis. *Gastroenterology.* 2015; 149(6): 1471-1478.
12. Romeo S. Genetic variation in PNPLA3 confers susceptibility to non-alcoholic fatty liver disease. *Nat Genet.* 2008; 40(12): 1461-1465.
13. Boursier J. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and a shift in the metabolic function of the gut microbiota. *Hepatology.* 2016; 63(3): 764-775.
14. Friedman SL. Mechanisms underlying NAFLD development and therapeutic strategies. *Nat Med.* 2018; 24(7): 908-922.
15. Schuster S. Triggering and resolution of inflammation in NASH. *Nat Rev Gastroenterol Hepatol.* 2018; 15(6): 349-364.
16. Loomba R. Heterogeneity of hepatic fibrosis and steatosis in NAFLD. *Liver Int.* 2021; 41(Suppl 1): 72-79.
17. Younossi ZM. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology.* 2018; 68(1): 361-371.
18. Harrison SA. A blood-based biomarker panel (NIS4) for the non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis. *Hepatology.* 2020; 71(4): 1178-1189.
19. Francque SM. A randomized controlled trial of the pan-PPAR agonist lanifibranor in NASH. *N Engl J Med.* 2021; 385(17): 1547-1558.

20. Newsome PN. A placebo-controlled trial of subcutaneous semaglutide for nonalcoholic steatohepatitis. *N Engl J Med.* 2021; 384(12): 1113-1124.
21. Ratziu V. Cenicriviroc for the treatment of non-alcoholic steatohepatitis and liver fibrosis. *Hepatology.* 2020; 71(6): 2058-2073.
22. Neuschwander-Tetri BA. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis. *Lancet.* 2015; 385(9972): 956-965.
23. Harrison SA. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH. *J Hepatol.* 2020; 73(1): 26-39.
24. Loomba R. Combination therapies, including cilofexor and firso-costat, are used for bridging fibrosis and cirrhosis attributable to NASH. *Hepatology.* 2021; 73(2): 625-643.
25. Armstrong MJ. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicenter, double-blind, randomized, placebo-controlled phase 2 study. *Lancet.* 2016; 387(10019): 679-690.
26. Harrison SA. Resmetirom (MGL-3196) for the treatment of nonalcoholic steatohepat. *Lancet.* 2019; 394(10213): 2012-2024.
27. Anstee QM. From NASH to HCC: Current concepts and future challenges. *Nat Rev Gastroenterol Hepatol.* 2019; 16(7): 411-428.
28. Sanyal AJ. Endpoints and clinical trial design for non-alcoholic steatohepatitis. *Hepatology.* 2011; 54(1): 344-353.
29. Kleiner DE. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology.* 2005; 41(6): 1313-1321.
30. Bedossa P. Histopathological algorithm and scoring system for the evaluation of liver lesions in morbidly obese patients. *Hepatology.* 2012; 56(5): 1751-1759.
31. Brunt EM. Nonalcoholic fatty liver disease (NAFLD) activity score and histopathological diagnosis of NAFLD. *Hepatology.* 2011; 53(3): 810-820.
32. Ratziu V. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology.* 2005; 128(7): 1898-1906.
33. Merriman RB. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology.* 2006; 44(4): 874-880.
34. Bedossa P. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology.* 2003; 38(6): 1449-1457.
35. Vuppalanchi R. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2009; 7(4): 481-486.
36. Larson SP. NASH histology is associated with histopathological heterogeneity. *Clin Gastroenterol Hepatol.* 2013;11(12):1587-1591.
37. Rockey DC. Liver biopsy. *Hepatology.* 2009;49(3):1017-1044.
38. Seeff LB. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol.* 2010;8(10):877-883.
39. Tannapfel A. Indications for liver biopsy. *Dtsch Arztebl Int.* 2012;109(27-28):477-483.
40. Kleiner DE. Association of histologic disease activity with the progression of nonalcoholic fatty liver disease. *JAMA Netw Open.* 2019;2(10):e1912565.
41. Rousselet MC. Sources of variability in the histological scoring of chronic viral hepatitis. *Hepatology.* 2005;41(2):257-264.
42. Juluri R. Generalizability of the nonalcoholic steatohepatitis Clinical Research Network histologic scoring system for nonalcoholic fatty liver disease. *J Clin Gastroenterol.* 2011;45(1):55-58.
43. Younossi ZM. Pathologic criteria for nonalcoholic steatohepatitis: inter-protocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
44. Regev A. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol.* 2002;97(10):2614-2618.
45. Sporea I. Is liver biopsy still needed in the era of noninvasive tests? *World J Gastroenterol.* 2014;20(23):7242-7251.
46. Wong VW. Liver biopsy in the management of nonalcoholic fatty liver disease. *Clin Liver Dis.* 2018;22(4):789-802.
47. Ratziu V. Liver fibrosis in overweight patients. *Gastroenterology.* 2000;118(6):1117-1123.
48. Angulo P. Liver fibrosis, but no other histologic features, is associated with the long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2015;149(2):389-397.
49. Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver disease. *J Hepatol.* 2007;47(4):598-607.
50. Wai CT. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38(2):518-526.
51. Castera L. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2019;156(5):1264-1281.
52. Sterling RK. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43(6):1317-1325.
53. Vilar-Gomez E. Noninvasive assessment of nonalcoholic fatty liver disease. *Semin Liver Dis.* 2018;38(1):22-37.
54. McPherson S. Evidence of NAFLD progression from steatosis to fibrosing steatohepatitis using paired biopsies. *Hepatology.* 2015;62(4):1148-1158.
55. Sun W. Comparison of FIB-4 index, NAFLD fibrosis score, and BARD score for the prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol.* 2017;32(9):1611-1617.
56. Siddiqui MS. Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2019;17(1):156-163.
57. Musso G. Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med.* 2011;43(8):617-649.
58. Patel K. Limitations of non-invasive tests for the assessment of liver fibrosis. *JHEP Rep.* 2020;2(2):100067.
59. McPherson S. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol.* 2017;112(5):740-751.
60. Xiao G. Comparison of laboratory tests, ultrasound, and magnetic resonance elastography to detect fibrosis in patients with nonalcohol-

- ic fatty liver disease. *Clin Gastroenterol Hepatol*. 2017;15(10):1477-1486.
61. Shah AG. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009;7(10):1104-1112.
 62. Tapper EB. Performance of vibration-controlled transient elastography in a US cohort of patients with nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2016;111(5):677-684.
 63. Karlas T. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol*. 2017;66(5):1022-1030.
 64. Feldstein AE. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis. *Hepatology*. 2009;50(4):1072-1078.
 65. Vuppalanchi R. Performance characteristics of vibration-controlled transient elastography for the evaluation of nonalcoholic fatty liver disease. *Hepatology*. 2018;67(1):134-144.
 66. Petta S. Serial combination of noninvasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. *Aliment Pharmacol Ther*. 2017;46(6):617-627.
 67. Nasr P. A 3% weight loss was used to define histological improvement in clinical trials of NAFLD. *J Hepatol*. 2017;67(4):789-795.
 68. Vilar-Gomez E. Weight loss through lifestyle modification significantly reduces the features of non-alcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-378.
 69. Saadeh S. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology*. 2002;123(3):745-750.
 70. Hernaez R. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver. *Hepatology*. 2011;54(3):1082-1090.
 71. Palmentieri B. The role of bright liver echo pattern on ultrasound B-mode examination in the diagnosis of liver steatosis. *Dig Liver Dis*. 2006;38(7):485-489.
 72. Bohte AE. The diagnostic accuracies of US, CT, MRI, and 1H-MRS for the evaluation of hepatic steatosis were compared with those of liver biopsy. *Eur Radiol*. 2011;21(1):87-97.
 73. Pickhardt PJ. Specificity of unenhanced CT for noninvasive diagnosis of hepatic steatosis. *Radiology*. 2013;266(3):909-916.
 74. Park SH. Macrovesicular hepatic steatosis in living liver donors. *Radiology*. 2004;230(1):276-280.
 75. Kodama Y. Comparison of CT methods for determining liver fat content. *AJR Am J Roentgenol*. 2007;188(5):1307-1312.
 76. Reeder SB. Quantification of liver fat using magnetic resonance imaging. *Magn. Reson. Imaging Clin. N Am*. 2010;18(3):337-357.
 77. Yokoo T. Linearity, bias, and precision of hepatic proton density fat fraction measurements using MR imaging. *Radiology*. 2018;286(2):486-498.
 78. Singh S. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2015;13(3):643-654.
 79. Loomba R. Magnetic resonance elastography predicts advanced fibrosis in patients with non-alcoholic fatty liver disease. *Hepatology*. 2014;60(6):1920-1928.
 80. Idilman IS. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. *Radiology*. 2013;267(3):767-775.
 81. Park CC. Magnetic resonance elastography vs transient elastography in the detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Gastroenterology*. 2017;152(3):598-607.
 82. Castera L. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;128(2):343-350.
 83. Machado MV. Noninvasive diagnosis of non-alcoholic fatty liver disease. *J Gastrointest Liver Dis*. 2012;21(4):433-443.
 84. Tilg H. NAFLD and diabetes mellitus. *Nat Rev Gastroenterol Hepatol*. 2017;14(1):32-42.
 85. Loomba R. Advances in the noninvasive assessment of hepatic fibrosis. *Gut*. 2020;69(7):1343-1352.
 86. Ranjbar G. GLP-1 receptor agonists and SGLT-2 inhibitors in patients with NAFLD. *Trends Pharmacol Sci*. 2022;43(8):672-685.
 87. Cusi K. Long-term pioglitazone treatment in patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus. *Ann Intern Med*. 2016;165(5):305-315.
 88. Gastaldelli A. Importance of changes in adipose tissue insulin resistance to histological response during thiazolidinedione treatment in patients with nonalcoholic steatohepatitis. *Hepatology*. 2009;50(4):1087-1093.
 89. Lambert JE. Increased de novo lipogenesis is a distinct characteristic of individuals with non-alcoholic fatty liver disease. *Gastroenterology*. 2014;146(3):726-735.
 90. Kazankov K. The role of macrophages in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Nat Rev Gastroenterol Hepatol*. 2019;16(3):145-159.
 91. Krenkel O. Liver macrophages in tissue homeostasis and diseases. *Nat Rev Immunol*. 2017;17(5):306-321.
 92. Itoh M. Hepatic crown-like structure: a unique histological feature of non-alcoholic steatohepatitis in mice and humans. *PLoS One*. 2013;8(12):e82163.
 93. Issa D. Presence of the dynamic scar on transient elastography predicts significant liver fibrosis in patients with chronic hepatitis C. *J Viral Hepat*. 2019;26(11):1312-1319.
 94. Kisseleva T. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):151-166.
 95. Ellis EL. Clinical evidence of liver fibrosis regression. *J Hepatol*. 2012;56(5):1171-1180.
 96. Francque S. Noncirrhotic human nonalcoholic fatty liver disease induces portal hypertension related to the histological degree of steatosis. *Eur J Gastroenterol Hepatol*. 2010;22(12):1449-1457.
 97. Patel R. Addressing the vascular and metabolic pathology of nonalcoholic steatohepatitis. *Transl Res*. 2020;222:95-109.
 98. Hammoutene A. Defects in endothelial autophagy occur in patients with non-alcoholic steatohepatitis and promote inflammation and fibrosis. *J Hepatol*. 2020;72(3):528-538.
 99. European Association for the Study of Liver. EASL Clinical Practice Guidelines on non-invasive tests for the evaluation of liver disease

- severity and prognosis. *J Hepatol.* 2021;75(3):659-689.
100. Sanyal AJ. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med.* 2021;385(17):1559-1569.
 101. Pais R. Temporal trends, determinants, and outcomes of liver stiffness progression in a biopsy-proven NAFLD prospective cohort. *Hepatology.* 2021;74(3):1276-1289.
 102. Taylor RS. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology.* 2020;158(6):1611-1625.
 103. Eslam M. Genetics and epigenetics of NAFLD and NASH: clinical impact. *J Hepatol.* 2018;68(2):268-279.
 104. Stine JG. Changes in MRI-PDFF and histologic response in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol.* 2021;19(10):2274-2283.
 105. Marso SP. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2016;375(19):1834-1844.
 106. Sumida Y. Limitations of liver biopsy and noninvasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol.* 2014;20(2):475-485.
 107. Anstee QM. Progression of NAFLD to diabetes mellitus, cardiovascular disease, or cirrhosis. *Nat Rev Gastroenterol Hepatol.* 2013;10(6):330-344.
 108. Wong VW. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in non-alcoholic fatty liver disease. *Hepatology.* 2010;51(2):454-462.
 109. Lassailly G. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology.* 2015;149(2):379-388.
 110. Davison BA. The suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. *J Hepatol.* 2020;73(6):1322-1332.
 111. Colli A. Accuracy of a predictive model for severe portal hypertension in hepatitis C virus-induced cirrhosis. *World J Gastroenterol.* 2014;20(17):5079-5086.
 112. Wong VW. Running title: Reduction of liver stiffness after lifestyle modification in non-alcoholic fatty liver disease 2015;42(9):1039-1048.
 113. Petta S. Monitoring the occurrence of liver-related events and survival using transient elastography in patients with non-alcoholic fatty liver disease and compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol.* 2021;19(4):806-815.
 114. Harrison SA. Efruxifermin in non-alcoholic steatohepatitis. *Lancet.* 2023;401(10394):2074-2084.
 115. Cobbald JF. Transient elastography for biomarker development. *Gut.* 2012;61(12):1691-1696.
 116. Alberti KG. Harmonizing metabolic syndrome. *Circulation.* 2009;120(16):1640-1645.
 117. Harrison SA. Aldafermin in patients with non-alcoholic steatohepatitis (ALPINE 2/3). *Lancet Gastroenterol Hepatol.* 2022;7(7):603-616.
 118. Ratziu V. Novel biomarkers of NAFLD. *Liver Int.* 2020;40(Suppl 1):38-44.
 119. Konerman MA. Improvement of predictive models of the risk of disease progression in chronic hepatitis C by incorporating longitudinal data. *Hepatology.* 2015;61(6):1832-1841.
 120. Staels B. Hepatoprotective effects of the dual peroxisome proliferator-activated receptor α/δ agonist, GFT505, in rodent models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Hepatology.* 2013;58(6):1941-1952.
 121. Ratziu V. Elafibranor, an agonist of peroxisome proliferator-activated receptors α and δ , induces the resolution of nonalcoholic steatohepatitis without worsening fibrosis. *Gastroenterology.* 2016;150(5):1147-1159.
 122. Gawrieh S. Characteristics, etiologies, and trends of hepatocellular carcinoma in patients without cirrhosis. *Aliment Pharmacol Ther.* 2019;50(7):809-821.
 123. Loomba R, et al. Semaglutide 2.4 mg once a week in patients with non-alcoholic steatohepatitis-related cirrhosis. *J Hepatol.* 2023;79(3):718-727.
 124. Hartman ML. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of non-alcoholic steatohepatitis in patients with type 2 diabetes. *Diabetes Care.* 2020;43(6):1352-1355.
 125. Mantovani A. Glucagon-like peptide-1 receptor agonists for the treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatobiliary Surg Nutr.* 2021;10(1):58-72.
 126. Harrison SA. Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH. *Hepatol Commun.* 2021;5(4):573-588.
 127. Sinha RA. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. *Trends Endocrinol Metab.* 2018;29(9):610-619.
 128. Taub R. Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor- β agonist. *Atherosclerosis.* 2013;230(2):373-380.
 129. Fang S. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance in mice. *Nat Med.* 2015;21(2):159-165.
 130. Kowdley KV. A randomized trial of obeticholic acid monotherapy in patients with nonalcoholic steatohepatitis. *Hepatology.* 2020;71(6):2059-2073.
 131. Patel K. Obeticholic acid for the treatment of non-cirrhotic NASH steatohepatitis. *Expert Opin Investig Drugs.* 2020;29(4):311-321.
 132. Friedman SL. A randomized, placebo-controlled trial of cenicriviroc for the treatment of nonalcoholic steatohepatitis with fibrosis. *Hepatology.* 2018;67(5):1754-1767.
 133. Anstee QM. Targeting chemokine receptors 2 and 5 in non-alcoholic steatohepatitis. *J Hepatol.* 2021;74(6):1489-1499.
 134. Schuppan D. Determinants of fibrosis progression and regression in NASH. *J Hepatol.* 2018;68(2):238-250.
 135. Dulai PS. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH. *J Hepatol.* 2016;65(2):372-378.
 136. Ferraioli G. Ultrasound-based techniques for the diagnosis of liver steatosis. *World J Gastroenterol.* 2019;25(40):6053-6070.
 137. Sporea I. How to use multiparametric ultrasound for liver assessment in patients with metabolic-associated fatty liver disease. *J Clin Med.* 2021;10(19):4506.

138. Ferraioli G. Quantification of liver fat content using ultrasound. *Radiology*. 2022;302(3):495-507.
139. Bae JS. Quantitative assessment of hepatic steatosis using advanced imaging techniques. *Clin Mol Hepatol*. 2020;26(4):470-481.
140. Tada T. Attenuation imaging based on ultrasound technology for the assessment of hepatic steatosis. *J Med Ultrason*. 2022;49(1):3-11.
141. Friedrich-Rust M. Performance of transient elastography for staging liver fibrosis. *Gastroenterology*. 2008;134(4):960-974.
142. Ferraioli G. Reproducibility of real-time shear wave elastography in the evaluation of liver elasticity. *Eur J Radiol*. 2012;81(11):3102-3106.
143. Herrmann E. Assessment of biopsy-proven liver fibrosis using two-dimensional shear wave elastography. *Hepatology*. 2018;67(1):260-272.
144. Barr RG. Elastography assessment of liver fibrosis. *Ultrasound Q*. 2015;31(1):3-12.
145. Eddowes PJ. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with non-alcoholic fatty liver disease. *Gastroenterology*. 2019;156(6):1717-1730.
146. European Association for the Study of the Liver. EASL-ALEH Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol*. 2015;63(1):237-264.
147. Nightingale K. Derivation and analysis of viscoelastic properties of human liver. *Ultrasound Med Biol*. 2015;41(9):2463-2474.
148. Sugimoto K. Viscoelasticity measurement in rat livers using shear wave US elastography. *Ultrasound Med Biol*. 2018;44(10):2018-2024.
149. Deffieux T. Investigating liver stiffness and viscosity for fibrosis, steatosis, and activity staging using shear wave elastography. *J Hepatol*. 2015;62(2):317-324.
150. Colli A. Prognostic value of non-invasive tests in patients with non-alcoholic fatty liver disease. *Liver Int*. 2021;41(9):2050-2063.
151. Berzigotti A. Ultrasonographic evaluation of the liver surface and transient elastography in clinically doubtful cirrhosis. *J Hepatol*. 2010;52(6):846-853.
152. Iwao T. Hepatic artery hemodynamic responsiveness to altered portal blood flow in normal and cirrhotic livers. *Radiology*. 1996;200(3):793-798.
153. Colecchia A. Spleen stiffness measurements can predict clinical complications of compensated HCV-related cirrhosis. *J Hepatol*. 2014;60(6):1158-1164.
154. Stefanescu H. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in patients with liver cirrhosis. *J Gastroenterol Hepatol*. 2011;26(1):164-170.
155. Byra M. Liver fat assessment in multiview sonography using transfer learning with convolutional neural networks. *J Ultrasound Med*. 2022;41(1):175-184.
156. Gatos I. Focal liver lesion segmentation and classification in nonenhanced T2-weighted MRI. *Med Phys*. 2017;44(12):6292-6305.
157. Castera L. Noninvasive evaluation of NAFLD. *Nat Rev Gastroenterol Hepatol*. 2013;10(11):666-675.
158. Brunt EM. Complexity of ballooned hepatocyte feature recognition. *Hepatology*. 2009;49(3):808-812.
159. ter Haar G. Safety and bioeffects of ultrasound contrast agents. *Med Biol Eng Comput*. 2009;47(8):893-900.
160. Salvatore V. Performance of ultrasound techniques and the potential of artificial intelligence in the evaluation of hepatocellular carcinoma and non-alcoholic fatty liver disease. *Cancers*. 2021;13(12):2771.
161. Papatheodoridis G. The role of noninvasive tests in the management of patients with chronic hepatitis B virus infection. *Ann Gastroenterol*. 2014;27(3):218-228.
162. Tsochatzis EA. Elastography for the diagnosis of fibrosis severity in chronic liver disease. *Ther Adv Gastroenterol*. 2011;4(3):177-195.
163. Wong VW. Community screening for nonalcoholic fatty liver disease. *Hepatology*. 2021;73(1):423-435.
164. Kwok R. Screening patients with diabetes for non-alcoholic fatty liver disease using controlled attenuation parameter and liver stiffness measurements. *Gut*. 2016;65(8):1359-1368.
165. Goossens N. Noninvasive prediction of liver fibrosis in chronic hepatitis C using a panel of blood-based biomarkers. *Liver Int*. 2014;34(10):1510-1518.
166. Orlacchio A. Liver elasticity in patients with NASH was evaluated using real-time elastography (RTE). *Ultrasound Med Biol*. 2012;38(4):537-544.
167. Petta S. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. *Hepatology*. 2017;65(4):1145-1155.
168. Petta S. The severity of steatosis influences liver stiffness measurements in patients with nonalcoholic fatty liver disease. *Hepatology*. 2015;62(4):1101-1110.
169. de Lédinghen V. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2016;31(4):848-855.
170. Eslam M. MAFLD: a consensus-driven proposed nomenclature for metabolic-associated fatty liver disease. *Gastroenterology*. 2020;158(7):1999-2014.
171. Krag A. Non-selective beta-blockers in patients with cirrhosis are associated with increased mortality in a nationwide cohort study. *Aliment Pharmacol Ther*. 2016;43(10):1145-1153.
172. Ripoll C. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. 2007;133(2):481-488.
173. Mózes FE. Diagnostic accuracy of noninvasive tests for advanced fibrosis in patients with NAFLD. *Liver Int*. 2022;42(4):974-986.
174. Konerman MA. Machine learning models for predicting severe liver disease and portal hypertension in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2021;19(11):2335-2343.
175. Ioannou GN. Assessment of a deep learning model to predict non-alcoholic steatohepatitis using electronic health record data. *JAMA Netw Open*. 2020;3(9):e2015146.
176. Petroff D. Assessment of hepatic steatosis by controlled attenuation parameter using M and XL probes. *J Hepatol*. 2016;64(5):1036-1042.
177. Sasso M. Controlled attenuation parameter (CAP). *J Hepatol*. 2017;67(1):12-20.
178. Ajmera V. Magnetic resonance imaging proton density fat fraction is associated with the progression of fibrosis in patients with non-alcoholic fatty liver disease. *Gastroenterology*. 2018;155(2):307-310.

179. Imajo K. Magnetic resonance imaging classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease more accurately than transient elastography. *Gastroenterology*. 2016;150(3):626-637.
180. Papatheodoridi. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. *J Hepatol*. 2021;74(5):1109-1116.
181. Barr RG. Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement. *Radiology*. 2020;296(2):263-274.
182. Dietrich CF. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017. *Ultraschall Med*. 2017;38(4):e16-e47.
183. Ferraioli G. WFUMB guidelines and recommendations for the clinical use of ultrasound elastography. *Ultrasound Med Biol*. 2015;41(5):1161-1179.
184. Ferraioli G. Liver ultrasound elastography: an update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. *Ultrasound Med Biol*. 2018;44(12):2419-2440. 185
185. Petta S. Reliability of liver stiffness measurement in non-alcoholic fatty liver disease: the effects of body mass index. *Aliment Pharmacol Ther*. 2011;33(12):1350-1360.
186. Yoneda M. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). *Gut*. 2007;56(9):1330-1331.
187. Arena U. Acute viral hepatitis increases liver stiffness measured by transient elastography. *Hepatology*. 2008;47(2):380-384.
188. Millonig G. Extrahepatic cholestasis increases liver stiffness (FibroScan), irrespective of fibrosis. *Hepatology*. 2008;48(5):1718-1723.
189. Wong VW. Liver stiffness measurement using the XL probe in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2012;107(12):1862-1871.
190. Boursier J. Determination of reliability criteria for liver stiffness evaluation using transient elastography. *Hepatology*. 2013;57(3):1182-1191.
191. Petta S. Serial combination of noninvasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. *Aliment Pharmacol Ther*. 2017;46(6):617-627.
192. Singh S. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol*. 2015;13(3):440-451.
193. Tapper EB. Use of liver imaging and biopsy in clinical practice. *N Engl J Med*. 2017;377(8):756-768.
194. Rosenberg WM. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology*. 2004;127(6):1704-1713.
195. Chalasani N. Relationship between steatosis grade and zonal location to histological features of steatohepatitis in adult patients with non-alcoholic fatty liver disease. *J Hepatol*. 2008;48(5):829-834.
196. Foucher J. Diagnosis of cirrhosis using transient elastography (FibroScan): a prospective study. *Gut*. 2006;55(3):403-408.
197. Castéra L. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology*. 2010;51(3):828-835.
198. de Lédinghen V. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan. *J Hepatol*. 2012;56(4):833-839.
199. Myers RP. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology*. 2012;55(1):199-208.
200. Bota S. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. *Liver Int*. 2013;33(8):1138-1147.
201. Dietrich. Strain elastography: How to do it? *Ultrasound Int Open*. 2017;3(4):E137-E149.
202. Ferraioli G. Liver ultrasound elastography: An update to the WFUMB guidelines. *Ultrasound Med Biol*. 2018;44(12):2419-2440.
203. Thiele M. Accuracy of the enhanced liver fibrosis test vs. FibroTest, elastography, and indirect markers in the detection of advanced fibrosis in patients with alcoholic liver disease. *Gastroenterology*. 2018;154(5):1369-1379.
204. Mederacke I, et al. Food intake increases liver stiffness in patients with chronic or resolved hepatitis C infection. *Liver Int*. 2009;29(10):1500-1506.
205. Berzigotti A. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity. *Hepatology*. 2017;65(4):1293-1305.
206. Gaia S. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. *J Hepatol*. 2011;54(1):64-71.
207. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
208. Sandrin L. Transient elastography: a new noninvasive method for the assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29(12):1705-1713.
209. Brunt EM. Nonalcoholic steatohepatitis. *Semin Liver Dis*. 2004;24(1):3-20.
210. Fang C. Comparison of 2-D shear wave elastography and transient elastography for diagnosing liver fibrosis. *J Gastroenterol Hepatol*. 2017;32(1):253-259.
211. Cui J. Role of magnetic resonance elastography in the assessment of hepatic fibrosis. *Quant Imaging Med Surg*. 2016;6(3):338-344.
212. Venkatesh SK. Magnetic resonance elastography of the liver: technique, analysis, and clinical applications. *J Magn Reson Imaging*. 2013;37(3):544-555.
213. Banerjee R, et al. Multiparametric magnetic resonance for the noninvasive diagnosis of liver disease. *J Hepatol*. 2014;60(1):69-77.
214. Pavlides M. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. *J Hepatol*. 2016;64(2):308-315.
215. Thiele M. Transient and 2-dimensional shear-wave elastography provide comparable assessments of alcoholic liver fibrosis and cirrhosis. *Gastroenterology*. 2016;150(1):123-133.
216. Lee MS. Practical application of transient elastography in patients with chronic liver disease. *Clin Mol Hepatol*. 2013;19(2):89-96.
217. Nascimbeni F. From NAFLD in clinical practice to answers from guidelines. *J Hepatol*. 2013;59(4):859-871.

218. Ekstedt M. The fibrosis stage is the strongest predictor of disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology*. 2015;61(5):1547-1554.
219. Younossi ZM. Nonalcoholic steatofibrosis independently predicts mortality in nonalcoholic fatty liver disease. *Hepatol Commun*. 2017;1(5):421-428.
220. Nahon P. Liver stiffness measurement versus clinicians' prediction or MELD score for disease severity assessment in non-alcoholic fatty liver disease. *J Hepatol*. 2013;59(5):1065-1072.
221. Vergniol J. Prospective comparison of transient elastography, Fibro-Test, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;128(2):343-350.
222. Angulo P. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4):846-854.
223. Kim D. Advanced fibrosis in nonalcoholic fatty liver disease: Noninvasive assessment with MR elastography. *Radiology*. 2013;268(2):411-419.
224. Younossi ZM. Non-alcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)*, MD 2012;91(6):319-327.
225. Abenavoli L. Insulin resistance and liver steatosis in chronic hepatitis C infection of genotype 3. *World J Gastroenterol*. 2014;20(41):15233-15240.
226. Dongiovanni P. Iron depletion by deferoxamine upregulates glucose uptake and insulin signaling in hepatoma cells and rat liver. *Am J Pathol*. 2008;172(3):738-747.
227. Nelson JE. Relationship between the pattern of hepatic iron deposition and histological severity in non-alcoholic fatty liver disease. *Hepatology*. 2011;53(2):448-457.
228. Pietrangelo A. Iron and the liver. *Liver Int*. 2016;36(Suppl 1):116-123.
229. Kowdley KV. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology*. 2012;55(1):77-85.
230. Valenti L. Iron depletion by phlebotomy improves insulin resistance in patients with non-alcoholic fatty liver disease and hyperferritinemia. *J Clin Endocrinol Metab*. 2014;99(6):E1148-1154.
231. Dongiovanni P. Iron in fatty liver and metabolic syndrome: a promising therapeutic target. *J Hepatol*. 2011;55(4):920-932.
232. Fargion S. Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for non-alcoholic steatohepatitis. *Am J Gastroenterol*. 2001;96(8):2448-2455.
233. Rametta R. Increased BMI and age are major determinants of elevated serum ferritin levels in the general population. *Hepatol Int*. 2013;7(2):683-689.
234. Aigner E. Role of low hepatic copper concentrations in nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2010;105(9):1978-1985.
235. Tsukamoto H. Iron regulation of hepatic macrophage TNF- α expression. *Free Radic Biol Med*. 2002;32(4):309-313.
236. Beaton MD. Hepatic iron loading in patients with nonalcoholic fatty liver disease. *Hepatology*. 2013;57(3):1144-1145.
237. Du SX. Serum ferritin is associated with non-alcoholic fatty liver disease and liver fibrosis. *Clin Biochem*. 2011;44(14-15):1315-1320.
238. Sullivan JL. Iron in arterial plaque: a modifiable risk factor for atherosclerosis. *Biochim Biophys Acta*. 2009;1790(7):718-723.
239. Valenti L. Iron depletion via therapeutic phlebotomy improves metabolic control in patients with type 2 diabetes and iron overload. *Diabetes Care*. 2014;37(11):e249-250.
240. Fernández-Real JM. Bloodletting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. *Diabetes*. 2002;51(4):1000-1004.
241. Zuydam NR. Genome-wide association study of diabetic kidney disease in patients with type 2 diabetes. *Diabetes*. 2018;67(7):1414-1427.
242. Simcox JA. Iron and diabetes risk. *Cell Metab*. 2013;17(3):329-341.
243. Gabrielsen JS. Adipocyte iron regulates adiponectin levels and insulin sensitivity. *J Clin Invest*. 2012;122(10):3529-3540.
244. Manousou P. Enhanced liver fibrosis test and NAFLD fibrosis score in patients with and without metabolic syndrome. *Liver Int*. 2012;32(4):635-643.
245. Ryan JD. Hepatic iron is the major determinant of serum ferritin levels in patients with NAFLD. *Liver Int*. 2018;38(1):164-173.
246. Aigner E. Iron stores, liver transaminase levels, and metabolic risk in healthy teenagers. *Eur J Clin Invest*. 2010;40(2):155-163.
247. Valenti L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int*. 2009;20(4):549-555.
248. Adams LA. Hepcidin, iron homeostasis and insulin resistance. *Hepatology*. 2011;53(4):1190-1193.
249. Sumida Y. Lower serum ferritin levels predict liver fibrosis progression in older Japanese patients with nonalcoholic fatty liver disease. *J Gastroenterol*. 2012;47(6):712-718.
250. Adams PC. Impact of phlebotomy in nonalcoholic fatty liver disease: a prospective, randomized, controlled trial. *Hepatology*. 2015;61(5):1555-1564.
251. Britton L. Iron and nonalcoholic fatty liver disease. *World J Gastroenterol*. 2002;8(2):200-205.
252. Hernando D. Quantification of liver iron with MRI: state-of-the-art and remaining challenges. *J Magn Reson Imaging*. 2014;40(5):1003-1021.
253. Alústiza JM. MR quantification of hepatic iron concentration. *Radiology*. 2004;230(2):479-484.
254. Wood MJ. MRI R2 and R2* mapping accurately estimated hepatic iron concentration in patients with transfusion-dependent thalassemia and sickle cell disease. *Blood*. 2005;106(4):1460-1465.
255. Gandon Y. Noninvasive assessment of hepatic iron stores using MRI. *Lancet*. 2004;363(9406):357-362.
256. Brissot P. Haemochromatosis. *Nat Rev Dis Primers*. 2018;4:18016.
257. Sirlin CB. Quantification of hepatic steatosis with MRI: the effects of accurate fat spectral modeling. *J Magn Reson Imaging*. 2008;28(4):1048-1054.
258. Henninger B. R2* relaxometry for quantifying hepatic iron overload: biopsy-based calibration and comparison with the literature. *Rofo*. 2015;187(6):472-479.
259. Eddowes PJ. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2018;47(5):631-644.

260. Roulot D. Liver stiffness values in apparently healthy subjects: influence of sex and metabolic syndrome. *J Hepatol.* 2008;48(4):606-613.
261. Lazo M. Confluence of hepatitis C, diabetes, obesity, and chronic kidney disease epidemics in the United States population. *Clin Gastroenterol Hepatol.* 2017;15(12):1957-1964.
262. McPherson S. Evidence of NAFLD progression from steatosis to fibrosing steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol.* 2015;62(5):1148-1155.
263. Åberg F. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology.* 2018;67(6):2141-2149.
264. Lau K. Synergistic effects of alcohol and metabolic syndrome on liver disease: a nationwide cohort study. *Hepatology.* 2021;74(2):645-658.
265. Hagström H. Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease in later life. *J Hepatol.* 2018;68(3):505-510.
266. Hart CL. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of Scottish men with 21 years of follow-up. *BMJ.* 1999;318(7200):1725-1729.
267. Raynard B. Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology.* 2002;35(3):635-638.
268. Ekstedt M. Natural history of NAFLD/NASH. *Curr Hepatol Rep.* 2017;16:391-397.
269. Trépo E. Common genetic variations in alcohol-related hepatocellular carcinoma: a case-control genome-wide association study. *Lancet Oncol.* 2022;23(1):161-171.
270. Seitz HK. Alcoholic liver disease ALD. *Nat Rev Dis Primers.* 2018;4(1):16.
271. Younossi ZM. Global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol.* 2019;71(4):793-801.
272. Eslam M. MAFLD: a consensus-driven proposed nomenclature for metabolic-associated fatty liver disease. *Gastroenterology.* 2020;158(7):1999-2014.
273. Eslam M. Defining pediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. *Lancet Gastroenterol Hepatol.* 2021;6(10):864-873.
274. Chang Y. Alcoholic and non-alcoholic fatty liver disease and liver-related mortality: a cohort study. *Am J Gastroenterol.* 2019;114(4):620-629.
275. Parker R. Systematic review: thiazolidinediones for non-alcoholic steato Aliment Pharmacol Ther. 2012;36(11-12):1021-1029.
276. Bellentani S. Drinking habits as cofactors of risk for alcohol-induced liver damage. *Gut.* 1997;41(6):845-850.
277. Mueller S. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. *World J Gastroenterol.* 2010;16(8):966-972.
278. Michelena J. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology.* 2015;62(3):762-772.
279. Lemoine M. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut.* 2016;65(8):1369-1376.
280. Seto WK. Coronary artery disease in chronic hepatitis B infection: the role of traditional cardiovascular risk factors and viral factors. *Liver Int.* 2014;34(9):1373-1380.
281. Petta S. Hepatitis C virus infection is associated with increased cardiovascular mortality: A meta-analysis of observational studies. *Gastroenterology.* 2016;150(1):145-155.
282. Huang YW. Increased risk of cirrhosis and its decompensation in patients with chronic hepatitis B with newly diagnosed diabetes: a nationwide cohort study. *Clin Infect Dis.* 2015;60(2):202-210.
283. Machado MV. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol.* 2006;45(4):600-606.
284. Pais R. NAFLD and liver transplantation: current burden and expected challenges. *J Hepatol.* 2016;65(6):1245-1257.
285. Degasperis E. Hepatic fat: guilty until proven innocent? NAFLD and HCV infections. *Aliment Pharmacol Ther.* 2012;36(11-12):1002-1010.
286. Serfaty L. Determinants of outcomes of compensated hepatitis C virus-related cirrhosis. *Hepatology.* 1998;27(5):1435-1440.
287. Huang JF. Hepatic steatosis is associated with advanced fibrosis and prolonged HCV RNA decline during peginterferon plus ribavirin therapy in patients with dual chronic hepatitis C and B infections. *BMC Infect Dis.* 2015;15:190.
288. Petta S. Metabolic syndrome and severity of fibrosis in nonalcoholic fatty liver disease: an age-dependent risk profiling study. *Liver Int.* 2017;37(9):1389-1396.
289. Kawaguchi T. Interaction between hepatitis C virus and metabolic factors. *World J Gastroenterol.* 2014;20(11):2888-2901.
290. Bernsmeier C. Patients with liver disease have distinct gut microbial signatures. *Gut.* 2020;69(7):1327-1338.
291. Lohse AW. Autoimmune hepatitis. *J Hepatol.* 2010;53(1):171-179.
292. Tanaka A. Current understanding of primary biliary cholangitis. *Clin Mol Hepatol.* 2021;27(1):1-21.
293. Verma S. Metabolic syndrome and autoimmune hepatitis. *Am J Med Sci.* 2016;351(2):184-189.
294. Floreani A. Metabolic syndrome associated with primary biliary cirrhosis. *Eur J Gastroenterol Hepatol.* 2015;27(3):273-277.
295. Cotler SJ. Characteristics of hepatitis in an urban hospital serving an African American population. *Dig Dis Sci.* 2003;48(5):986-990.
296. Hennes EM. Simplified criteria for diagnosing autoimmune hepatitis. *Hepatology.* 2008;48(1):169-176.
297. Czaja AJ. Frequency and significance of antibodies against asialoglycoprotein receptors in type 1 autoimmune hepatitis. *Dig Dis Sci.* 1996;41(8):1733-1740.
298. Hurtado-Nedelec M. Characterization of alternatively activated human macrophages. *Br J Haematol.* 2007;137(4):305-316.
299. Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver diseases. *World J Gastroenterol.* 2014;20(10):2515-2532.
300. Manns MP. Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010;51(6):2193-2213.
301. Sookoian S. Meta-analysis of the influence of the I148M variant of

- patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology*. 2011;53(6):1883-1894.
302. Kozlitina J. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2014;46(4):352-356.
303. Liu YL. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with nonalcoholic fatty liver disease. *Nat Commun*. 2014;5:4309.
304. Dongiovanni P. PNPLA3 I148M polymorphism and progressive liver disease. *World J Gastroenterol*. 2013;19(41):6969-6978.
305. Valenti L. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology*. 2010;51(4):1209-1217.
306. Rotman Y. Association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology*. 2010;52(3):894-903.
307. Speliotes EK. Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits. *PLoS Genet*. 2011;7(3):e1001324.
308. Dongiovanni P. Genetic predisposition in NAFLD and NASH: impact on the severity of liver disease and response to treatment. *Curr Pharm Des*. 2013;19(29):5219-5238.
309. Krawczyk M. PNPLA3-associated steatohepatitis: Toward a gene-based classification of fatty liver disease. *Semin Liver Dis*. 2013;33(4):369-379.
310. Salomone F. PNPLA3 and TM6SF2 polymorphisms in NAFLD: potential therapeutic targets. *J Hepatol*. 2015;63(3):579-583.
311. Anstee QM. Genome-wide association study of non-alcoholic fatty liver disease and steatohepatitis in a histologically characterized cohort. *J Hepatol*. 2020;73(3):505-515.
312. Abul-Husn NS. A protein-truncating HSD17B13 variant protects against chronic liver disease. *N Engl J Med*. 2018;378(12):1096-1106.
313. Mancina RM. The MBOAT7-TMC4 variant rs641738 increases the risk of nonalcoholic fatty liver disease in individuals of European descent. *Gastroenterology*. 2016;150(5):1219-1230.
314. Luukkonen PK. The PNPLA3 I148M variant increases the hepatic retention of polyunsaturated fatty acids. *JCI Insight*. 2019;4(16):e127902.
315. Nobili V. NAFLD in children: a prospective clinical-pathological study and the effect of lifestyle advice. *Hepatology*. 2006;44(2):458-465.
316. Papatheodoridis GV. The role of diabetes mellitus in chronic hepatitis B and C infections. *Liver Int*. 2006;26(2):125-136.
317. Buzzetti E. Multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016;65(8):1038-1048.
318. Hardy T. Nonalcoholic fatty liver disease: Pathogenesis and disease spectrum. *Annu Rev Pathol*. 2016;11:451-496.
319. Lonardo A. Hypertension, diabetes, atherosclerosis, and nonalcoholic fatty NASH: cause or 2018;68(2):335-352.
320. Cusi K. Role of obesity and lipotoxicity in the development of non-alcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology*. 2012;142(4):711-725.
321. Bril F. Use of plasma biomarker panels as a novel approach to optimize the selection of patients at risk for NASH. *Diabetes Care*. 2020;43(8):1766-1775.
322. Vilar-Gomez E. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multinational cohort study. *Gastroenterology*. 2018;155(2):443-457.
323. Ratziu V. Sampling variability in the diagnostic biomarkers of NAFLD. *J Hepatol*. 2019;70(6):1074-1083.
324. White DL. Association between nonalcoholic fatty liver disease and risk of hepatocellular cancer: a systematic review. *Clin Gastroenterol Hepatol*. 2012;10(12):1342-1359.
325. Ferraioli G. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 3: Liver. *Ultrasound Med Biol*. 2015;41(5):1161-1179.
326. Schwenzer NF. Noninvasive assessment and quantification of liver steatosis using ultrasound, computed tomography, and magnetic resonance. *J Hepatol*. 2009;51(3):433-445.
327. Lin SC. Noninvasive diagnosis of nonalcoholic fatty liver disease and quantification of liver fat using a new quantitative ultrasound technique. *Clin Gastroenterol Hepatol*. 2015;13(7):1337-1345.
328. Bae JS. Hepatic steatosis: Investigation with quantitative US. *Radiology*. 2015;276(3):766-774.
329. Forlano R. Multiparametric MRI for the improved diagnosis of hepatocellular carcinoma in chronic liver disease. *Radiology*. 2020;296(3):597-608.
330. Liang W. Artificial intelligence for stepwise diagnosis and monitoring of COVID-19. *Eur Radiol*. 2022;32(4):2235-2245.