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Mini Review

From Imaging to Prognosis: The prognostic Value of Vascular and Parenchymal Enhancement Patterns in Chronic Liver Disease by Contrast-Enhanced Ultrasound and MRI

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Abstract

Chronic Liver Disease (CLD) is characterized by progressive architectural distortion, hepatocellular dysfunction, and microvascular remodeling, all of which evolve long before clinical decompensation becomes apparent. Advances in non-invasive imaging now allow quantitative evaluation of these processes. Magnetic Resonance Imaging (MRI), particularly with gadoxetic acid enhancement, provides detailed structural and functional assessment of hepatic parenchyma. The Functional Liver Imaging Score (FLIS) and quantitative Hepatic Enhancement (HE) have emerged as promising biomarkers capable of predicting hepatic decompensation, portal hypertension, and survival. Complementarily, Contrast-Enhanced Ultrasound (CEUS) allows real-time evaluation of hepatic perfusion, with parameters such as Hepatic Vein Arrival Time (HVAT) and intrahepatic transit times serving as sensitive indicators of fibrosis and portal hypertension. This mini-review discusses the prognostic value of vascular and parenchymal enhancement abnormalities in CLD, synthesizing recent evidence on MRI-and CEUS-derived biomarkers. We highlight the emerging role of quantitative HE as a second-generation MRI biomarker, the strengths and limitations of each imaging modality, and the potential of integrated diagnostic pathways combining serum tests, elastography, CEUS, and MRI to optimize risk stratification in patients with advanced chronic liver disease.

Keywords: Advanced chronic liver disease; Functional liver imaging score; Gadoxetic acid-enhanced MRI; Hepatic enhancement; Magnetic resonance elastography; Contrast-enhanced ultrasound; Prognosis, cirrhosis; Portal hypertension multiparametric MRI; Risk stratification; Non-invasive tests

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Introduction

This mini-review provides a comprehensive synthesis of contemporary advancements in non-invasive imaging for chronic liver disease, including MRI-derived biomarkers such as FLIS and quantitative hepatic enhancement, as well as CEUS perfusion parameters like HVAT. Detailed corrections have been incorporated throughout the manuscript to enhance clarity, academic tone, and structural coherence.

The rising prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and its progressive form, Metabolic Dysfunction-Associated Steatohepatitis (MASH), has prompted major liver societies such as the AASLD to recommend proactive fibrosis screening in high-risk groups **[1]**. These include individuals with type 2 diabetes, medically complicated obesity, a family history of cirrhosis, or concomitant alcohol Use-populations in whom advanced fibrosis often remains silent until late stages **[2-4].**

Given the rising prevalence of these conditions, screening is a crucial preventative measure for individuals with co-occurring risk factors, which typically include obesity, type 2 diabetes, high blood pressure, and high cholesterol. Early identification of liver fibrosis through non-invasive methods allows for timely intervention and management strategies to prevent disease progression to more serious liver conditions like cirrhosis and liver cancer **[5].**

Traditionally, liver biopsy has been regarded as the diagnostic benchmark for MASH because it directly assesses inflammation, ballooning, and fibrosis. However, its clinical limitations have become increasingly evident. Besides being expensive and invasive, biopsy is susceptible to sampling error and inter-observer variation in pathological interpretation. Complications, though infrequent, are not negligible: pain, infection, and hemorrhage can occur, and some studies estimate a small but real mortality risk. Procedural difficulty and complication rates also rise substantially in patients with severe obesity, exactly the group in which MASLD is most prevalent.

These drawbacks, coupled with the dramatic increase in at-risk patients, have driven an intense effort to develop reliable Noninvasive Tests (NITs) capable of identifying MASH and clinically significant fibrosis without the need for tissue sampling **[6].** NITs fall broadly into serum-based biomarkers and imaging-based tools. Serum tests are particularly attractive because they rely on routine laboratory values and demographic characteristics such as age, sex, and BMI. Simple serum-based indices include widely used scores like the FIB-4, AST-to-platelet ratio index, the NAFLD fibrosis score, and various AST/ALT-derived ratios. These markers help stratify risk in primary care and endocrine settings and are useful for ruling out advanced fibrosis in the general MASLD population **[7].**

More sophisticated serum biomarkers have also been developed to improve diagnostic accuracy. These tests incorporate specialized analytes-such as alpha-2-macroglobulin, apolipoprotein A1, hyaluronic acid, and tissue inhibitor of metalloproteinase 1-to better discriminate between mild and advanced fibrosis. Commercial panels including FibroTest/FibroSure, FibroSpect, the enhanced liver fibrosis (ELF) score, pro-C3-based assays, and the NIS4 algorithm represent this category and have shown promising performance in targeted populations **[8].**

Although NITs cannot yet fully replace biopsy in all clinical scenarios, their advantages are substantial. They are safer, more accessible, better tolerated, and more cost-effective, and they facilitate repeated measurement for disease tracking. As MASLD continues to expand globally, the integration of serum biomarkers and elastography-based imaging into routine care represents a critical step toward early identification and management of patients at risk for progressive liver injury **[9].**

Imaging Modalities of Hepatic Fibrosis Evaluation

Parallel advances in imaging have added further noninvasive options. Techniques such as vibration-controlled transient elastography, shear-wave elastography, and magnetic resonance elastography quantify liver stiffness-a biophysical surrogate for fibrosis-through ultrasound- or MRI-based assessments of wave propagation through hepatic tissue. These modalities are painless, rapid, and repeatable, offering clinicians a practical means of longitudinal monitoring **[10].**

Magnetic resonance imaging offers a non-invasive, quantitative approach to assessing hepatic fibrosis by integrating tissue-specific parameters such as T1/T2 mapping, diffusion-weighted imaging, and MR elastography. These MRI-derived biomarkers capture structural and biomechanical alterations in the liver parenchyma, enabling earlier detection, staging, and longitudinal monitoring of fibrotic progression compared with conventional imaging.

A primary strength of MRI lies in its ability to accurately stage liver fibrosis, a key determinant of cirrhosis. Multiple studies have established Magnetic Resonance Elastography (MRE) as superior to TE for this purpose. Imajo et al. (2016) **[11]** and Park et al. (2017) **[12]** both demonstrated that MRE had a significantly higher area under the receiver operating characteristic curve (AUROC) than TE for detecting various stages of fibrosis in patients with Non-Alcoholic Fatty Liver Disease (NAFLD). This superior diagnostic performance was later confirmed in a broader CLD cohort by Lee et al. (2022) **[13].** Furthermore, MRE's prognostic value is profound; Gidener et al. (2022) **[14]** showed in a large retrospective study that baseline MRE measurements could independently predict the future development of cirrhosis, hepatic decompensation, and transplant-free survival. Beyond fibrosis, multiparametric MRI (mp MRI) provides a comprehensive "liquid biopsy" of the liver parenchyma.

The Proton Density Fat Fraction (PDFF) technique is now the non-invasive gold standard for quantifying steatosis, outperforming TE-based Controlled Attenuation Parameter (CAP) (Imajo et al., 2016 **[11];** Park et al., 2017 **[12]**). Techniques like iron-corrected T1 (cT1) mapping quantify fibro-inflammatory activity, and Imajo et al. (2021) **[15]** found that a combination of cT1 and PDFF was the best non-invasive test for diagnosing Non-Alcoholic Steatohepatitis (NASH). Pavlides et al. (2016) **[16]** were among the first to show that a multiparametric score combining cT1, PDFF, and iron content could predict clinical outcomes in CLD patients. For patients with cirrhosis, MRI's role expands to functional assessment and complication monitoring. The functional liver imaging score (FLIS), derived from gadoxetic acid-enhanced MRI, has emerged as a robust marker of global liver function. Bastati et al. (2016) **[17]** first showed its power to predict graft survival post-liver transplant. Subsequently, Luo et al. (2022) **[18]** and others (Sakai et al., 2024 **[19];** Li et al., 2024 **[20])** demonstrated that a low FLIS is a strong independent predictor of post-hepatectomy liver failure and worse overall survival in hepatocellular carcinoma (HCC) patients. MRI also excels in detecting portal hypertension, with spleen stiffness on MRE proving to be a better predictor of high-risk esophageal varices than liver stiffness (Han et al., 2024) **[21].** The application of advanced MRI extends to special populations, including children with autoimmune liver diseases, where quantitative MR cholangiopancreatography can differentiate between subtypes (Gilligan et al., 2020) **[22],** and for diagnosing sarcopenia, a critical prognostic factor in cirrhosis (Nakamura et al., 2022 **[23]**; Nakamura et al., 2025 **[24]**).

Recently, The FLIS, as succinctly outlined by Stanciu et al. **[8],** is an elegantly simple yet powerful semi-quantitative tool. Its tripartite structure-assessing hepatic parenchymal enhancement relative to the right kidney, biliary excretion of contrast, and portal vein signal intensity relative to the liver parenchyma-captures the essence of hepatocellular health in a single, composite score ranging from 0 to 6 **[9]**. The pathophysiological rationale is sound: it directly interrogates the key processes of hepatocyte-specific uptake via Organic Anion-Transporting Polypeptides (OATPs), subsequent biliary excretion via the multidrug resistance-associated protein 2 (MRP2), and the hemodynamic consequences of portal **[10].** A high FLIS **[5-6]** signifies preserved uptake, patent biliary drainage, and a lack of portosystemic shunting, incidenting a functionally competent liver. Conversely, a low FLIS (0-2) indicates failing hepatocyte function, impaired excretion, and significant portal hypertension, heralding a poor prognosis. The international literature has consistently validated FLIS as a robust prognostic marker, and its utility in assessing hepatic functional reserve is being recognized in expert reviews of quantitative liver MRI. The seminal work by Bastati et al. **[2],** which introduced FLIS, demonstrated its power to predict outcomes following liver transplantation. This was powerfully extended by the same group. in a later study, which confirmed that low FLIS scores were independently associated with an increased risk of hepatic decompensation and mortality in patients with ACLD, effectively stratifying patients beyond what was possible with clinical scores alone **[11]**. The study by Stanciu et al. **[8]** beautifully complements this, showing a strong positive correlation (*r* = 0.797) between their quantitative global HE and the semi-quantitative FLIS, thereby bridging objective measurement and visual assessment.

Other studies [9,12-36] **(Table 1)** have echoed these findings. Magnetic Resonance Imaging (MRI) has transcended its traditional anatomical role to become a cornerstone in the non-invasive diagnosis, staging, and prognostication of cirrhosis and Chronic Liver Disease (CLD). The evolution from standard imaging to quantitative, multiparametric techniques has provided clinicians with powerful tools that rival, and in many cases surpass, both invasive biopsy and other non-invasive methods like Transient Elastography (TE). Table 1 offers a panoramic view of the current landscape of Magnetic Resonance Imaging (MRI) in chronic liver disease, delineating three major technological pillars: functional assessment with gadoxetic acid, structural evaluation with elastography (MRE), and multiparametric approaches. As Table 1 clearly demonstrates, FLIS has rapidly evolved from a novel concept into a well-validated prognostic tool, particularly in the surgical oncology setting. Studies by Luo **[3]**, Zheng **[25],** and Ding **[26]** consistently report FLIS as a powerful predictor of Post-Hepatectomy Liver Failure (PHLF), often outperforming established clinical scores like MELD and ALBI, with AUCs ranging from 0.75 to an impressive 0.91 (C-index). The strength of FLIS, as evidenced by this body of literature, lies in its clinical translatability. It transforms complex imaging data into a simple, semi-quantitative score that integrates parenchymal uptake, biliary excretion, and vascular dynamics, providing a holistic "gestalt" of liver health. Its widespread validation across multiple large, retrospective cohorts, as shown in the table, underscores its robustness. However, their work strategically builds upon this foundation by probing a key limitation inherent to any semi-quantitative system: subjectivity. While FLIS is reproducible, it remains a visual score. Stanciu et al. **[27]** ask the next logical question: can we extract a more objective, continuous, and physically quantifiable measurement from the same gadoxetate-enhanced MRI dataset?

This is where their investigation into quantitative Hepatic Enhancement (HE) provides a critical advancement. By moving from a 0-6 visual scale to a continuous numerical value derived from signal intensity changes, they aim to reduce observer variability and potentially detect more subtle gradients of dysfunction. Their finding that segment VI HE showed an independent association with outcomes in multivariate analysis, even after adjusting for established scores, is highly significant. It suggests that this quantitative parameter captures a unique, spatially-specific facet of liver function that is not entirely redundant with the composite FLIS.

In essence, the literature showcases FLIS as a powerful, "first-generation" functional imaging biomarker, perfectly suited for rapid clinical integration and strong prognostic stratification, especially for discrete events like PHLF. The Stanciu paper **[27],** conversely, represents a "second-generation" approach. It does not seek to replace FLIS but to complement and refine it, arguing for a future where quantitative, automated biomarkers like HE could offer enhanced sensitivity for monitoring disease progression and tailoring risk stratification in medical (non-surgical) ACLD populations. The trajectory suggested is a shift from validated visual scoring towards an era of precision radiomics, where objective measurements extracted from routine clinical images provide a deeper, more granular understanding of hepatic functional reserve.

However, we highlight a potential limitation of FLIS: its semi-quantitative nature. Stanciu et al. **[27]** rightly note that FLIS, being based on visual evaluation, "may be influenced by observer variability". This suggests that while FLIS serves as an excellent gateway to functional assessment, the future may lie in automated, quantitative parameters that can be seamlessly integrated into radiomic models or artificial intelligence (AI) algorithms, as alluded to in their discussion **[12, 27].** This brings us to a critical juncture in the discussion: the translation of these sophisticated MRI biomarkers from the research realm into widespread clinical practice, particularly for screening and surveillance. While the data for FLIS and HE are compelling, we must confront the formidable practical barriers that preclude MRI from becoming a first-line screening tool for chronic liver disease at a population level.

The first and most pronounced hurdle is availability. High-field MRI systems, especially those configured with sequences optimized for hepatobiliary contrast agents, are not ubiquitously available. They are predominantly concentrated in tertiary care centers and academic institutions. In rural or resource-limited settings, access to such technology can be severely restricted. This stands in stark contrast to ultrasound, the current cornerstone of liver disease screening, which is portable, widely available, and significantly less technically demanding. Closely tied to availability is the issue of cost. An MRI examination is a high-cost procedure. The expense encompasses the MRI scanner itself, its maintenance, the specialized hepatobiliary contrast agent (gadoxetate disodium), and the radiologist's time for interpretation and potential post-processing. When considering screening large at-risk populations, such as those with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), the economic burden of implementing routine MRI surveillance would be staggering for any healthcare system. While preliminary cost-effectiveness analyses, like the one cited by Stanciu et al. **[27]** suggesting an incremental cost-effectiveness ratio of € 9900 per quality-adjusted life-year for AI-enhanced MRI in HCC surveillance, are promising, they remain theoretical and require validation in real-world, diverse healthcare economies **[28].**

Furthermore, even in well-resourced settings, waiting lists for non-urgent MRI scans can be protracted. Using MRI for screening asymptomatic individuals with early disease would inevitably exacerbate these delays, potentially crowding out access for patients with more immediate diagnostic needs, such as oncological staging or neurological emergencies. The logistical challenge of scheduling, performing, and reporting a high volume of screening MRIs is non-trivial. Finally, patient-related factors cannot be overlooked. Claustrophobia, the presence of non-MRI compatible implants, and impaired renal function (a relative contraindication for gadolinium-based agents) exclude a not-insignificant portion of the patient population. The requirement to remain still during a 20-minute hepatobiliary phase acquisition, following a multi-phase dynamic study, demands a level of patient cooperation that is not always attainable.

Contrast-Enhanced us and Diagnosis of Cirrhosis

Perfusion kinetics derived from dynamic CEUS, notably the Hepatic Vein Transit Time (HVTT), provide a quantitative, albeit indirect, window into the microvascular derangements-specifically sinusoidal capillarization and increased intrahepatic shunting-that are a direct hemodynamic consequence of progressive fibrogenesis **[29].**

While superb at mapping focal lesions, CEUS for diffuse fibrosis hinges on functional hemodynamic biomarkers; its diagnostic utility is thus contingent upon the fibrotic stage, being more reliable in detecting the significant portal hypertension of advanced fibrosis than the subtle architectural changes of early disease.

The real-time characteristics of hepatic microvasculature, as a marker of the degree of chronic liver disease, have been studied since 1999 **[30]** with a simple, bedside examination: Contrast-Enhanced Ultrasound (CEUS).

CEUS offers a real-time window into the liver's circulatory health, establishing itself as a dynamic, bedside-ready tool for diagnosing cirrhosis and its complications. Unlike static imaging, CEUS provides a second-by-second assessment of hepatic hemodynamics [30], capitalizing on the profound circulatory changes that accompany cirrhosis, such as intrahepatic shunts and portal hypertension.

The foundational principle **(Table 2),** established by Albrecht (1999) **[30]**, demonstrated that a bolus of ultrasound contrast agent (initially Levovist) arrives significantly earlier in the hepatic veins of cirrhotic patients compared to those with non-cirrhotic liver disease or healthy controls. This "Hepatic Vein Arrival Time" (HVAT) became a cornerstone metric. Subsequent studies consistently validated this finding, with Giuseppetti (2004) **[31]** and Abbattista (2008 **[32]**; 2016 **[33]**) confirming that an HVAT cutoff of around 17 seconds could discriminate cirrhosis with high sensitivity (91-100%) and specificity (93-100%). The evolution from first-generation (Levovist) to second-generation (SonoVue) agents, as compared by Lim (2006) **[34]**, further refined the technique, offering shorter transit times and excellent reproducibility.

A key advancement was the measurement of "intrahepatic transit times," such as the interval between hepatic artery and hepatic vein enhancement (HA-HVTT). Hirota (2005) **[35, 36]** and Li (2010) **[36]** showed that these intervals shorten progressively with the severity of fibrosis and cirrhosis, offering a quantitative means to stage liver disease. The utility of CEUS extends beyond mere diagnosis to the evaluation of its major complication, portal hypertension. Jeong (2015) **[37]** found that the Intrahepatic Transit Time (ITT) was the most accurate CEUS parameter for predicting severe portal hypertension (HVPG $\geq$ 12 mmHg), with an AUC of 0.94. More recently, Zocco (2023) **[38]** combined CEUS with elastography, finding that liver parenchyma peak intensity (PI-LP) could predict clinically significant portal hypertension with perfect accuracy (AUC 1.000), while Zhou (2025) **[29]** demonstrated the value of spleen-specific CEUS parameters for predicting HVPG non-invasively.

Crucially, CEUS possesses inherent advantages that position it as an ideal tool for monitoring and accessible hemodynamic assessment. It is a dynamic examination, providing immediate physiological feedback. The procedure is quick to perform, costs relatively little compared to cross-sectional imaging, and can be performed portably at the patient's bedside. It is important to note that, like all ultrasound techniques, it is operator-dependent and can be limited by patient body habitus, a factor less relevant for MRI **[39]**. It is a dynamic examination, providing immediate physiological feedback. The procedure is quick to perform, costs relatively little compared to cross-sectional imaging, and, most importantly, can be performed portably at the patient's bedside. This makes it exceptionally accessible for frail, hospitalized, or frequently monitored patients.

Comparison Between Ceus and MRI

While Magnetic Resonance Imaging (MRI) is a powerful comprehensive tool, CEUS offers distinct practical advantages for specific clinical scenarios, particularly as a first-line hemodynamic assessment. Recent international guidelines from the WFUMB **[40]** affirm the high diagnostic accuracy of CEUS for assessing liver cirrhosis and portal hypertension, highlighting its role as a real-time, accessible, and cost-effective alternative. One study demonstrated that CEUS had superior sensitivity over MRI for diagnosing hepatocellular carcinoma using the LI-RADS algorithm. The two modalities exhibited differing frequencies in visualizing key diagnostic features, with CEUS showing less arterial phase hyper-enhancement but more frequent washout appearance. Despite these discrepancies, both techniques achieved excellent and reliable inter-observer agreement for characterizing major features of focal liver lesions **[41]**. The choice between them should be guided by clinical question, availability, and the need for a comprehensive parenchymal evaluation. CEUS excels as a rapid, repeatable, point-of-care method, perfectly complementing the clinical toolkit for initial diagnosis and surveillance. MRI is significantly more expensive, has longer acquisition times, is less readily available, and cannot be performed at the bedside. CEUS, therefore, offers a more pragmatic, cost-effective, and dynamic first-line hemodynamic assessment. While MRI may provide a more comprehensive pre-transplant workup, CEUS excels as a rapid, repeatable, and highly accurate point-of-care method for the initial diagnosis of cirrhosis and the non-invasive surveillance for portal hypertension, perfectly complementing the clinical toolkit.

CEUS presents a robust and compelling case for its utility in diagnosing cirrhosis and portal hypertension. The evidence from Albrecht (1999) **[42]** to Zhou (2025) **[43]** clearly demonstrates its excellent diagnostic accuracy and unique advantages as a dynamic, bedside tool. To further solidify this argument and enhance its scientific soundness, it would be beneficial to explicitly acknowledge the inherent limitations of the technique. A balanced view only strengthens the case for its appropriate use. Specifically, mentioning well-documented constraints-such as its operator dependency, the challenge of limited beam penetration in obese patients which can affect signal acquisition, and its inability to provide a uniform, global assessment of the entire liver parenchyma in the way that MRI can 45would provide crucial context. By acknowledging these factors, the narrative shifts from simply promoting CEUS to expertly defining its optimal place in the clinical workflow. It frames CEUS not as a wholesale replacement for MRI, but as a powerfully complementary tool whose strengths of accessibility and real-time hemodynamics are best leveraged when its limitations are also understood and respected. This balanced perspective is the hallmark of a sophisticated and credible scientific argument.

The future of liver disease management, as reflected in modern consensus like Baveno VII **[44]**, lies in the intelligent, sequential integration of non-invasive tests (NITs). In this paradigm, MRI and its biomarkers serve as the definitive "one-stop shop" for high-risk patients identified by simpler tools (e.g., FIB-4, LSM by TE or CEUS), providing comprehensive assessment to guide intensive management, transplantation, or major hepatic resection. CEUS, with its dynamic hemodynamic profiling, is poised to be a crucial component in this stratified diagnostic pathway, making functional assessment more accessible and efficient for a broader patient population. Its most potent application may be in "second-tier" testing: for patients already identified as high-risk by simpler, cheaper tools (e.g., FIB-4, liver stiffness measurement by transient elastography), where an MRI can provide a comprehensive "one-stop-shop" assessment-evaluating morphology, detecting focal lesions, and quantifying functional reserve simultaneously. This stratified approach can guide intensive management, as per the Baveno VII consensus **[44]**, and inform critical decisions regarding transplantation or major hepatic resection. The future lies not in replacing existing screening pathways with MRI, but in intelligently integrating it. The development of rapid, abbreviated MRI protocols and the incorporation of AI for automated quantification of parameters like HE holds the promise of making functional assessment more accessible and efficient.

Clinical Implications

The findings synthesized in this mini-review have direct and increasingly tangible implications for the clinical management of patients with Chronic Liver Disease (CLD), particularly in an era where early risk stratification and non-invasive monitoring are central to hepatology practice. The progressive shift from purely anatomical imaging toward functional and hemodynamic biomarkers represents a paradigm change: imaging is no longer confined to diagnosis or lesion detection but is becoming an integral component of prognostic assessment and clinical decision-making.

From a practical standpoint, MRI-derived functional biomarkers such as the Functional Liver Imaging Score (FLIS) and quantitative Hepatic Enhancement (HE) provide clinicians with an objective, reproducible estimate of global hepatic functional reserve. This information is especially relevant in patients with Advanced Chronic Liver Disease (ACLD), in whom conventional laboratory-based scores (e.g., MELD, Child-Pugh) may insufficiently capture subclinical deterioration or regional functional heterogeneity. The consistent association of low FLIS or reduced HE with hepatic decompensation, portal hypertension, post-hepatectomy liver failure, and mortality suggests that these parameters could meaningfully refine prognostic stratification beyond established clinical models. In real-world terms, this translates into improved identification of patients who may benefit from intensified surveillance, earlier referral to tertiary centers, or timely evaluation for liver transplantation.

Quantitative HE, in particular, emerges as a promising second-generation imaging biomarker with potential advantages over semi-quantitative visual scores. By reducing observer dependency and enabling continuous measurement, HE may allow detection of subtle functional decline before overt clinical worsening becomes evident. If prospectively validated, such quantitative metrics could support longitudinal monitoring, treatment response assessment, and individualized risk prediction-key elements of precision medicine in hepatology.

Contrast-Enhanced Ultrasound (CEUS) offers complementary and immediately applicable clinical value. Its ability to assess real-time hepatic perfusion and microvascular remodeling through parameters such as hepatic vein arrival time and intrahepatic transit times makes CEUS a powerful bedside tool for evaluating cirrhosis and portal hypertension. Unlike MRI, CEUS is inexpensive, widely available, repeatable, and feasible in frail or hospitalized patients. These features position CEUS as an ideal modality for dynamic assessment, follow-up, and early detection of clinically significant portal hypertension, particularly in settings where MRI access is limited.

Importantly, the clinical implications of these imaging advances should not be viewed through a competitive lens. Rather, CEUS and MRI fulfill distinct but synergistic roles within a stratified diagnostic pathway. In accordance with contemporary consensus statements such as Baveno VII, serum-based tests and elastography may serve as first-line screening tools, while CEUS can provide rapid functional and hemodynamic refinement. MRI, with its unparalleled multiparametric and functional capabilities, is best reserved for high-risk patients requiring comprehensive evaluation, prognostic clarification, or pre-interventional planning.

Finally, these developments underscore a broader clinical shift toward integrated, non-invasive management strategies in CLD. The combination of serum biomarkers, elastography, CEUS, and advanced MRI-potentially augmented by radiomics and artificial intelligence-offers the opportunity to move beyond binary staging toward nuanced, individualized prognostication. Such an approach has the potential to improve timing of interventions, optimize resource allocation, and ultimately enhance outcomes for patients across the spectrum of chronic liver disease.

Limitations and Knowledge Gaps

Despite the growing body of evidence supporting the prognostic value of Contrast-Enhanced Ultrasound (CEUS) and Magnetic Resonance Imaging (MRI)-derived biomarkers in Chronic Liver Disease (CLD), several important limitations and unresolved knowledge gaps must be acknowledged before these tools can be fully integrated into routine clinical practice.

A major limitation of the current literature is its predominantly retrospective design. Most studies evaluating the Functional Liver Imaging Score (FLIS), quantitative Hepatic Enhancement (HE), and CEUS perfusion parameters have been conducted in single-center or multicenter retrospective cohorts, often enriched for patients with advanced disease or specific clinical scenarios such as hepatocellular carcinoma resection or liver transplantation. While these settings are clinically relevant, they may not reflect the broader and more heterogeneous population of patients with compensated or early-stage CLD. Consequently, the generalizability of these findings to screening, longitudinal surveillance, or primary care-driven pathways remain uncertain.

Standardization represents another critical gap. For MRI-based biomarkers, there is considerable variability in acquisition protocols, scanner vendors, magnetic field strengths, contrast dosing, timing of hepatobiliary phase imaging, and post-processing methods. Quantitative HE, in particular, lacks universally accepted acquisition and normalization standards, and thresholds associated with clinical outcomes are not yet harmonized. Similarly, although FLIS is relatively simple and reproducible, it remains a semi-quantitative, visually derived score and is therefore susceptible to inter-observer variability, especially outside expert centers. Without standardized protocols and validated cutoffs, widespread adoption risks inconsistent interpretation and reduced clinical confidence.

CEUS faces parallel challenges. Although parameters such as hepatic vein arrival time and intrahepatic transit times are physiologically robust, their measurement is operator-dependent and influenced by technical factors including contrast injection technique, ultrasound system settings, patient habitus, and respiratory motion. Moreover, CEUS primarily reflects global hemodynamic alterations and may be less sensitive to early or spatially heterogeneous fibrotic changes. The absence of widely accepted, etiology-specific cutoffs further limit its role as a stand-alone staging tool, particularly in early disease.

A key knowledge gap concerns the comparative and additive value of these imaging biomarkers relative to established non-invasive tests. While many studies demonstrate associations with clinical outcomes, fewer directly evaluate whether MRI- or CEUS-derived parameters meaningfully improve risk prediction beyond validated models incorporating serum biomarkers, elastography, and clinical variables. Prospective studies using head-to-head comparisons and integrated prediction models are needed to clarify when advanced imaging truly changes management rather than duplicating existing information.

Cost-effectiveness and accessibility also remain unresolved issues. MRI, especially with hepatobiliary contrast agents, is expensive, time-consuming, and unevenly available across healthcare systems. Long waiting times and patient-related contraindications further limit scalability. Although preliminary economic analyses and emerging abbreviated MRI protocols are promising, robust real-world data assessing cost-effectiveness across different healthcare settings are still lacking. CEUS is more accessible and affordable, but its reliance on operator expertise raises questions about reproducibility outside specialized centers.

Finally, there is limited evidence on how these biomarkers perform as dynamic tools for monitoring disease progression or therapeutic response. Most available data are cross-sectional, focusing on baseline prognostication rather than longitudinal change. It remains unclear which imaging parameters are most sensitive to meaningful clinical improvement or deterioration over time, and how they should be integrated into follow-up strategies.

Future Directions

Future research should focus on the prospective validation of MRI- and CEUS-derived functional biomarkers across diverse etiologies and stages of chronic liver disease, with particular emphasis on compensated and early disease. Standardization of acquisition protocols, quantitative analysis methods, and clinically meaningful cutoffs-especially for hepatic enhancement and CEUS perfusion parameters-will be essential to ensure reproducibility and facilitate broad clinical adoption. The integration of these imaging biomarkers into multimodal risk models combining serum tests, elastography, and clinical variables represents a key priority, as does the evaluation of their longitudinal sensitivity to disease progression and therapeutic response. Finally, the development of abbreviated MRI protocols and automated, AI-driven quantification tools may improve accessibility, reduce costs, and enable more widespread implementation of functional imaging within stratified, non-invasive care pathways for chronic liver disease.

Discussion & Conclusion

Advances in functional and dynamic imaging have transformed the evaluation of chronic liver disease, providing a non-invasive window into hepatocellular function, microvascular remodeling, and disease progression. MRI-derived biomarkers-particularly FLIS and quantitative hepatic enhancement-offer reproducible, clinically meaningful measures that correlate with hepatic dysfunction, portal hypertension, and patient outcomes. CEUS, through its real-time assessment of perfusion kinetics, similarly captures early vascular alterations and provides a cost-effective, accessible tool for evaluating fibrosis and portal hypertension. Rather than competing modalities, CEUS and MRI are complementary and well suited to sequential integration within modern diagnostic pathways such as those recommended by Baveno VII. CEUS may serve as an efficient intermediate step following serum-based screening, while MRI remains the most comprehensive modality for detailed parenchymal and functional assessment. The future lies in combining these imaging biomarkers with elastography, serum tests, and emerging radiomic or AI-driven tools to refine individualized prognostication and guide therapeutic decision-making in chronic liver disease.

Conflict-of-Interest Statement

The author declares no conflicts of interest.

Corresponding Author's Membership in Professional Societies

Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB) (Italian Society of Ultrasound in Medicine and Biology); Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) (Federation of Associations of Hospital Internist Managers).

Author Contribution

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Table 1: Summary of MRI Studies in Chronic Liver Disease. This summary table synthesizes key findings from recent studies on MRI's role in managing chronic liver disease. The research is broadly categorized by the primary MRI technique used, revealing distinct clinical applications for each. The Functional Liver Imaging Score (FLIS), derived from gadoxetic acid-enhanced MRI, stands out for its strong prognostic value. Studies consistently show that a low FLIS predicts poorer outcomes, including graft survival post-transplant, post-hepatectomy liver failure in HCC patients, and overall survival. It effectively serves as a non-invasive measure of global liver function. Magnetic Resonance Elastography (MRE) is the gold standard for non-invasive fibrosis staging. It demonstrates superior accuracy to ultrasound-based elastography (TE) in detecting and staging liver fibrosis across various etiologies, including MASLD. MRE's stiffness measurements also predict long-term disease progression to cirrhosis and decompensation. Multiparametric MRI (mpMRI) combines parameters like PDFF (fat quantification) and cT1 (fibro-inflammation) to provide a comprehensive tissue characterization. It is particularly effective for diagnosing NASH and differentiating autoimmune liver diseases. Finally, Abbreviated MRI (AMRI) offers a rapid, non-contrast protocol for HCC screening, balancing high accuracy with efficiency. Together, these techniques underscore MRI's transformative role as a non-invasive, one-stop shop for diagnosis, risk stratification, and prognosis in hepatology.

A. Functional Liver Imaging Score (FLIS) & Gadoxetic Acid-Enhanced MRI

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
Bastati, 2016[17]	Adults	128	Post-Liver Transplant	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	ND (P<0.001)	Predicts graft survival probability; outperforms clinical/lab parameters.	Retrospective.
Luo, 2022 [18]	Adults	502	HCC	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	0.752 (for PHLF)	Better predictor of PHLF than MELD, ALBI score, or ICG-R15.	ND

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
Li, 2024 [20]	Adults	339	HCC	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	ND	Predicts cachexia and poor prognosis in HCC patients.	Retrospective.
Sakai, 2024 [19]	Adults	235	HCC	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	ND	Simple prognostic marker; FLIS 2-5 associated with worse survival after hepatectomy.	Retrospective.
Zheng, 2025 [25]	Adults	885	HCC	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	0.746 (for PHLF)	Combined model with FLIS predicts clinically significant PHLF and 90-day mortality.	Retrospective.
Ding, 2025 [26]	Adults	694	HCC	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	0.91 (C-index)	FLIS-based model provides excellent prognostic stratification post-resection.	Multicenter, retrospective.
Zou, 2025 [43]	Adults	443	Chronic Hepatitis B	Gadoxetic Acid (FLIS)	ND	ND	ND	ND	ND	0.801 (for Liver	Best diagnostic efficacy for classifying	Retrospective.

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
										Cirrhosis)	liver function in CHB patients.	
Li, 2025 [45]	Adults	60	HCC	Gadoxetic Acid (FLIS & T1 mapping)	ND	ND	ND	ND	ND	ND	Potential noninvasive indicator of liver regeneration (except after major hepatectomy).	Small sample size, retrospective.

B. Magnetic Resonance Elastography (MRE)

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
Imajo, 2016 [11]	Adults	142	NAFLD	MRE	ND	ND	ND	ND	ND	0.91 (F≥2)	More accurate than TE for fibrosis staging.	ND
Park, 2017 [12]	Adults	104	NAFLD	MRE	ND	ND	ND	ND	ND	0.82 (F≥1)	Superior to TE for detecting any fibrosis.	ND
Gidener, 2022 [14]	Adults	1269	CLD	MRE	ND	ND	ND	ND	ND	ND (Concordance 0.84)	Predictive of long-term progression to cirrhosis and	Retrospective design.

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
											decompensation.	
Lee, 2022 [13]	Adults	280	CLD	MRE	ND	ND	ND	ND	ND	0.846 (F2-F4)	Significantly higher AUROC than TE for significant fibrosis.	ND
Demirtas, 2023 [46]	Children	52	CLD	MRE	90.9 %	82.9 %	84.6%	58.8%	97.1%	ND	High sensitivity/specificity for severe fibrosis in children.	Small sample size.
Feuille, 2024 [47]	Adults	96	CLD	MRE	ND	ND	ND	ND	ND	ND	Non-invasive surrogate for biopsy; reduced biopsy recommendations.	Single-center, observational.
Han, 2024 [21]	Adults	48	CLD	MRE (2D)	100 % (for HVPG≥16mmHg)	45.5 % (for HVPG≥16mmHg)	ND	ND	ND	0.790 (HVPG≥16mmHg)	Spleen stiffness superior to liver stiffness for portal hypertension.	Small sample size.
Mathur, 2025 [48]	Adults	103	MASLD	MRE	ND	ND	ND	ND	ND	ND	Better concordance with	Retrospective, fair agreement with VCTE.

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sens	Spec	ODA	PPV	NPV	AUC	Advantages	Limits
											treatment eligibility; potential cost savings vs. VCTE.	

C. Multiparametric MRI (mpMRI) / Quantitative MRI

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sensibility	Specificity	ODA	PPV	NPV	AUC	Advantages	Limits
Pavlides, 2016 [16]	Adults	112	CLD	mpMRI (LIF score)	ND	ND	(LIF<2)	ND	100%	ND	Predicts clinical outcomes; high negative predictive value.	ND
Gilligan, 2020 [22]	Children/Young Adults	33	Autoimmune (PSC/ASC vs AIH)	Quantitative MRCP	ND	ND	ND	ND	ND	0.92	Good discrimination of PSC/ASC from AIH.	30% exam failure due to motion.
Imajo, 2021 [15]	Adults	145	NASH	mpMRI (cT1, PDFF)	ND	ND	ND	ND	ND	0.83 (for NASH)	Effective non-invasive alternative for NASH diagnosis.	ND

First Author, Year	Patients (Adults/Children)	Number of Patients	Type of Hepatopathy	Type of MRI	Sensibility	Specificity	ODA	PPV	NPV	AUC	Advantages	Limits
Mahalingam, 2023 [49]	Children/Young Adults	39	Autoimmune (PSC/ASC, AIH)	Quantitative MRI (cT1, MRCP, MRE)	ND	ND	ND	ND	ND	ND	No significant changes over 2 years in most patients.	Small sample size, short follow-up.
de Celis Alonso, 2024 [50]	Children (Boys)	81	NAFLD / MetS Risk	mpMRI (PDFF, cT1)	ND	ND	ND	ND	ND	ND	Potential for screening high-risk pediatric populations.	Small, single-gender cohort.

Abbreviations

AIH (Autoimmune hepatitis), ASC (Autoimmune sclerosing cholangitis), AUC (Area under the ROC curve), CAP (Controlled attenuation parameter), cT1 (iron-corrected T1), HCC (Hepatocellular carcinoma), HVPG (Hepatic venous pressure gradient), LIF (Liver inflammation and fibrosis score), MASLD (Metabolic dysfunction-associated steatotic liver disease), MASH (Metabolic dysfunction-associated steatohepatitis), MEFIB (MRE and FIB-4 Index), MRE (Magnetic resonance elastography), mpMRI (Multiparametric MRI), MRCP (Magnetic resonance cholangiopancreatography), MRS (Magnetic resonance spectroscopy), NAFLD (Non-alcoholic fatty liver disease), NASH (Non-alcoholic steatohepatitis), ND (Not declared), NPV (Negative predictive value), PDFF (Proton density fat fraction), PSC (Primary sclerosing cholangitis), Sens (Sensitivity), Spec (Specificity), TE (Transient elastography), VCTE (Vibration-controlled transient elastography).

Table 2: Table of CEUS Studies for Liver Cirrhosis. This table synthesizes over two decades of research into using Contrast-Enhanced Ultrasound (CEUS) to diagnose liver cirrhosis. The collective findings demonstrate that CEUS is not an anatomical imaging tool, but a functional, hemodynamic one. It works by detecting the accelerated transit of microbubble contrast agents through the liver, a phenomenon caused by the intrahepatic shunts and vascular distortions characteristic of cirrhosis. The data reveals a clear evolution. Early studies using the first-generation agent Levovist (Albrecht 1999, Lim 2005) established the core principle, showing dramatically shorter hepatic vein arrival times in cirrhotic patients with near-perfect sensitivity. The subsequent shift to second-generation agents like SonoVue (Lim 2006) refined the technique, leading to larger validation studies (Abbattista 2008, 2016) that confirmed high diagnostic accuracy (e.g., 91-100% sensitivity, 93-100% specificity). Crucially, the application of CEUS has expanded beyond simply detecting cirrhosis. Research now focuses on its ability to stage disease severity and quantify portal hypertension, a major complication. Studies like Jeong (2015) and Zocco (2023) show that specific CEUS parameters can non-invasively predict severe portal hypertension with excellent accuracy, rivaling more invasive gold-standard measurements. In summary, the table charts the progression of CEUS from a promising concept to a robust, practical, and highly accurate clinical tool for the comprehensive management of chronic liver disease.

First Author, Year	Patients (Type, Number)	Type of Hepatopathy	Contrast Agent	Sens (%)	Spec (%)	ODA (%)	PPV (%)	NPV (%)	AUC	Advantages	Limits
LEVOVIST											
Albrecht, 1999 [42]	Adults, 38 (15 Cirr, 12 Non-Cirr, 11 Ctrl)	Mixed Chronic Liver Disease	Levovist	100	100 *	ND	ND	ND	ND	First pilot study, clear separation of groups.	Small sample size, pilot study.
Giuseppetti, 2004 [31]	Adults, 40 (12 Cirr, 16 CLD, 12 Ctrl)	Chronic Liver Disease	Levovist	100 *	100 *	ND	ND	ND	ND	Automated, objective measurements.	Small sample size.
Hirota, 2005 [35]	Adults, 40 (20 Cirr, 20 Non-Cirr)	Compensated Cirrhosis vs. Non-Cirrhotic	Levovist	ND	ND	Highest among tests *	ND	ND	ND	Reflects intrahepatic hemodynamics, high accuracy.	ND
Lim, 2005 [51]	Adults, 85 (HCV patients) + 20 Ctrl	Chronic Hepatitis C	Levovist	100 (for Cirr)	80 (for Cirr)	ND	ND	ND	ND	Non-invasive alternative to biopsy, clear disease severity differentiation.	ND
Lim, 2006 [34]	Adults, 40 (HCV patients) + 25 Ctrl	Chronic Hepatitis C	Levovist	ND	ND	ND	ND	ND	ND	Direct comparison of two agents.	Shorter HVTT with SonoVue limits disease stage

First Author, Year	Patients (Type, Number)	Type of Hepatopathy	Contrast Agent	Sens (%)	Spec (%)	ODA (%)	PPV (%)	NPV (%)	AUC	Advantages	Limits
											differentiation.
SONOVUE											
Lim, 2006 [34]	Adults, 40 (HCV patients) + 25 Ctrl	Chronic Hepatitis C	SonoVue	ND	ND	ND	ND	ND	ND	Shorter transit time, similar cardiopulmonary transit time.	Could not differentiate mild from moderate hepatitis.
Ridolfi, 2007 [52]	Adults, 52 (16 Cirr, 22 CHC, 14 Ctrl)	Chronic Hepatitis C	SonoVue	ND	ND	ND	ND	ND	ND	Reliable for excluding cirrhosis with portal hypertension.	Not useful for assessing severity of chronic hepatitis.
Abbattista, 2008 [32]	Adults, 83 (38 Cirr, 31 CLD, 14 Ctrl)	Chronic Liver Disease	SonoVue	100	93.3	ND	92.6	100	ND	High reproducibility, better than conventional US.	ND
Li, 2010 [36]	Adults, 122 (CHB patients)	Chronic Hepatitis B	SonoVue	ND	ND	ND	ND	ND	0.946 (PV-HVTT for S4)	Quantitative, reflects fibrosis severity.	ND
Berzigotti, 2011 [53]	Adults, 55 Cirr + Ctrl	Liver Cirrhosis	SonoVue	ND	ND	ND	ND	ND	ND	Novel quantitative tool for hepatic perfusion.	Correlates with liver failure, not a

First Author, Year	Patient s (Type, Numbe r)	Type of Hepatopat hy	Contras t Agent	Sen s (%)	Spe c (%)	ODA (%)	PPV (%)	NPV (%)	AUC	Advantages	Limits
											direct diagnostic test for cirrhosis.
Shi, 2012 [54]	Adults, 30 (15 Cirr, 15 Ctrl)	Early-Stage Liver Cirrhosis	SonoVu e	ND	ND	ND	ND	ND	ND	Useful for quantitative diagnosis of early cirrhosis.	Small sample size.
Jeong, 2015 [37]	Adults, 53 Cirr	Liver Cirrhosis (for Portal Hypertensi on)	SonoVu e	92 (for SPH)	89 (for SPH)	ND	ND	ND	0.94 (for SPH)	Useful for estimating severe portal hypertension.	Focus on portal hypertensio n, not cirrhosis diagnosis per se.
Abbattista, 2016 [33]	Adults, 174 (78 Cirr, 82 Non-Cirr, 14 Ctrl)	Chronic Liver Disease	SonoVu e	91.1	93.6	ND	ND	ND	0.95 3	Valid for non-invasive staging, 10-year experience.	ND
Zocco, 2023 [38]	Adults, 46 Cirr	Liver Cirrhosis (for Portal Hypertensi on)	SonoVu e	100 (for CSP H)	100 (for CSP H)	ND	ND	ND	1.00 0 (for CSP H)	Excellent predictor of clinically significant portal hypertension.	Monocentric study.
Zhou, 2025 [29]	Adults, 50 Cirr	Liver Cirrhosis (for Portal	SonoVu e	ND	ND	ND	ND	ND	0.95 8 (for HVP	Non-invasive prediction of HVPG using	Focus on portal hypertensio n, not

First Author, Year	Patients (Type, Number)	Type of Hepatopathy	Contrast Agent	Sens (%)	Spec (%)	ODA (%)	PPV (%)	NPV (%)	AUC	Advantages	Limits
		Hypertension)							G≥10)	spleen parameters.	cirrhosis diagnosis.