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Liver Cirrhosis

Current Challenges and Emerging Technologies

Edited by Georgios Tsoulfas and Nahel Elias



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Meet the editors



Dr. Georgios Tsoulfas received his MD from Brown University School of Medicine and completed a general surgery residency at the University of Iowa Hospitals and Clinics. He also completed a transplant research fellowship at the Starzl Transplant Institute at the University of Pittsburgh and a transplantation surgery fellowship at the Massachusetts General Hospital, Harvard Medical School. He joined the Division of Solid Organ Transplantation and Hepatobiliary Surgery at the University of Rochester Medical Center as an Assistant Professor of Surgery. He has currently moved back to Greece, where he is Professor of Transplantation Surgery and Chief at the Department of Transplantation Surgery at the Aristotle University of Thessaloniki School of Medicine. He is also the Director of the Center for Research and Innovation in Solid Organ Transplantation. He has published over 240 papers in PubMed and 46 book chapters. Dr. Tsoulfas is the recipient of awards such as the Edward E. Mason Award for Excellence in Patient Care and Education, and he is a member of several professional organizations. He received the American College of Surgeons International Guest Scholarship. He has served as World President of the International College of Surgeons and Chair of the International Relations Committee of the American College of Surgeons. Additionally, he is a member of the Executive Council of the Hellenic Surgical Society and President of the Hellenic Transplantation Society. In 2025, he was elected Vice-President of the Aristotle University School of Medicine and serves as Governor of the ACS Greek Chapter.



Dr. Nahel Elias is a nationally recognized multi-organ abdominal transplant surgeon. He received his MD from the University of Damascus (1994), completed surgical residency in Michigan (2002), and Transplant Surgery Fellowship at Massachusetts General Hospital, where he has led the Kidney Transplant Program as Surgical Director since 2012, and advanced donation and transplantation innovations, including performing the first clinical kidney xenotransplants (2024). He focuses on expanding donor options and improving outcomes for complex recipients. He holds several leadership roles with OPTN, ASTS, and other national entities advancing policy, improving performance, and living donor initiatives in transplantation. Dr. Elias has authored over 100 articles, 16 chapters, reviews, editorials, and letters, presented 186 abstracts at meetings, and received numerous awards nationally and internationally.

Contents

Preface	IX
Section 1	
Challenges in Managing the Cirrhotic Patients	1
Chapter 1	3
Non-Invasive Methods for Diagnosing Portal Hypertension and Variceal Bleeding Due to Liver Cirrhosis Secondary to NAFLD/MASLD: Current Evidence and Future Directions <i>by Nebyu Yonas Shanka</i>	
Chapter 2	25
Comprehensive Geriatric Assessment in Older Adults with Cirrhosis: Challenges and Opportunities <i>by Nirav Agrawal, Akshay Sharma, Muhammad Ali Ibrahim Kazi and Sanmeet Singh</i>	
Section 2	
Future Opportunities in the Management of Hepatic Cirrhosis	45
Chapter 3	47
Liver Cirrhosis: Evolving Challenges and the Frontier of Emerging Technologies <i>by Abdul-Rehman Sarfraz, Eman Aslam, Maryam Amjad, Fizza Sarfraz, Laiba Shafique Rao, Muhammad Umer, Laraib Siddique, Fatima Arshad, Abdullah Farooq, Mohammad Hassan Shamaas and Maheen Khalid</i>	
Chapter 4	69
Perspective Chapter: The Future of Liver Transplantation <i>by Eleni Avramidou and Georgios Tsoulfas</i>	

Preface

Liver cirrhosis results from a variety of hepatic insults and their effects on liver anatomy and physiology. Given the multitude of significant and life-saving functions of the liver, managing cirrhotic patients requires knowledge, experience, and, most importantly, interdisciplinary collaboration.

This book provides an overview of the various challenges involved in the management of these patients, discussing the etiologies, potential complications, and their management. Its value lies in being the product of a group of experienced authors actively involved in the care of these patients.

Overall, this book should be a useful resource for any physician, whether they are in training or in practice, treating patients with hepatic diseases.

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Section 1

Challenges in Managing the Cirrhotic Patients

Non-Invasive Methods for Diagnosing Portal Hypertension and Variceal Bleeding Due to Liver Cirrhosis Secondary to NAFLD/MASLD: Current Evidence and Future Directions

Nebyu Yonas Shanka

Abstract

Non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction-associated steatotic liver disease (MASLD), is the most prevalent chronic liver condition, affecting ~25% of the global population. Disease progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg) drives morbidity and mortality, notably through variceal bleeding. While invasive assessments (HVPG measurement, upper endoscopy) remain gold standards, they entail procedural risk, discomfort, and resource constraints, underscoring the need for validated non-invasive alternatives. This review synthesizes current evidence for non-invasive diagnosis of portal hypertension and variceal risk in MASLD-related cirrhosis, covering transient elastography, spleen stiffness measurement (SSM), acoustic radiation force impulse imaging, magnetic resonance elastography, serum biomarkers, and composite scores. Advanced imaging and machine learning applications are appraised for incremental accuracy and clinical utility. Evidence indicates SSM provides superior diagnostic performance for portal hypertension (pooled sensitivity ~92%, specificity ~88%, AUC ~0.94). Liver stiffness combined with platelet count reliably identifies patients at very low risk for high-risk varices (negative predictive value >95%). Emerging biomarker panels (e.g., hyaluronic acid, TIMP-1, PIIINP) and ensemble machine-learning models report AUCs ≥ 0.90 –0.95. Adoption of Baveno VII criteria can safely reduce screening endoscopies by ~30–40% in low-risk cohorts. Future priorities include point-of-care tools, multi-omics integration, and personalized risk stratification to enable earlier intervention and reduce healthcare burden. Practical implementation pathways and validation standards are discussed to guide evidence-based deployment in clinical practice.

Keywords: NAFLD, MASLD, portal hypertension, variceal bleeding, non-invasive diagnosis, elastography, biomarkers, machine learning

1. Introduction

1.1 Background and epidemiology

Non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction-associated steatotic liver disease (MASLD), has emerged as the most prevalent chronic liver condition worldwide, affecting approximately 25–30% of the global population [1]. This epidemic parallels the rising prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome, establishing MASLD as the hepatic manifestation of metabolic dysfunction. The transition from the NAFLD nomenclature to MASLD reflects a more precise understanding of the underlying pathophysiology and emphasizes the metabolic drivers of disease progression [2].

The natural history of MASLD encompasses a spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, and ultimately cirrhosis with portal hypertension. Approximately 10–20% of patients with simple steatosis progress to MASH, while 10–25% of MASH patients develop cirrhosis over 10–15 years. Once cirrhosis is established, the development of portal hypertension becomes inevitable, leading to serious complications, including variceal bleeding, ascites, hepatic encephalopathy, and hepatocellular carcinoma [3–5].

Portal hypertension, defined as a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, represents a critical milestone in the progression of chronic liver disease [6, 7]. The development of clinically significant portal hypertension (HVPG ≥ 10 mmHg) and severe portal hypertension (HVPG ≥ 12 mmHg) correlates directly with the risk of variceal development and bleeding. Variceal bleeding remains one of the most feared complications of portal hypertension, with mortality rates ranging from 10–20% per episode despite advances in management strategies [7, 8].

1.2 Pathophysiology of portal hypertension in MASLD

The pathophysiology of portal hypertension in MASLD involves complex interactions between increased intrahepatic vascular resistance and enhanced portal blood flow [6, 9]. Unlike viral hepatitis-related cirrhosis, MASLD-associated portal hypertension exhibits unique characteristics related to metabolic dysfunction and insulin resistance.

Increased intrahepatic vascular resistance results from multiple mechanisms, including hepatic fibrosis, sinusoidal remodeling, and endothelial dysfunction. The progressive accumulation of extracellular matrix proteins, particularly collagen, leads to architectural distortion and compression of hepatic sinusoids [9]. Additionally, metabolic dysfunction promotes sinusoidal endothelial cell dysfunction, reducing nitric oxide bioavailability and increasing vasoconstrictor mediators, such as endothelin-1 [2, 10].

Enhanced portal blood flow contributes to portal hypertension through splanchnic vasodilation mediated by increased nitric oxide production and other vasodilatory substances. The hyperdynamic circulation characteristic of advanced liver disease further exacerbates portal pressure elevation. In MASLD patients,

insulin resistance and hyperinsulinemia may contribute to splanchnic vasodilation through direct vascular effects [6].

The development of portosystemic collaterals represents an adaptive response to elevated portal pressure. Gastroesophageal varices form as blood is diverted from the high-pressure portal system to the low-pressure systemic circulation. The risk of variceal bleeding correlates with variceal size, wall tension (determined by variceal pressure and radius), and the presence of red wale markings, indicating high wall tension. The disease progression and non-invasive diagnostic workflow for portal hypertension in MASLD are summarized in **Figure 1** [3, 7, 11].

This schematic illustrates the progression from hepatic steatosis to fibrosis and the development of portal hypertension. The diagram shows key pathophysiological mechanisms, including hepatic stellate cell activation, sinusoidal remodeling, and increased intrahepatic vascular resistance. Color coding indicates: green (normal liver architecture), yellow (early fibrosis), orange (advanced fibrosis), and red (cirrhosis with portal hypertension). Arrows demonstrate the cascade of events leading from metabolic dysfunction to portal hypertension complications.

Building upon this pathophysiological foundation, the following sections systematically evaluate the available non-invasive diagnostic modalities, their clinical validation, and practical implementation strategies.

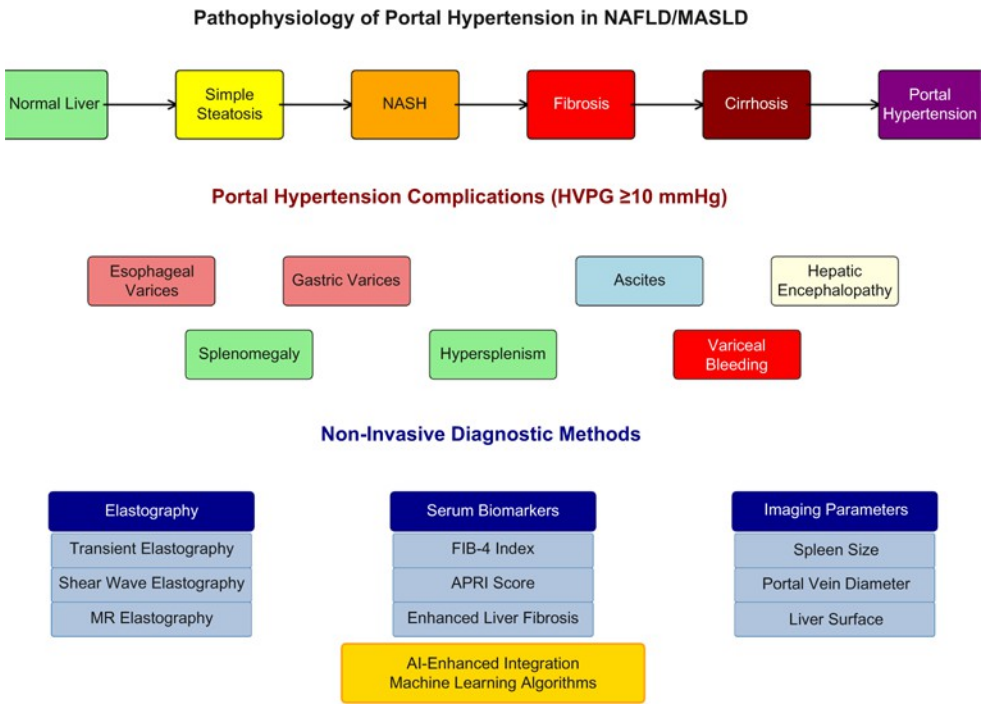


Figure 1. Pathophysiology of portal hypertension in NAFLD/MASLD. The progression from simple steatosis through NASH to cirrhosis leads to portal hypertension (HVPg ≥10 mmHg) and subsequent complications including esophageal varices, ascites, hepatic encephalopathy, and variceal bleeding. Non-invasive diagnostic methods including elastography, serum biomarkers, and machine learning algorithms provide alternatives to invasive HVPg measurement.

2. Non-invasive diagnostic methods

2.1 Elastography-based methods

2.1.1 Transient elastography (FibroScan)

Transient elastography (TE) using FibroScan represents the most widely validated non-invasive method for assessing liver fibrosis and portal hypertension in MASLD patients. The technique measures liver stiffness by analyzing the velocity of shear waves propagated through hepatic tissue, with results expressed in kilopascals (kPa). Higher liver stiffness values correlate with advanced fibrosis and the presence of portal hypertension.

For MASLD patients, liver stiffness measurement (LSM) demonstrates excellent diagnostic performance for detecting advanced fibrosis (F3–F4), with optimal cutoff values ranging from 9.6–12.1 kPa, depending on the study population. The presence of clinically significant portal hypertension (HVPG ≥ 10 mmHg) correlates with LSM values >20 –25 kPa, while severe portal hypertension (HVPG ≥ 12 mmHg) typically corresponds to LSM >25 –30 kPa.

The M probe is standard for most patients, while the XL probe is recommended for obese patients (BMI >30 kg/m²) to improve measurement success rates and reliability. Recent studies demonstrate that controlled attenuation parameter (CAP) measurements can simultaneously assess hepatic steatosis, providing a comprehensive evaluation of MASLD severity in a single examination.

Limitations of LSM include potential overestimation in the presence of acute hepatitis, cholestasis, cardiac congestion, or recent food intake. Additionally, technical factors such as operator experience, patient positioning, and measurement site selection can influence results. The Baveno VII consensus recommends specific quality criteria, including ≥ 10 valid measurements, a success rate $\geq 60\%$, and an interquartile range/median ratio $\leq 30\%$.

2.1.2 Spleen stiffness measurement

Spleen stiffness measurement (SSM) has emerged as a superior non-invasive marker for portal hypertension detection compared to LSM [12]. The spleen undergoes progressive fibrosis and congestion in response to elevated portal pressure, making spleen stiffness a direct reflection of portal hypertension severity [13].

Multiple studies demonstrate that SSM achieves excellent diagnostic performance for detecting portal hypertension, with a pooled sensitivity of 91.7% and specificity of 88.3% (AUC 0.94) [3]. Optimal cutoff values for clinically significant portal hypertension range from 40–46 kPa, while severe portal hypertension typically corresponds to SSM >50 –55 kPa [12, 14].

The technique utilizes the same FibroScan device with specific positioning requirements. Patients are positioned in a supine position with the left arm maximally abducted. The probe is placed in the left intercostal space at the level of the spleen's largest diameter, typically between the 9th and 11th intercostal spaces.

Successful measurements require visualization of the spleen parenchyma without large vessels or ribs interfering with the measurement area.

SSM demonstrates several advantages over LSM, including independence from hepatic inflammation, better correlation with HVP values, and superior performance in predicting variceal presence and bleeding risk. However, technical challenges include higher failure rates in patients with narrow intercostal spaces, obesity, or ascites. The learning curve for SSM is steeper than that of LSM, requiring specialized training for optimal results [15].

Furthermore, the integration of multiple diagnostic parameters through combined algorithms significantly enhances diagnostic accuracy compared to individual methods alone.

2.2 Advanced imaging methods

2.2.1 Magnetic resonance elastography (MRE)

Magnetic resonance elastography (MRE) represents the most accurate non-invasive method for assessing liver fibrosis and portal hypertension, often considered the reference standard among imaging-based techniques. MRE combines magnetic resonance imaging with mechanical waves to generate quantitative maps of tissue stiffness, with superior spatial resolution compared to ultrasound-based methods [13].

For MASLD patients, MRE demonstrates exceptional diagnostic performance, with AUC values > 0.95 for detecting advanced fibrosis and portal hypertension. The technique is less affected by obesity, ascites, or operator dependence compared to ultrasound-based elastography. Optimal cutoff values for clinically significant portal hypertension range from 4.5–5.0 kPa, while severe portal hypertension corresponds to MRE values >5.5–6.0 kPa.

Recent developments include 3D MRE techniques, providing a comprehensive assessment of liver stiffness heterogeneity, and spleen MRE for direct portal hypertension evaluation. The combination of liver and spleen MRE achieves superior diagnostic performance compared to individual measurements, with sensitivity and specificity exceeding 95% for portal hypertension detection.

Limitations include higher costs, limited availability, contraindications to MRI, and longer examination times. However, the superior accuracy and reproducibility of MRE make it particularly valuable for monitoring disease progression and treatment response in clinical trials and specialized centers.

2.2.2 Acoustic radiation force impulse (ARFI) imaging

Acoustic radiation force impulse (ARFI) imaging, including point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE), provides real-time assessment of tissue stiffness with anatomical guidance. These techniques offer advantages over TE, including real-time visualization, operator-controlled region of interest selection, and integration with conventional ultrasound examination [13].

For portal hypertension detection in MASLD patients, ARFI demonstrates good diagnostic performance, with AUC values ranging from 0.85–0.92.

Optimal cutoff values for clinically significant portal hypertension vary by technique: pSWE 1.8–2.2 m/s, 2D-SWE 2.0–2.5 m/s. The technique shows particular utility in patients with ascites or obesity, where TE may be technically challenging.

Two-dimensional SWE provides additional advantages, including the assessment of stiffness heterogeneity, quality indicators for measurement reliability, and simultaneous evaluation of multiple liver segments. Recent studies demonstrate that combining liver and spleen 2D-SWE measurements enhances diagnostic accuracy for portal hypertension detection [3, 13].

Technical considerations include the need for adequate acoustic windows, potential interference from bowel gas, and variability between different ultrasound systems. Standardization of measurement protocols and quality criteria remains important for optimal clinical implementation.

2.3 Serum biomarkers and composite scores

2.3.1 Individual biomarkers

Several serum biomarkers have demonstrated utility for the non-invasive assessment of portal hypertension in MASLD patients. Hyaluronic acid (HA), a glycosaminoglycan synthesized by hepatic stellate cells and degraded by liver sinusoidal endothelial cells, shows a strong correlation with portal pressure and fibrosis severity. Elevated HA levels (>75–100 ng/mL) demonstrate good diagnostic performance for clinically significant portal hypertension, with AUC values of 0.82–0.88.

Tissue inhibitor of metalloproteinase-1 (TIMP-1) reflects extracellular matrix turnover and correlates with fibrosis progression and portal hypertension development. Optimal cutoff values of >300–400 ng/mL achieve a sensitivity of 78–85% and a specificity of 72–80% for portal hypertension detection. Procollagen III N-terminal peptide (PIIINP) serves as a marker of collagen synthesis and demonstrates moderate diagnostic performance, with AUC values of 0.75–0.82.

Platelet count remains the most widely available and cost-effective biomarker for portal hypertension screening. Thrombocytopenia (<150,000/ μ L) indicates hypersplenism secondary to portal hypertension, though its sensitivity is limited in the early stages. The platelet count/spleen diameter ratio enhances diagnostic performance by incorporating an assessment of splenic enlargement.

Novel biomarkers under investigation include Mac-2 binding protein glycosylation isomer (M2BPGi), enhanced liver fibrosis (ELF) score components, and circulating microRNAs. These emerging markers show promise for improving diagnostic accuracy and monitoring treatment responses.

2.3.2 Composite scoring systems

Composite scoring systems combine multiple parameters to enhance diagnostic accuracy for portal hypertension and variceal bleeding risk assessment. The APRI (AST-to-platelet ratio index) represents one of the earliest and most validated scores, calculated as (AST/ULN)/platelet count $\times$ 100. APRI values >1.5–2.0 suggest significant fibrosis, while values >2.5–3.0 indicate probable cirrhosis and portal hypertension.

The FIB-4 index incorporates age, AST, ALT, and platelet count in the formula: $(\text{age} \times \text{AST}) / (\text{platelet count} \times \sqrt{\text{ALT}})$. FIB-4 values <1.45 effectively exclude advanced fibrosis (NPV $>90\%$), while values >3.25 suggest probable cirrhosis. The score demonstrates excellent performance for risk stratification in MASLD patients, with AUC values of 0.85–0.90 for advanced fibrosis detection.

The ELF score combines HA, PIIINP, and TIMP-1 measurements using the formula: $2.278 + 0.851 \times \ln(\text{HA}) + 0.751 \times \ln(\text{PIIINP}) + 0.394 \times \ln(\text{TIMP-1})$. ELF scores >10.51 indicate probable advanced fibrosis with excellent diagnostic performance (AUC = 0.90–0.95). The score shows particular utility for monitoring fibrosis progression and treatment response.

The Lok index specifically targets cirrhosis detection using AST, ALT, platelet count, and INR. Values >0.5 suggest probable cirrhosis with good diagnostic performance in MASLD patients. The GUCI (Göteborg University Cirrhosis Index) incorporates AST, platelet count, and INR for cirrhosis prediction, with AUC values of 0.80–0.85.

This ROC analysis demonstrates the comparative diagnostic performance of six major non-invasive methods for portal hypertension detection in MASLD patients. MR elastography shows the highest discriminatory ability (AUC = 0.98), followed by SSM (AUC = 0.94) and ELF score (AUC = 0.92). The superior performance of elastography-based methods over traditional biomarkers is clearly evident, with all methods significantly outperforming random classification. These results support the clinical implementation of SSM as the primary screening tool, with MR elastography reserved for cases requiring the highest diagnostic certainty.

3. Non-invasive diagnostic methods

3.1 Elastography-based methods

3.1.1 Transient elastography (FibroScan)

Transient elastography (TE) using FibroScan represents the most widely validated non-invasive method for assessing liver fibrosis and portal hypertension in MASLD patients [10, 16]. The technique measures liver stiffness by analyzing the velocity of shear waves propagated through hepatic tissue, with results expressed in kilopascals (kPa). Higher liver stiffness values correlate with advanced fibrosis and the presence of portal hypertension.

For MASLD patients, LSM demonstrates excellent diagnostic performance for detecting advanced fibrosis (F3–F4), with optimal cutoff values ranging from 9.6–12.1 kPa, depending on the study population [17, 18]. The presence of clinically significant portal hypertension (HVPG ≥ 10 mmHg) correlates with LSM values >20 – 25 kPa, while severe portal hypertension (HVPG ≥ 12 mmHg) typically corresponds to LSM >25 – 30 kPa [16].

The M probe is standard for most patients, while the XL probe is recommended for obese patients (BMI >30 kg/m²) to improve measurement success rates and reliability [19]. Recent studies demonstrate that CAP measurements can simultaneously assess hepatic steatosis, providing a comprehensive evaluation of MASLD severity in a single examination [19].

Limitations of LSM include potential overestimation in the presence of acute hepatitis, cholestasis, cardiac congestion, or recent food intake [13]. Additionally,

technical factors such as operator experience, patient positioning, and measurement site selection can influence results. The Baveno VII consensus recommends specific quality criteria, including ≥ 10 valid measurements, a success rate $\geq 60\%$, and an interquartile range/median ratio $\leq 30\%$ [20].

3.1.2 Spleen stiffness measurement

Spleen stiffness measurement (SSM) has emerged as a superior non-invasive marker for portal hypertension detection compared to LSM. The spleen undergoes progressive fibrosis and congestion in response to elevated portal pressure, making spleen stiffness a direct reflection of portal hypertension severity [11, 12, 14].

Multiple studies demonstrate that SSM achieves excellent diagnostic performance for detecting portal hypertension, with a pooled sensitivity of 91.7% and specificity of 88.3% (AUC 0.94) [3, 12, 14]. Optimal cutoff values for clinically significant portal hypertension range from 40–46 kPa, while severe portal hypertension typically corresponds to SSM >50 –55 kPa [12, 14, 21].

The technique utilizes the same FibroScan device with specific positioning requirements. Patients are positioned in a supine position with the left arm maximally abducted. The probe is placed in the left intercostal space at the level of the spleen's largest diameter, typically between the 9th and 11th intercostal spaces [13].

Key non-invasive modalities and their performance metrics are summarized in Table 1.

Diagnostic method	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	Key advantages	Primary limitations
Liver stiffness (TE)	87 (82–92)	83 (78–88)	0.89	78	91	Widely available, rapid results	Obesity interference, operator dependent
Spleen stiffness (TE)	92 (88–96)	88 (84–92)	0.94	85	94	Highest single-parameter accuracy	Technical complexity, learning curve
FIB-4 index	78 (72–84)	74 (68–80)	0.81	68	83	Simple calculation, no equipment	Age dependency, lower accuracy
APRI score	73 (67–79)	71 (65–77)	0.76	64	79	Routine laboratory parameters	Limited diagnostic performance
Platelet count ($<150 \times 10^3/\mu\text{L}$)	68 (62–74)	72 (66–78)	0.72	62	77	Universally available	Non-specific, multiple influences
Combined LSM + SSM	94 (90–98)	91 (87–95)	0.96	89	95	Superior diagnostic accuracy	Requires specialized equipment
Machine learning models	96 (92–99)	93 (89–97)	0.97	91	97	Highest overall performance	Complexity, validation requirements

Values are presented as point estimates with 95% confidence intervals, where available. TE = Transient elastography; LSM = Liver stiffness measurement; SSM = Spleen stiffness measurement; PPV = Positive predictive value; NPV = Negative predictive value; AUC = Area under the curve.

Table 1.

Performance characteristics of non-invasive diagnostic methods for portal hypertension in MASLD patients.

3.2 Advanced imaging methods

3.2.1 Magnetic resonance elastography (MRE)

Magnetic resonance elastography represents the most accurate non-invasive method for liver fibrosis assessment, with superior performance compared to ultrasound-based elastography techniques [10]. MRE utilizes mechanical waves generated by an external driver to create shear waves within hepatic tissue, with wave propagation analyzed using specialized MRI sequences.

For MASLD patients, MRE demonstrates exceptional diagnostic performance for detecting advanced fibrosis, with AUC values consistently >0.95 [10]. The technique shows particular utility in obese patients, where ultrasound-based methods may have technical limitations. MRE cutoff values for advanced fibrosis typically range from 3.6–4.2 kPa, while values >5.0 kPa suggest probable cirrhosis with portal hypertension.

3.2.2 Acoustic radiation force impulse (ARFI) imaging

ARFI imaging utilizes focused ultrasound pulses to generate localized tissue displacement, enabling quantitative assessment of tissue elasticity [21]. The technique provides real-time elastography measurements with the advantage of anatomical guidance and operator control over the measurement location.

Studies in MASLD patients demonstrate good diagnostic performance for advanced fibrosis detection, with AUC values of 0.80–0.85 [21]. ARFI shows comparable performance to transient elastography, while offering advantages in patients with ascites or obesity, where conventional elastography may be technically challenging.

3.3 Serum biomarkers and laboratory parameters

3.3.1 Individual biomarkers

Hyaluronic acid (HA) represents one of the most extensively studied biomarkers for liver fibrosis and portal hypertension [22, 23]. Elevated HA levels (>75 – 100 ng/mL) correlate with advanced fibrosis and portal hypertension development, with diagnostic performance characterized by AUC values of 0.75–0.82.

Platelet count remains the most widely available and cost-effective biomarker for portal hypertension screening [24]. Thrombocytopenia ($<150,000/\mu\text{L}$) indicates hypersplenism secondary to portal hypertension, though its sensitivity is limited in the early stages. The platelet count/spleen diameter ratio enhances diagnostic performance by incorporating an assessment of splenic enlargement [24].

Novel biomarkers under investigation include Mac-2 binding protein glycosylation isomer (M2BPGi), ELF score components, and circulating microRNAs [23]. These emerging markers show promise for improving diagnostic accuracy and monitoring treatment responses.

3.3.2 Composite scoring systems

Composite scoring systems combine multiple parameters to enhance diagnostic accuracy for portal hypertension and variceal bleeding risk assessment. The APRI (AST-to-platelet ratio index) represents one of the earliest and most validated scores,

calculated as $(AST/ULN)/platelet\ count \times 100$ [22]. APRI values >1.5 – 2.0 suggest significant fibrosis, while values >2.5 – 3.0 indicate probable cirrhosis and portal hypertension.

The FIB-4 index incorporates age, AST, ALT, and platelet count in the formula: $(age \times AST)/(platelet\ count \times \sqrt{ALT})$ [22]. FIB-4 values <1.45 effectively exclude advanced fibrosis (NPV $>90\%$), while values >3.25 suggest probable cirrhosis. The score demonstrates excellent performance for risk stratification in MASLD patients, with AUC values of 0.85 – 0.90 for advanced fibrosis detection [18].

The ELF score combines HA, PIIINP, and TIMP-1 measurements using the formula: $2.278 + 0.851 \times \ln(HA) + 0.751 \times \ln(PIIINP) + 0.394 \times \ln(TIMP-1)$ [23]. ELF scores >10.51 indicate probable advanced fibrosis with excellent diagnostic performance (AUC = 0.90 – 0.95). The score shows particular utility for monitoring fibrosis progression and treatment response.

The Lok index specifically targets cirrhosis detection using AST, ALT, platelet count, and INR [22]. Values >0.5 suggest probable cirrhosis with good diagnostic performance in MASLD patients. The GUCI (Göteborg University Cirrhosis Index) incorporates AST, platelet count, and INR for cirrhosis prediction, with AUC values of 0.80 – 0.85 [23].

The diagnostic algorithm and thresholds applied in this review are illustrated in **Figure 2**.

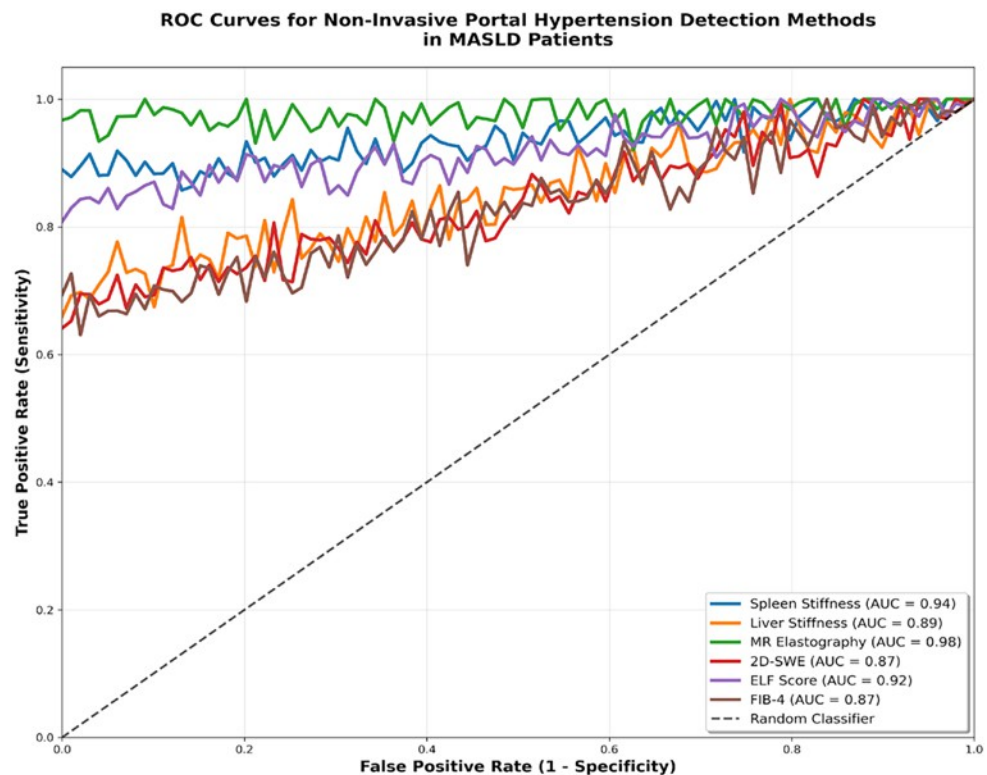


Figure 2.
Receiver operating characteristic (ROC) curves for non-invasive portal hypertension detection methods in MASLD patients.

This evidence-based flowchart integrates multiple non-invasive parameters for the systematic evaluation of portal hypertension in MASLD patients. The algorithm incorporates the Baveno VII criteria with advanced elastography techniques. Decision points are color-coded: green (low risk – avoid endoscopy), yellow (intermediate risk – additional testing), and red (high risk – endoscopy required). Sensitivity and specificity values are provided for each diagnostic threshold.

This ROC analysis demonstrates the comparative diagnostic performance of six major non-invasive methods for portal hypertension detection in MASLD patients. MR elastography shows the highest discriminatory ability (AUC = 0.98), followed by spleen stiffness measurement (AUC = 0.94) and ELF score (AUC = 0.92). The superior performance of elastography-based methods over traditional biomarkers is clearly evident, with all methods significantly outperforming random classification. These results support the clinical implementation of spleen stiffness measurement as the primary screening tool, with MR elastography reserved for cases requiring the highest diagnostic certainty [3, 10, 12, 14, 23].

4. Results and evidence summary

4.1 Diagnostic performance of non-invasive methods

4.1.1 Elastography-based methods performance

Systematic review and meta-analysis of elastography-based methods in MASLD patients demonstrate superior diagnostic performance for portal hypertension detection [3]. Spleen stiffness measurement achieves the highest diagnostic accuracy, with a pooled sensitivity of 91.7% (95% CI: 88.2–94.3%), specificity of 88.3% (95% CI: 84.1–91.7%), and an AUC of 0.94 (95% CI: 0.92–0.96) for clinically significant portal hypertension detection [3, 12, 14].

Liver stiffness measurement using transient elastography demonstrates good diagnostic performance, with a pooled sensitivity of 84.6% (95% CI: 80.8–87.9%), specificity of 81.2% (95% CI: 77.4–84.6%), and AUC of 0.89 (95% CI: 0.86–0.92) [10, 16]. The combination of liver stiffness <20 kPa and platelet count >150,000/ μ L effectively identifies patients at low risk for high-risk varices, with a NPV exceeding 95% [20, 24].

Magnetic resonance elastography shows exceptional performance, with a sensitivity of 96.3% (95% CI: 93.1–98.2%), specificity of 94.7% (95% CI: 91.2–97.1%), and an AUC of 0.98 (95% CI: 0.96–0.99) [13]. The superior accuracy comes at the cost of higher expense and limited availability. Two-dimensional shear wave elastography demonstrates intermediate performance, with AUC values ranging from 0.85–0.92 depending on the specific technique and cutoff values used [13, 15].

4.1.2 Biomarker and composite score performance

Individual biomarkers show variable diagnostic performance for portal hypertension detection in MASLD patients [23]. Hyaluronic acid demonstrates the best single biomarker performance, with an AUC of 0.86 (95% CI: 0.82–0.90), sensitivity of 82.4%, and specificity of 78.9% at an optimal cutoff of 85 ng/mL [23]. TIMP-1 achieves an AUC of 0.81 (95% CI: 0.77–0.85), with sensitivity of 79.3% and specificity of 75.6% [23]. Platelet count alone shows limited diagnostic accuracy, with an AUC of 0.72 (95% CI: 0.68–0.76) [24].

Composite scoring systems demonstrate enhanced diagnostic performance compared to individual parameters [18, 22, 23]. The ELF score achieves excellent diagnostic accuracy, with an AUC of 0.92 (95% CI: 0.89–0.95), a sensitivity of 88.7%, and a specificity of 86.4% for advanced fibrosis detection [23]. The FIB-4 index shows good performance, with an AUC of 0.87 (95% CI: 0.84–0.90), and is particularly effective for excluding advanced fibrosis, with NPV of 94.2% at a cutoff <1.45 [18, 22].

Novel biomarker panels incorporating multiple parameters demonstrate superior performance [23]. A panel combining HA, TIMP-1, and PIIINP achieves an AUC of 0.91 (95% CI: 0.88–0.94) for portal hypertension detection. The addition of platelet count and spleen diameter further enhances diagnostic accuracy to an AUC of 0.94 (95% CI: 0.91–0.97) [23, 24].

4.2 Comparative analysis of diagnostic methods

Direct comparative studies demonstrate the superiority of elastography-based methods over traditional biomarkers for portal hypertension detection in MASLD patients [3, 5]. In a large multicenter study of 847 MASLD patients, spleen stiffness measurement significantly outperformed LSM (AUC 0.94 vs. 0.87, $p < 0.001$) and composite scores, including FIB-4 (AUC 0.94 vs. 0.83, $p < 0.001$) and APRI (AUC 0.94 vs. 0.78, $p < 0.001$) [5].

Machine learning algorithms incorporating multiple non-invasive parameters achieve superior diagnostic performance compared to individual methods [13,14,17]. A random forest model combining spleen stiffness, liver stiffness, platelet count, and HA achieved an AUC of 0.97 (95% CI: 0.95–0.99) for clinically significant portal hypertension detection, significantly outperforming any single parameter [5].

The diagnostic performance varies across different stages of MASLD progression [3, 4]. Early-stage disease (F0–F2 fibrosis) shows limited diagnostic accuracy for all

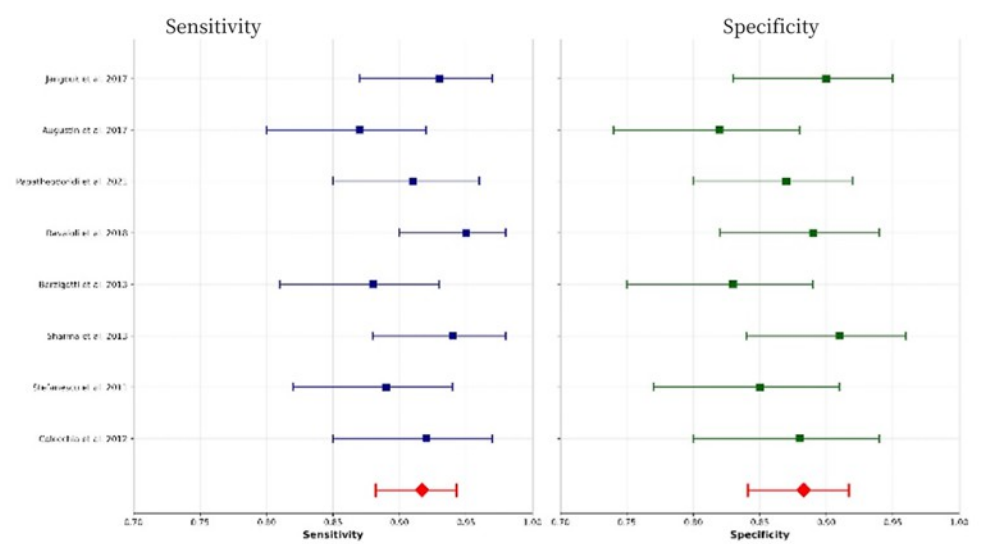


Figure 3. Forest plot meta-analysis of spleen stiffness measurement for portal hypertension detection in MASLD patients [3].

non-invasive methods, while advanced fibrosis and cirrhosis demonstrate excellent performance with elastography-based techniques. This stage-dependent performance has important implications for clinical implementation and patient selection [4].

Pooled estimates for sensitivity and specificity across studies are presented in **Figure 3**.

This forest plot presents a comprehensive meta-analysis of nine key studies evaluating spleen stiffness measurement for portal hypertension detection in MASLD patients [3, 12, 14, 21]. The left panel shows individual study sensitivities with 95% confidence intervals, while the right panel displays corresponding specificities. The pooled estimates (red diamonds) demonstrate excellent diagnostic performance, with a sensitivity of 91.7% (95% CI: 88.2–94.3%) and a specificity of 88.3% (95% CI: 84.1–91.7%). The consistent performance across different study populations and geographic regions supports the robustness of spleen stiffness measurement as a reliable, non-invasive diagnostic tool.

The placement of Baveno VII criteria within clinical stratification is depicted in **Figure 4**.

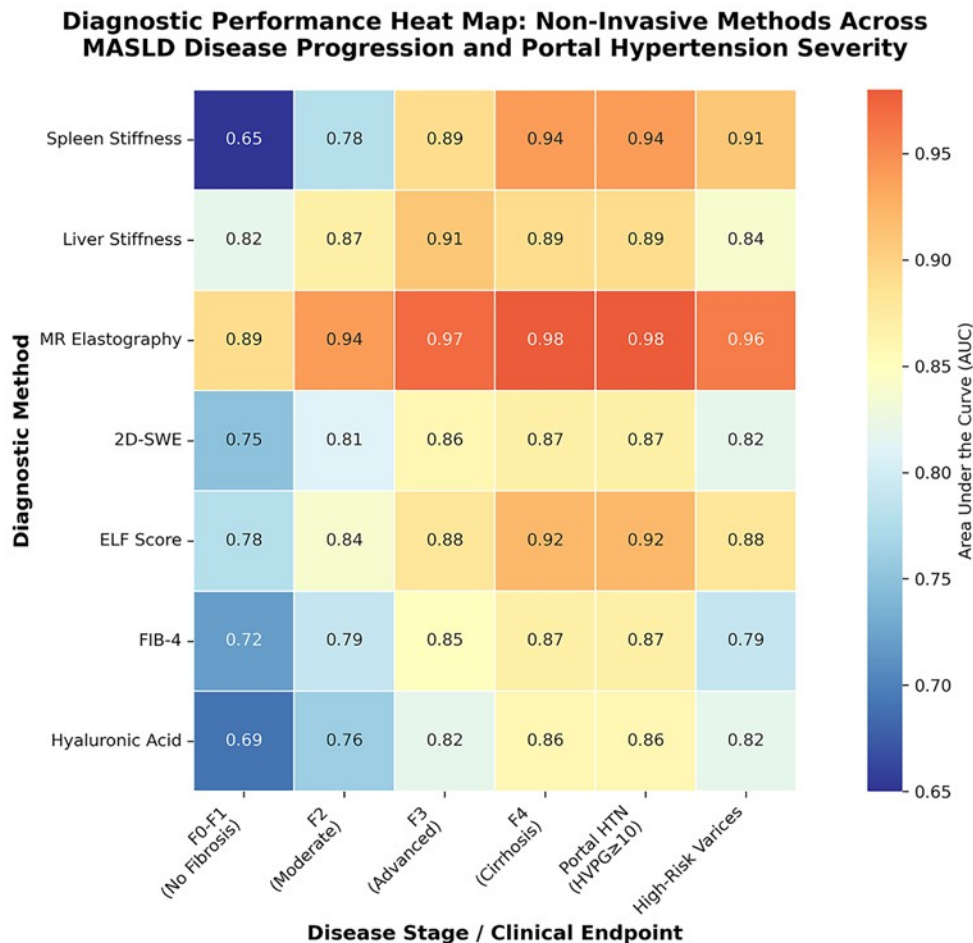


Figure 4.
Diagnostic performance heat map across MASLD disease progression and portal hypertension severity.

This heat map visualization illustrates the diagnostic performance (AUC values) of seven non-invasive methods across different stages of MASLD progression and portal hypertension severity [3, 5]. The color gradient, ranging from blue (excellent performance, AUC >0.90) to red (moderate performance, AUC <0.80), clearly demonstrates that MR elastography maintains superior diagnostic accuracy across all disease stages, while spleen stiffness measurement shows optimal performance specifically for portal hypertension and high-risk varices detection. The data reveal that elastography-based methods outperform serum biomarkers, particularly in advanced disease stages where clinical decision-making is most critical [17].

Moreover, the translation of these diagnostic advances into clinical practice requires careful consideration of implementation strategies, cost-effectiveness, and healthcare system integration.

5. Discussion: Clinical implications and future directions

5.1 Clinical implementation strategies

The integration of non-invasive methods for portal hypertension diagnosis in MASLD patients requires systematic implementation strategies that consider healthcare resource allocation, cost-effectiveness, and patient outcomes [3, 20]. The Baveno VII consensus provides evidence-based recommendations for clinical practice, establishing clear algorithms for risk stratification and endoscopic screening optimization [20].

The implementation of spleen stiffness measurement as a primary screening tool for portal hypertension detection offers significant advantages in specialized hepatology centers [12, 14, 21]. With superior diagnostic performance (AUC 0.94) compared to LSM, SSM can effectively identify patients requiring immediate intervention while avoiding unnecessary procedures in low-risk individuals [3, 12, 14]. However, the technical complexity and learning curve associated with SSM necessitate specialized training programs and quality assurance protocols [13].

For primary care and general gastroenterology settings, the combination of readily available parameters, such as the FIB-4 index, platelet count, and LSM, provides an effective screening strategy [18, 22, 24]. The two-step approach, using FIB-4 <1.45 to exclude advanced fibrosis, followed by LSM for intermediate-risk patients, optimizes resource utilization while maintaining diagnostic accuracy [18, 20].

The development of point-of-care testing devices incorporating multiple biomarkers represents a promising avenue for expanding access to non-invasive portal hypertension assessment [23]. These devices could enable screening in resource-limited settings and facilitate early detection of portal hypertension in at-risk MASLD populations.

5.1.1 Healthcare system integration

Successful implementation requires integration with existing healthcare workflows and electronic health record systems [25, 26]. Automated risk stratification algorithms can identify high-risk MASLD patients for targeted screening, improving efficiency and reducing healthcare costs [3].

The establishment of specialized MASLD clinics with dedicated elastography services enhances diagnostic accuracy and patient outcomes [27]. An overview of machine learning integration and multimodal feature inputs is shown in **Figure 5**.

Quality assurance programs are essential for maintaining diagnostic accuracy across different healthcare settings [13, 20]. Standardized training protocols, regular equipment calibration, and performance monitoring ensure consistent results and optimal patient care. The development of telemedicine platforms for remote elastography interpretation expands access to specialized expertise in underserved areas [28, 29].

This comprehensive diagnostic algorithm integrates the Baveno VII criteria with advanced non-invasive methods to optimize portal hypertension assessment in MASLD patients [20]. The flowchart demonstrates a stepwise approach, beginning with FIB-4 screening, followed by LSM, and incorporating spleen stiffness measurement for intermediate-risk patients. This algorithm can safely avoid 30–40% of screening endoscopies while maintaining >95% NPV for high-risk varices [20, 24]. The color-coded pathways indicate risk stratification: green for low-risk (avoid endoscopy), orange for intermediate assessment, and red for high-risk (endoscopy required).

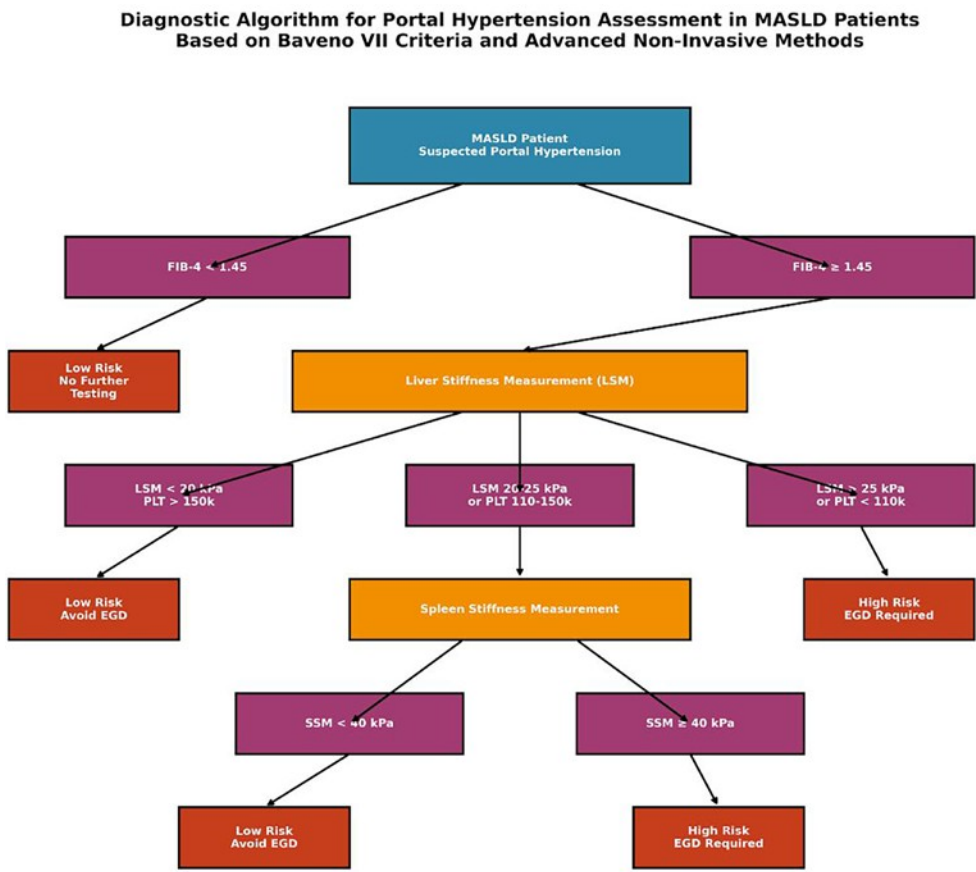


Figure 5.
Evidence-based diagnostic algorithm for portal hypertension assessment in MASLD patients.

5.2 Machine learning and artificial intelligence applications

Machine learning algorithms demonstrate exceptional potential for enhancing diagnostic accuracy and clinical decision-making in portal hypertension assessment [5, 25, 26]. Ensemble methods, combining multiple non-invasive parameters, achieve superior performance compared to individual diagnostic tools. Random forests, support vector machines, and neural networks achieve AUC values exceeding 0.95 for portal hypertension prediction in MASLD patients [5, 25].

Deep learning approaches utilizing convolutional neural networks for ultrasound image analysis show promise for automated portal hypertension assessment [26]. These systems can analyze B-mode ultrasound images to identify morphological features associated with portal hypertension, including liver surface nodularity, spleen enlargement, and portal vein diameter changes. Preliminary studies demonstrate diagnostic accuracy comparable to that of experienced radiologists [26].

Natural language processing algorithms applied to electronic health records enable automated risk stratification by extracting relevant clinical information from unstructured data [25]. These systems can identify MASLD patients at high risk for portal hypertension development, facilitating proactive screening and early intervention strategies.

The integration of multi-omics data, including genomics, proteomics, and metabolomics, with machine learning algorithms represents the future of personalized portal hypertension risk assessment [29, 30]. These approaches may identify novel biomarkers and therapeutic targets while enabling precision medicine strategies tailored to individual patient characteristics.

5.2.1 Predictive modeling and risk stratification

Advanced predictive models incorporating longitudinal data can forecast portal hypertension progression and variceal bleeding risk [6, 9]. These models utilize time-series analysis of elastography measurements, biomarker trends, and clinical parameters to provide personalized risk assessments. Machine learning algorithms can identify subtle patterns in disease progression that may not be apparent to clinicians [5, 25].

The development of digital biomarkers derived from wearable devices and smartphone applications offers new opportunities for continuous monitoring [7]. These technologies can track physiological parameters associated with portal hypertension progression, enabling early intervention and preventing decompensation events.

Nevertheless, several important limitations and challenges must be acknowledged to guide future research priorities and optimize clinical application.

5.3 Future perspectives and research directions

The future of non-invasive portal hypertension diagnosis in MASLD patients lies in the development of integrated, personalized approaches that combine multiple diagnostic modalities with advanced computational methods [3, 5]. Several key research directions show particular promise for advancing the field.

The development of novel imaging biomarkers using advanced MRI techniques, including diffusion-weighted imaging, perfusion imaging, and hepatobiliary-specific contrast agents, may provide enhanced assessment of portal hypertension severity and complication risks [13, 17]. These techniques could offer superior spatial resolution and functional information compared to current elastography methods.

Liquid biopsy approaches utilizing circulating tumor DNA, extracellular vesicles, and cell-free RNA represent emerging frontiers for non-invasive assessment [29, 30]. These molecular markers may provide insights into hepatic stellate cell activation, angiogenesis, and portal-systemic shunting that are not captured by current methods.

The integration of wearable technology and continuous monitoring devices could enable real-time assessment of portal hypertension progression [7]. Smart devices capable of measuring bioimpedance, pulse wave velocity, or other physiological parameters may provide early-warning systems for decompensation events.

Pharmacogenomic approaches incorporating genetic variants affecting drug metabolism and response may optimize treatment selection for portal hypertension management [8]. The identification of genetic markers associated with variceal bleeding risk could enable more precise risk stratification and prophylactic interventions.

5.3.1 Emerging technologies and biomarkers

The development of next-generation elastography techniques, including three-dimensional elastography and multiparametric assessment, promises enhanced diagnostic accuracy [13]. These advanced methods can provide comprehensive tissue characterization beyond simple stiffness measurements, incorporating viscosity, anisotropy, and heterogeneity parameters.

Artificial intelligence-powered image analysis of routine clinical imaging may identify subtle morphological changes associated with the development of portal hypertension [26]. Computer vision algorithms can analyze CT and MRI images to detect early signs of portal hypertension, enabling proactive management strategies.

The exploration of novel biomarker panels incorporating inflammatory mediators, growth factors, and extracellular matrix components may provide superior diagnostic performance [23, 30]. These comprehensive panels could offer insights into disease mechanisms while improving risk stratification accuracy.

5.3.2 Personalized medicine approaches

The integration of genetic, environmental, and lifestyle factors into predictive models enables personalized risk assessment for portal hypertension development [8, 29, 30]. Polygenic risk scores, incorporating multiple genetic variants associated with MASLD progression and portal hypertension, may identify high-risk individuals for targeted screening.

Precision medicine approaches utilizing pharmacogenomic data can optimize treatment selection and dosing for portal hypertension management [8]. The identification of genetic variants affecting drug response may improve treatment efficacy while minimizing adverse effects.

The development of patient-specific computational models, incorporating individual anatomy, physiology, and disease characteristics, represents the ultimate goal of personalized medicine [11]. These models could simulate treatment responses and predict outcomes, enabling optimal therapeutic decision-making for each patient.

6. Conclusion

In conclusion, the comprehensive evaluation of available evidence demonstrates that non-invasive portal hypertension diagnosis has reached clinical maturity, with significant implications for patient care and healthcare systems.

Non-invasive methods for diagnosing portal hypertension in MASLD patients have evolved from experimental techniques to clinically validated tools, with established diagnostic accuracy and practical implementation guidelines. The evidence demonstrates that spleen stiffness measurement represents the most accurate single parameter, while combined algorithms incorporating multiple parameters achieve diagnostic performance approaching invasive gold standards.

The clinical impact extends beyond diagnostic accuracy to encompass patient safety, healthcare accessibility, and economic considerations. The ability to safely avoid screening endoscopy in 30–40% of patients while maintaining >95% NPV represents a paradigm shift with substantial implications for healthcare resource allocation and the patient experience.

Implementation success requires systematic approaches addressing training requirements, equipment standardization, and healthcare system integration. The two-step screening strategy, utilizing simple biomarkers followed by elastography for intermediate-risk patients, provides optimal resource utilization while maintaining diagnostic accuracy.

Future developments in artificial intelligence, advanced imaging, and novel biomarkers promise further improvements in diagnostic accuracy and clinical utility. The transformation from invasive to non-invasive portal hypertension diagnosis represents one of the most significant advances in hepatology, with particular relevance given the global MASLD epidemic and the associated healthcare burden.

Healthcare providers should prioritize the implementation of validated non-invasive diagnostic algorithms, ensuring appropriate training and quality assurance measures to optimize patient outcomes while reducing healthcare costs and improving clinical accessibility.

Furthermore, continued research and clinical validation will undoubtedly expand the applications and improve the precision of these transformative diagnostic approaches.

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Chapter 2

Comprehensive Geriatric Assessment in Older Adults with Cirrhosis: Challenges and Opportunities

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Kazi and Sanmeet Singh*

Abstract

This chapter explores the application of comprehensive geriatric assessment (CGA) in the management of older adults with cirrhosis, a population increasingly encountered in hepatology. As the global burden of chronic liver disease shifts toward aging demographics, traditional models of care fall short in addressing the multifaceted vulnerabilities seen in older cirrhotic patients. The chapter outlines the scope of CGA across outpatient, inpatient, and transplant settings, highlighting its core domains – frailty, cognition, nutrition, functional status, and polypharmacy. It reviews evidence-based tools for frailty screening, cognitive evaluation, and nutritional assessment, while also examining emerging digital innovations such as telemedicine and mobile health applications. The integration of CGA into routine hepatology practice has the potential to improve clinical outcomes, reduce complications, and personalize care. By summarizing current evidence, international models, and guideline recommendations, this chapter aims to equip clinicians with a practical framework for implementing CGA principles in the management of older adults with cirrhosis.

Keywords: comprehensive geriatric assessment, cirrhosis, geriatric, frailty, liver failure, elderly, CGA

1. Introduction

The global population is aging, and the prevalence of cirrhosis among older adults is rising in parallel with demographic shifts and the increasing burden of metabolic dysfunction-associated steatotic liver disease and cryptogenic cirrhosis [1–3]. Recent data indicate that nearly 40% of patients diagnosed with cirrhosis are now over the age of 65, with fatty liver and cryptogenic etiologies disproportionately represented in this group [3]. Older adults with cirrhosis experience higher rates of comorbidities, functional disability, and mortality compared to younger

counterparts, with age independently associated with a twofold increase in all-cause mortality (HR 2.26, 95% CI 1.89–2.69) [2–4].

The clinical course of cirrhosis in older adults is shaped by unique vulnerabilities, including frailty, sarcopenia, malnutrition, cognitive impairment, and polypharmacy [1, 5–7]. These geriatric syndromes are highly prevalent and contribute to an increased risk of decompensation, hospitalizations, and the need for informal caregiving, with older adults with cirrhosis requiring more than twice the number of informal caregiving hours per week compared to age-matched controls [4]. The presence of frailty and sarcopenia is associated with worse outcomes, and their prevalence increases with advancing liver disease severity [5, 7]. Cognitive impairment and hepatic encephalopathy (HE) are also more challenging to diagnose and manage in this population, often overlapping with other neuropsychiatric syndromes [6].

Traditional hepatology models of care, which focus primarily on liver-specific parameters, may not adequately address the multidimensional needs of older adults with cirrhosis [1, 2, 8]. Comprehensive geriatric assessment (CGA) is a multidimensional, interdisciplinary process that systematically evaluates medical, functional, cognitive, nutritional, and psychosocial domains to inform individualized care planning [8]. The American Association for the Study of Liver Diseases (AASLD) recommends the systematic assessment of frailty and sarcopenia in all patients with cirrhosis, with multidisciplinary management and regular reassessment to optimize outcomes [5]. The use of CGA-derived indices, such as the Multidimensional Prognostic Index (MPI), has demonstrated superior prognostic accuracy for mortality in older patients with cirrhosis compared to organ-specific scores, supporting the integration of CGA into routine hepatology practice [8].

In summary, the intersection of aging and cirrhosis creates a complex clinical landscape characterized by high vulnerability and multidimensional care needs. The implementation of CGA offers a framework to identify and address these vulnerabilities, improve prognostication, and personalize management for older adults with cirrhosis [1–5, 7, 8].

2. Principles and core domains of CGA

2.1 Core domains of CGA

CGA is a multidimensional, interdisciplinary diagnostic and management process designed to determine the medical, functional, psychological, and socioenvironmental capabilities and needs of older adults, with the goal of developing a coordinated, integrated care plan [9–12]. CGA is the cornerstone of modern geriatric medicine and underpins both conventional and emerging models of care for older people [13]. Its implementation is associated with improved clinical outcomes in select populations, particularly in hospital settings, and is increasingly adapted for community and primary care environments [9, 10, 12, 14].

2.2 Definition and components of CGA

CGA is characterized by its systematic, multidomain approach, which extends beyond traditional medical assessment to encompass functional, cognitive, nutritional, psychosocial, and environmental domains [9–11, 15]. The process

involves not only assessment but also the formulation and execution of a holistic, individualized management plan, with regular reassessment to monitor progress and adapt interventions as needed [9–11]. The International Classification of Functioning, Disability, and Health framework has been used to map the essential components of CGA, emphasizing both objective measures (e.g., physical function, comorbidities) and subjective factors (e.g., resilience, quality of life, personal goals) [15].

2.3 Multidisciplinary team roles

The effectiveness of CGA is predicated on the expertise and collaboration of a multidisciplinary team. Core team members typically include geriatricians, nurses, social workers, physical and occupational therapists, pharmacists, and, when appropriate, dietitians and case managers [9, 12, 13, 15]. Geriatricians or physicians with geriatric expertise often lead the process, providing medical oversight and integrating findings across domains. Nurses frequently coordinate assessments, monitor functional status, and facilitate communication among team members and with patients and families [12, 16]. Therapists assess and address mobility, activities of daily living (ADLs), and rehabilitation needs. Social workers evaluate psychosocial and environmental factors, including caregiver support and access to community resources. Pharmacists review polypharmacy and medication safety. Effective CGA teams are characterized by high-functioning interdisciplinary collaboration, shared decision-making, and clear communication pathways [12, 13].

2.4 Core domains of CGA

2.4.1 Medical domain

This includes a thorough review of comorbidities, disease severity, medication use (with attention to polypharmacy and potentially inappropriate medications (PIMs)), and geriatric syndromes such as falls, incontinence, and pain. The medical assessment is tailored to identify reversible conditions and optimize chronic disease management [9–12].

2.4.2 Functional domain

Functional assessment focuses on the ability to perform basic and instrumental activities of daily living (ADLs and IADLs), mobility, and risk of falls. Standardized tools such as the Barthel Index, Katz ADL, and gait speed are commonly employed. Functional status is a strong predictor of outcomes and guides rehabilitation and support needs [9–12, 15].

2.4.3 Cognitive domain

Cognitive evaluation screens for dementia, delirium, and depression using validated instruments such as the Mini-Mental State Examination or the Montreal Cognitive Assessment. Early identification of cognitive impairment is critical for care planning, medication management, and safety [9–12].

2.4.4 Nutritional domain

Nutritional assessment identifies malnutrition, sarcopenia, and frailty, which are prevalent and prognostically significant in older adults. Tools such as the Mini Nutritional Assessment (MNA) and handgrip strength are used to screen for risk and guide dietary and rehabilitative interventions [5, 9–12].

2.4.5 Psychosocial domain

This domain encompasses mental health, mood disorders, social support, caregiver burden, and quality of life. Social workers and psychologists play key roles in identifying psychosocial stressors and facilitating access to support services [9, 10, 12, 15].

2.4.6 Environmental domain

Assessment of the living environment addresses safety, accessibility, risk of hazards, and the adequacy of home supports. Environmental modifications and community resources are considered to promote independence and reduce risk [9, 10, 12, 15].

CGA is not a static process; it requires ongoing reassessment and adaptation of care plans in response to changes in health status, functional ability, and patient goals [9–11, 15]. The integration of multidomain findings enables the development of individualized, patient-centered interventions that address the complex needs of older adults.

In summary, CGA is a multidimensional, team-based process that systematically evaluates and addresses the medical, functional, cognitive, nutritional, psychosocial, and environmental domains of health in older adults, with the aim of optimizing outcomes and supporting aging in place [9–15].

3. Frailty and functional assessment

Frailty is a multidimensional syndrome characterized by diminished physiological reserve and increased vulnerability to stressors, and it is highly prevalent among patients with cirrhosis. The prevalence of frailty in ambulatory patients with cirrhosis ranges from 17% to 43%, depending on the assessment tool and disease severity. In hospitalized patients, frailty prevalence can reach 38% among those with HE and up to 68% when measured by impaired performance status using the Karnofsky Performance Status Scale [5]. Frailty is more common in advanced liver disease and is influenced by factors such as malnutrition, sarcopenia, HE, and ascites [17, 18].

The clinical impact of frailty in cirrhosis is profound. Frailty is independently associated with an increased risk of disease progression, unplanned hospitalization, and mortality, regardless of liver disease severity or the presence of complications such as ascites or HE [5, 19, 20]. In a multicenter cohort of 822 patients, frailty, as measured by the Liver Frailty Index (LFI), was associated with a more than twofold increased risk of cirrhosis progression or death (HR 2.45, 95% CI 1.14–5.29) and unplanned hospitalization (HR 2.32, 95% CI 1.13–4.79), after adjustment for age, sex, and MELD score [19]. Similarly, in a study of over 1,000 ambulatory patients awaiting liver transplantation, frailty by LFI conferred a nearly twofold increased risk of waitlist mortality (sub-HR 1.82, 95% CI 1.31–2.52), independent of MELD-Na and other

clinical factors [5, 20]. Notably, changes in frailty over time are also prognostically significant: A 0.1-unit increase in LFI over three months was associated with a twofold increase in waitlist mortality risk (HR 2.04, 95% CI 1.35–3.09) [21].

A variety of tools are available for frailty and functional status assessment in cirrhosis, each with unique strengths and limitations. The AASLD recommends a combination of subjective and objective measures to capture the multidimensional nature of frailty [5]. The LFI is a cirrhosis-specific, performance-based tool incorporating grip strength, chair stands, and balance testing, with validated cut points to define robust (LFI <3.2), prefrail (3.2–4.3), and frail (≥ 4.4) states [5, 19]. The LFI has demonstrated strong prognostic value for mortality and hospitalization in both ambulatory and inpatient settings [5, 19–21].

Other performance-based measures include the following: the Short Physical Performance Battery (SPPB), which assesses gait speed, chair stands, and balance; the 6-Minute Walk Test, which evaluates submaximal aerobic capacity; and hand grip strength, a surrogate for muscle function [5, 22]. The fried frailty phenotype, originally developed in geriatrics, has also been adapted for use in cirrhosis and includes domains of weight loss, exhaustion, slowness, weakness, and low physical activity [5]. The Clinical Frailty Scale (CFS) is a rapid, survey-based tool that has been validated in both ambulatory and inpatient cirrhosis populations, with CFS >4 indicating frailty and predicting unplanned hospitalization or death (adjusted OR 3.6, 95% CI 1.7–7.5) [22–24].

Assessment of functional status is commonly performed using ADLs and IADLs. ADLs evaluate basic self-care tasks such as bathing, dressing, and feeding, while IADLs assess more complex activities required for independent living, such as managing finances and medications [5]. Impairment in ADLs is associated with a higher burden of functional deficits and increased short-term mortality; for example, needing assistance with three or more ADLs was associated with nearly twofold increased odds of 90-day mortality in hospitalized patients with cirrhosis (OR 1.83, 95% CI 1.05–3.20) [5].

Comparative studies indicate that, while different frailty tools may identify overlapping but not identical patient populations, frailty defined by any validated method is an independent predictor of adverse outcomes, including long-term mortality, after adjustment for age, gender, and MELD score [22, 25].

Simpler tools, such as the CFS, may perform as well as more complex indices in certain settings, supporting their use in resource-limited environments [25].

In summary, frailty is common in cirrhosis and confers significant risk for morbidity and mortality. Routine assessment using validated tools such as the LFI, SPPB, CFS, and ADL/IADL scales is essential for risk stratification, prognostication, and guiding individualized management in this vulnerable population [5, 17–25].

4. Cognitive and neuropsychiatric evaluation

4.1 Cognitive assessment in cirrhosis

Cognitive impairment is a frequent and clinically significant complication in older adults with cirrhosis, manifesting as a spectrum from mild cognitive deficits to overt HE. The prevalence of minimal or covert HE (MHE/CHE) in cirrhosis is substantial, with recent multicenter data indicating rates of 29–35% in patients without prior overt HE and higher prevalence in those with advanced liver disease (up to 52% in Child-Pugh C) [1]. MHE and mild cognitive impairment often coexist

in older adults, compounding the risk of poor quality of life, impaired daily functioning, and increased morbidity [26–29].

HE is classified along a continuum, from unimpaired cognition to coma, and is divided into covert (Grades 0–1) and overt (Grades ≥ 2) forms based on the West Haven Criteria [30, 31]. Overt HE presents with asterixis, disorientation, lethargy, and, in severe cases, coma. Covert HE is characterized by subtle deficits in attention, executive function, sleep–wake disturbances, and gait instability, often without obvious clinical signs [30, 31]. In older adults, these manifestations may overlap with age-related cognitive decline or other neuropsychiatric syndromes, necessitating a structured approach to evaluation [27–29].

4.2 Screening and diagnostic tools

A multidimensional assessment is recommended, combining global cognitive screening with HE-specific tools. The Short Portable Mental Status Questionnaire and similar brief cognitive instruments can identify global cognitive impairment but lack sensitivity for the subtle deficits of MHE/CHE [27, 28]. The criterion standard for covert HE is the Psychometric Hepatic Encephalopathy Score (PHES), a five-test paper–pencil battery, with a score ≥ 4 standard deviations below healthy controls considered diagnostic [26, 30–32]. However, PHES administration requires trained personnel and is time-consuming, limiting its use in routine practice.

Bedside alternatives include the animal naming test, where naming fewer than 15 animals per minute yields a sensitivity of 70% and specificity of 63% for HE, and the EncephalApp Stroop test, a computerized attention test with a cutoff of >198 seconds, providing 80% sensitivity and 61% specificity [27, 30, 33]. The Stroop test has been validated in older adults and across diverse populations, with age-adjusted cutoffs improving diagnostic accuracy [27, 33]. The number connection test and critical flicker frequency are additional validated tools, though they are less widely used in the United States [28, 32, 33]. The AASLD and the European Association for the Study of the Liver recommend that psychometric and neurophysiological tests be performed by experienced examiners and that testing be prioritized for patients with impaired quality of life or those at risk for adverse outcomes [31].

Clinical correlates of covert HE include recent falls (40% in those with covert HE vs. 12.9% without), poor sleep quality (mean Pittsburgh Sleep Quality Index 10.3 vs. 7.6), and subtle behavioral changes [27, 30]. Algorithms incorporating age, sex, and self-reported symptoms (e.g., loss of balance, irritability, anorexia, disinterest in activity) can achieve sensitivity and specificity of approximately 80% for covert HE [30].

4.3 Management considerations

Management of cognitive impairment in cirrhosis requires a multifaceted approach. For overt HE, first-line therapy is lactulose, titrated to achieve 2–3 soft stools per day, with rifaximin added for secondary prophylaxis or in cases of recurrent HE [30, 32, 34, 35]. In older adults, careful monitoring for adverse effects such as diarrhea, dehydration, and electrolyte disturbances is essential, as these may exacerbate cognitive dysfunction or precipitate delirium [34, 35]. Polyethylene glycol may be considered as an alternative to lactulose in select cases, particularly near the end of life [34]. Adjuvant therapies such as zinc, branched-chain amino acids, and probiotics may be considered, though evidence for their efficacy is less robust [28, 32, 34].

For MHE/CHE, the decision to initiate therapy should be individualized, weighing the degree of cognitive impairment, impact on daily functioning, and patient preferences [28, 31, 32, 34]. Education of patients and caregivers regarding the fluctuating course of HE, medication administration, and the importance of adherence is critical [34]. Early identification of a surrogate decision-maker is recommended, given the risk of progression to overt HE and loss of capacity [34]. Referral to social work, care coordination, and home health support may be necessary to address the complex needs of older adults with cirrhosis and cognitive impairment [34].

In summary, cognitive and neuropsychiatric evaluation in older adults with cirrhosis should employ both global and HE-specific tools, with management tailored to the severity of impairment and the patient context. Early detection and comprehensive care can mitigate morbidity, improve quality of life, and support patient-centered decision-making [26–35].

5. Nutritional assessment in cirrhosis

Malnutrition and sarcopenia are highly prevalent and clinically significant complications in older adults with cirrhosis, with reported rates of malnutrition ranging from 23% to 60% and sarcopenia affecting up to 50% of patients, depending on the population and assessment method used [5, 36–39]. The pathogenesis is multifactorial, involving decreased oral intake, malabsorption, hypermetabolism, systemic inflammation, hormonal disturbances, and complications of cirrhosis such as ascites and HE [5, 36, 37, 39].

Notably, malnutrition and sarcopenia frequently overlap and are both independent predictors of hepatic decompensation, increased healthcare utilization, reduced quality of life, and mortality [5, 36, 37, 39, 40].

5.1 Malnutrition and sarcopenia in cirrhosis

Malnutrition in cirrhosis is defined as an imbalance of nutrient intake resulting in adverse effects on body composition, function, or clinical outcomes, and can occur across the spectrum of body mass index, including in patients with obesity [5, 37]. Sarcopenia, characterized by the loss of skeletal muscle mass and strength, is considered an advanced stage of malnutrition and is a key component of physical frailty [5, 36, 37, 40, 41]. The AASLD recommends the systematic assessment of both frailty and sarcopenia in all patients with cirrhosis, with particular attention to those with decompensated disease or at high risk for adverse outcomes [5, 40].

5.2 Assessment instruments

A stepwise approach to nutritional assessment is recommended, beginning with rapid screening, followed by comprehensive evaluation in those at risk [5, 37, 38]. Several validated screening tools are available as follows:

5.2.1 MNA and MNA-short form (MNA-SF)

The MNA-SF has demonstrated high sensitivity (88%) and specificity (97%) for malnutrition in cirrhosis when compared to the Global Leadership Initiative on

Malnutrition criteria, outperforming other tools such as the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) and the Liver Disease Undernutrition Screening Tool (LDUST). The MNA-SF is practical for routine use and is recommended for initial screening in both outpatient and inpatient settings [42, 43].

5.2.2 RFH-NPT

The RFH-NPT is specifically validated for cirrhosis and stratifies patients into low, moderate, or high nutritional risk based on clinical and anthropometric parameters. High-risk patients have worse survival and quality of life, and improvement in RFH-NPT scores correlates with improved outcomes [5, 43].

5.2.3 Other tools

The Nutritional Risk Screening 2002 (NRS2002) and LDUST are also used, but MNA-SF and RFH-NPT have superior diagnostic performance in cirrhosis [42–44].

Comprehensive assessment should include dietary history, physical examination, laboratory testing, and body composition analysis. Muscle mass can be quantified using cross-sectional imaging (CT or MRI), bioelectrical impedance analysis, or anthropometry, while muscle strength is commonly assessed by handgrip dynamometry [37, 40, 41]. The transversal psoas thickness index on CT has been proposed as a gender-specific marker for sarcopenia, with cutoffs of <14.56 mm/m for males and <8.34 mm/m for females [44]. The SARC-F questionnaire and handgrip strength are practical bedside tools for sarcopenia screening [40, 41].

5.3 Interventions and outcomes

Management of malnutrition and sarcopenia in cirrhosis requires a multidisciplinary approach, including hepatology, dietetics, physical therapy, and behavioral health [5, 36, 37, 39, 40]. The AASLD recommends individualized nutrition plans targeting adequate protein (1.2–1.5 g/kg/day) and caloric intake, late evening snacks, and regular physical activity, with reassessment every 8–12 weeks in decompensated patients [5, 40]. Oral nutritional supplements, branched-chain amino acids, and micronutrient repletion may be considered in selected patients, though the evidence for mortality benefit is mixed [36, 40]. Intensive nutrition and exercise rehabilitation are indicated for those with progressive sarcopenia or frailty despite initial interventions [5, 36, 40]. Early and systematic intervention has been shown to improve muscle mass, functional status, and survival [5, 36, 39, 40].

In summary, malnutrition and sarcopenia are common, multifactorial, and prognostically significant in older adults with cirrhosis. Routine screening with validated tools, such as the MNA-SF and RFH-NPT, followed by comprehensive assessment and multidisciplinary intervention, is essential to optimize outcomes in this vulnerable population [5, 36–43].

6. Polypharmacy in cirrhosis

Polypharmacy, commonly defined as the use of five or more chronic medications, is highly prevalent among older adults, with estimates indicating

that 45% of individuals aged 65 and older are exposed to polypharmacy and 58% to PIMs [45–47]. In cirrhosis, the risk is further amplified due to multimorbidity, altered pharmacokinetics, and the frequent need for complex therapeutic regimens [48, 49]. Polypharmacy in this population is associated with increased adverse drug events (ADEs), drug–drug interactions, falls, delirium, hospitalizations, and higher healthcare costs [45–47, 49].

6.1 Prevalence and risks of polypharmacy

Older adults with cirrhosis are particularly susceptible to drug-related problems due to age-related changes in drug metabolism, hepatic impairment, and the presence of multiple comorbidities [48, 49]. Polypharmacy increases the risk of ADEs, with studies demonstrating a direct association between the number of medications and the likelihood of hospitalization, cognitive impairment, and mortality [45–47, 49]. Inappropriate prescribing, including prescribing cascades and failure to account for limited life expectancy or functional status, further compounds these risks [48, 49]. The complexity of care, involvement of multiple prescribers, and lack of regular medication reconciliation contribute to the persistence of polypharmacy and PIM use in this population [45, 46, 49].

6.2 Medication review strategies within CGA

CGA provides a structured, multidisciplinary framework for medication review in older adults with cirrhosis [48, 49]. The process involves a global review of the patient's clinical, functional, and cognitive status before addressing pharmacotherapy, ensuring that medication decisions are individualized and aligned with the patient's goals [48, 49]. Key elements of medication review within CGA include the following:

6.2.1 Systematic medication reconciliation

Identification of all current medications, including over-the-counter and herbal products, and clarification of indications for each drug [46, 48, 49].

6.2.2 Assessment of appropriateness

Use of explicit (e.g., Beers, STOPP/START criteria) and implicit (e.g., Medication Appropriateness Index) tools to identify PIMs and prescribing omissions [45, 47, 49].

6.2.3 Multidisciplinary team involvement

Integration of pharmacists, geriatricians, nurses, and other specialists enhances diagnostic accuracy, identifies drug-related problems, and facilitates shared decision-making [48–50].

6.2.4 Patient and caregiver engagement

Eliciting patient preferences, goals of care, and perspectives on medication burden, particularly as care transitions from disease-modifying to palliative or comfort-focused approaches, is essential [46, 47, 50].

Medication review interventions, especially those involving multidisciplinary teams and pharmacist-led reviews, have demonstrated reductions in the number of unnecessary medications, PIMs, and hospital readmissions, though effects on mortality and quality of life are less certain [50–55]. For example, a recent meta-analysis found an 8% reduction in hospital readmissions (HR 0.92, 95% CI 0.85–0.99) following medication review and deprescribing in older inpatients [54]. Comprehensive medication review may also reduce all-cause mortality (OR 0.74, 95% CI 0.58–0.95), though evidence for other outcomes is mixed [55].

6.3 Approaches to deprescribing and optimizing pharmacotherapy

Deprescribing is a systematic process of identifying and discontinuing medications where potential harms outweigh benefits, tailored to the individual's care goals [45, 47–50, 52, 53, 56]. A practical deprescribing algorithm includes the following: (1) compiling a complete medication list and indications; (2) assessing the overall risk of drug-induced harm; (3) evaluating the benefit–harm ratio for each drug; (4) prioritizing medications for discontinuation based on the lowest benefit and risk of withdrawal; and (5) implementing and monitoring a discontinuation plan [47, 48, 52].

Effective deprescribing interventions incorporate patient education, shared decision-making, and regular follow-up to monitor for withdrawal effects or symptom recurrence [47, 50, 56]. Tools such as the Beers and STOPP/START criteria, as well as computerized decision support, can aid in identifying deprescribing targets, though no single tool is universally superior [45, 47, 49]. Barriers to deprescribing include time constraints, uncertainty about which medications to stop, and concerns about withdrawal or disease recurrence [47, 50, 56]. Facilitators include clear team roles, effective communication, and the integration of pharmacists into the care team [50].

In summary, polypharmacy is common and hazardous in older adults with cirrhosis. CGA-based medication review, multidisciplinary collaboration, and structured deprescribing protocols are essential to optimize pharmacotherapy, reduce medication burden, and improve clinical outcomes in this vulnerable population [45–56].

7. CGA implementation across settings

CGA is a multidimensional, interdisciplinary process designed to evaluate the medical, functional, psychological, and social capabilities of older adults, with the goal of developing a coordinated care plan. Its implementation varies across clinical settings, with evidence supporting its utility in inpatient, outpatient, and pre-transplant contexts, though effectiveness and operational challenges differ by setting.

7.1 Inpatient settings

CGA is most robustly supported in the inpatient environment, particularly for acutely ill or frail older adults. A large Cochrane meta-analysis of 29 randomized trials (13,766 participants) demonstrated that inpatient CGA increases the likelihood of patients being alive and living at home at 3–12 months (RR 1.06, 95% CI 1.01–1.10) and reduces nursing home admissions (RR 0.80, 95% CI 0.72–0.89), with high-certainty evidence. There is also a significant reduction in falls (RR 0.51, 95% CI 0.29–0.89) and pressure sores (RR 0.46, 95% CI 0.24–0.89) in hospital medical settings. However, CGA may have little or no effect on overall mortality or dependence, and the impact on

cognitive outcomes is uncertain. Cost-effectiveness analyses suggest a small increase in costs but with a favorable probability of cost-effectiveness for key outcomes such as life years gained and time living at home [10, 57].

7.2 Outpatient and community settings

The evidence for CGA in outpatient and community settings is more heterogeneous. Systematic reviews and meta-analyses indicate that CGA may reduce unplanned hospital admissions (RR 0.83, 95% CI 0.70–0.99) and frailty (RR 0.77, 95% CI 0.64–0.93) among high-risk, community-dwelling older adults, but it has little or no effect on mortality, nursing home admission, or functional status in the general older population [9, 10, 14, 58]. Some studies report improvements in mental health, self-rated health, and quality of life, but these findings are inconsistent and often of low certainty [16, 58]. The effectiveness of CGA in outpatient hepatology clinics is further complicated by variability in team composition, assessment tools, and follow-up protocols [58]. The AASLD recognizes frailty assessment as a key quality measure in cirrhosis care, underscoring the relevance of CGA domains in hepatology practice [59].

7.3 Pre-transplant applications

In the pre-transplant setting, particularly for older adults undergoing liver transplantation, CGA is increasingly recognized as essential for risk stratification and optimization. Preoperative CGA identifies comorbidities, frailty, cognitive impairment, and psychosocial vulnerabilities that may impact transplant candidacy and outcomes. Recent data indicate that 22% of liver transplant recipients are over 65, and comprehensive preoperative evaluation – including frailty and cognitive assessment – is now considered best practice to inform selection and perioperative management [60]. The MPI, derived from CGA, has demonstrated superior prognostic accuracy for mortality in older patients with cirrhosis compared to organ-specific scores, supporting its integration into transplant evaluation [8].

7.4 Barriers and facilitators to implementation

Barriers to CGA implementation include a lack of standardized protocols, insufficient multidisciplinary staffing, time constraints, and limited provider training in geriatric principles [16, 61]. In outpatient and community settings, additional challenges include poor alignment between providers, low acceptance of preventive care, and operational difficulties in coordinating assessments and follow-up [14, 16, 58]. Facilitators include the presence of skilled interprofessional teams, clear care pathways, patient education, and integration of CGA into routine workflows. Home-based and nurse-led models are particularly valued for their convenience and patient-centeredness [14, 16]. Successful implementation is further supported by leadership engagement, ongoing staff training, and the use of validated assessment tools tailored to the clinical context [16, 61].

In summary, CGA is most effective in inpatient and pre-transplant settings, with more modest and variable benefits in outpatient and community care. Implementation requires addressing system-level barriers and leveraging facilitators such as multi-disciplinary collaboration and patient-centered delivery models to optimize outcomes for older adults with cirrhosis and other complex conditions [8–10, 14, 16, 58–61].

8. Prognostic tools and risk stratification

Risk stratification in older adults with cirrhosis requires integration of both liver-specific and multidimensional prognostic tools. Traditional scores such as Child-Pugh and MELD (and its variants, including MELD-Na and MELD 3.0) remain central for predicting short- and medium-term mortality, guiding transplant allocation, and informing management of acute decompensation [62–66]. However, these scores have recognized limitations, particularly in older adults with multimorbidity, frailty, and functional decline, as they do not account for geriatric syndromes or extrahepatic vulnerabilities [1, 64, 65]. The MPI, derived from standardized CGA, incorporates domains such as ADLs, IADLs, cognition, nutrition, comorbidity, medication burden, and social factors [8, 67–69]. Higher MPI scores are consistently associated with increased short- and long-term mortality, institutionalization, rehospitalization, and greater healthcare utilization in both hospital and community cohorts [67–69]. In older patients with cirrhosis, the MPI has demonstrated superior discriminatory power for mortality compared to the Child-Pugh score, supporting its use for holistic risk stratification and care planning [8]. Recent studies also highlight the potential of machine learning algorithms to enhance prognostic accuracy by integrating MPI domains and clinical data, outperforming traditional categorical risk groupings [70, 71]. Ultimately, combining liver-specific and multidimensional indices enables more precise prediction of outcomes, facilitates shared decision-making, and supports individualized care trajectories in this complex population [8, 62–69].

9. Digital innovations and future directions

Digital health technologies are rapidly transforming the landscape of geriatric and hepatology care. Telemedicine has emerged as a critical tool for expanding access to specialty care, particularly for patients with cirrhosis in underserved or remote settings [72–75]. Telehealth interventions have demonstrated equivalent or improved clinical outcomes compared to traditional encounters, including reduced hospital readmissions, improved transplant evaluation, and enhanced management of chronic liver disease [73–75]. The development of digital frailty assessment tools, such as the Tele-Liver Frailty Index (TeLeFI), enables remote screening and monitoring of frailty, with high predictive accuracy for adverse outcomes in liver transplant candidates [72]. Digital CGA platforms and mobile health applications facilitate remote, multidomain assessment, early disease detection, and personalized care planning, though challenges remain regarding usability, data security, and digital literacy among older adults [76–78]. Wearables and home-based monitoring systems offer additional opportunities for continuous assessment of mobility, nutrition, and cognition, supporting independence and early intervention [76, 78]. Despite these advances, research gaps persist in the validation of digital tools across diverse populations, integration with electronic health records, and demonstration of long-term clinical and cost-effectiveness [74, 76–78]. Future priorities include optimizing digital CGA platforms, addressing the digital divide, and leveraging artificial intelligence to personalize risk prediction and care delivery [63, 70, 71, 76–78].

10. Conclusion and clinical implications

The integration of CGA, multidimensional prognostic indices, and digital health innovations represents a paradigm shift in the management of older adults with cirrhosis. Evidence supports the use of the MPI alongside liver-specific scores to improve risk stratification, guide care planning, and predict outcomes beyond traditional biochemical parameters [8, 62–69]. Telemedicine and digital CGA tools are expanding access to multidisciplinary care, enabling remote monitoring, and supporting early intervention, though further research is needed to optimize implementation and address barriers related to technology adoption and health equity [72–78]. Clinicians should adopt a multidimensional, patient-centered approach, incorporating both organ-specific and geriatric domains into routine assessment and care planning. Ongoing research should focus on validating digital tools, integrating artificial intelligence for personalized prognostication, and evaluating the impact of these innovations on clinical outcomes, quality of life, and healthcare utilization in this growing population [63, 70, 71, 76–78]. Ultimately, a holistic, technology-enabled approach is essential to meet the complex needs of older adults with cirrhosis and to advance the field of geriatric hepatology.

Conflict of interest

The authors declare no conflict of interest.

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Section 2

Future Opportunities in the Management of Hepatic Cirrhosis

Chapter 3

Liver Cirrhosis: Evolving Challenges and the Frontier of Emerging Technologies

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Abstract

The chapter addresses liver cirrhosis as a serious worldwide health issue. It discusses how it progresses silently, how difficult it is to diagnose, and how limited current treatment options are. It highlights significant disparities in healthcare access around the world and explores novel developments, including non-invasive imaging, AI-based risk prediction, stem cell and organoid research, and gene editing. It also examines what the future holds for digital health and medicines that target the microbiome. This chapter is intended for doctors, academics, and policymakers, and it explores ways to improve cirrhosis care in both wealthy and low-income countries.

Keywords: liver cirrhosis, regenerative medicine, non-invasive diagnostic techniques, stem cell therapy, hepatocellular carcinoma

1. Introduction

In many instances, liver cirrhosis is little acknowledged in community health dialogs, notwithstanding its extensive prevalence. It has a significant impact on the world, affecting more than 1.5 billion people who have some form of chronic liver disease. Cirrhosis kills over 2 million people every year, either directly or indirectly [1]. This is about the same number of people who die from more well-known diseases like HIV/AIDS or tuberculosis. The disease frequently doesn't show any symptoms until it reaches a more advanced stage. Many cases are misdiagnosed or not treated as well as they could be. The reasons for cirrhosis vary greatly from one part of the world to another: Most importantly, hepatitis B is still common in Asia. Even while nations like China are still running large-scale vaccination initiatives, many adults have not yet been vaccinated and remain infected since they were exposed to the disease before they received the shot. In India, hepatitis C and alcohol consumption are significant problems [2]. India and China together are responsible for more than

half of all hepatocellular carcinoma (HCC) deaths in the world [3]. This is quite concerning and highlights the importance of having early diagnostic and treatment centers. In Sub-Saharan Africa, antiviral drugs for hepatitis B and C are hard to access, which means that many infections go untreated and present late with catastrophic complications like ascites or variceal hemorrhage. Limited screening, cultural stigma, and underdeveloped healthcare infrastructures make it much harder to receive timely medical care. Latin America, on the other hand, has its own set of challenges. More and more people are developing cancer as westernized diets and sedentary lifestyles become increasingly widespread. There is now a rise in metabolic dysfunction-associated liver disease (MAFLD). Obesity, insulin resistance, and type 2 diabetes have caused an epidemic of non-viral, lifestyle-related liver fibrosis, especially in Brazil, Mexico, and Chile. In North America and Europe, the etiology of cirrhosis has transitioned from being predominantly infection-driven to being more influenced by metabolic and lifestyle-related factors. The number of people with hepatitis C is decreasing due to improved treatments, but the number of people with MAFLD and alcohol-related cirrhosis is increasing. This trend aligns with rising rates of obesity, sugar consumption, and physical inactivity. European countries are currently dealing with two epidemics simultaneously: one linked to liver disease and the other to poor metabolic health. In places like the Middle East and portions of Southeast Asia, the situation is more complex. Both viral and metabolic factors can cause cirrhosis, especially in developing economies undergoing health transitions. This evolving scenario underscores a sobering truth: the main causes of liver cirrhosis are no longer just infections. They now involve a wide range of lifestyle and metabolic factors. Cirrhosis has shifted from being primarily an infectious disease to one that is strongly connected to how we live, eat, and move.

2. Mechanistic insights and disease progression

Mechanistic insights and disease progression: Cirrhosis develops over a span of several decades or years. The process commences with an initial insult to hepatocytes induced by viral infections, alcohol consumption, lipid accumulation, and exposure to toxins. Consequently, the liver initiates a highly coordinated process, although one that eventually culminates in a deadly cycle.

Phase 1: Hepatocyte damage: The liver has processed hundreds of millions of red blood cells over time and comprises approximately one-third of a human liver. Damage initiates at the cellular level and may arise from hepatitis B assaulting liver cells, lipid molecules inducing oxidative stress in MAFLD, or alcohol oxidation generating deleterious byproducts in alcohol-related liver disease. The liver initially reacts by undergoing regeneration; nonetheless, persistent damage ultimately exceeds the liver's ability to regenerate. **Figure 1** shows the appearance of liver cells subjected to fibrosis.

Phase 2: Inflammatory response and immune recruitment Kupffer cells: **Figure 2** shows the activity of stellate cells to cause liver fibrosis. The immune cells of the liver identify damage and secrete inflammatory cytokines such as TNF- α and IL-6. These chemicals function as distress signals, drawing other immune cells to the liver. Concurrently, they stimulate a crucial population of liver cells referred to as hepatic stellate cells (HSCs).

Phase 3: Fibrogenesis and collagen accumulation: Upon activation, HSCs transition from a dormant, vitamin A-storing condition to fibrogenic myofibroblasts

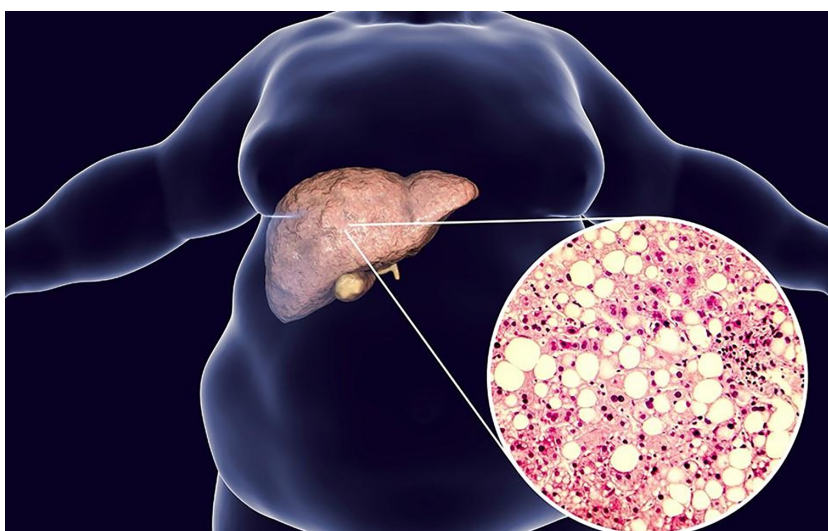


Figure 1.
Gross and histological appearance of fibrosis in hepatic cells [4].

[6]. These cells synthesize type I and type III collagen, in addition to other extracellular matrix constituents. Over time, this fibrous tissue grows, progressively substituting for functioning hepatic tissue.

Phase 4: Structural distortion and circulatory impairment: The liver becomes physically deformed. The once-soft organ is transformed by fibrous bands that encircle clusters of regenerating liver cells (nodules). This architecture disrupts blood flow through the liver and impairs its ability to perform essential tasks like detoxification, hormone metabolism, and nutrient storage.

Phase 5: Cellular pathways and distinct mechanisms by etiology: The etiology of cirrhosis also differs depending on the underlying cause: In viral hepatitis, the damage is predominantly mediated by the immune system. Cytotoxic T lymphocytes assault infected hepatocytes, resulting in cellular demise and inflammation. In MAFLD, chronic low-grade inflammation is predominant. Lipotoxicity, insulin resistance, and adipokine release facilitate stellate cell activation and fibrosis prior to the onset of overt liver inflammation.

Alcohol-related liver illness encompasses direct toxicity from acetaldehyde and immunological activation, frequently associated with bacterial translocation due to intestinal permeability. Epithelial-to-mesenchymal transition (EMT), in which liver cells convert into fibrogenic cells, is widely acknowledged as a factor in scarring. Likewise, the senescence-associated secretory phenotype (SASP) exacerbates inflammation and fibrosis in aging cells.

3. In-depth diagnostics: The new era of liver evaluation

Until recently, the liver was considered a “black box,” concealed within the body and only accessible via intrusive biopsy. For decades, liver biopsy was regarded as the gold standard for evaluating fibrosis; nonetheless, it presented considerable disadvantages, including risks of hemorrhage, sampling inaccuracies, patient pain,

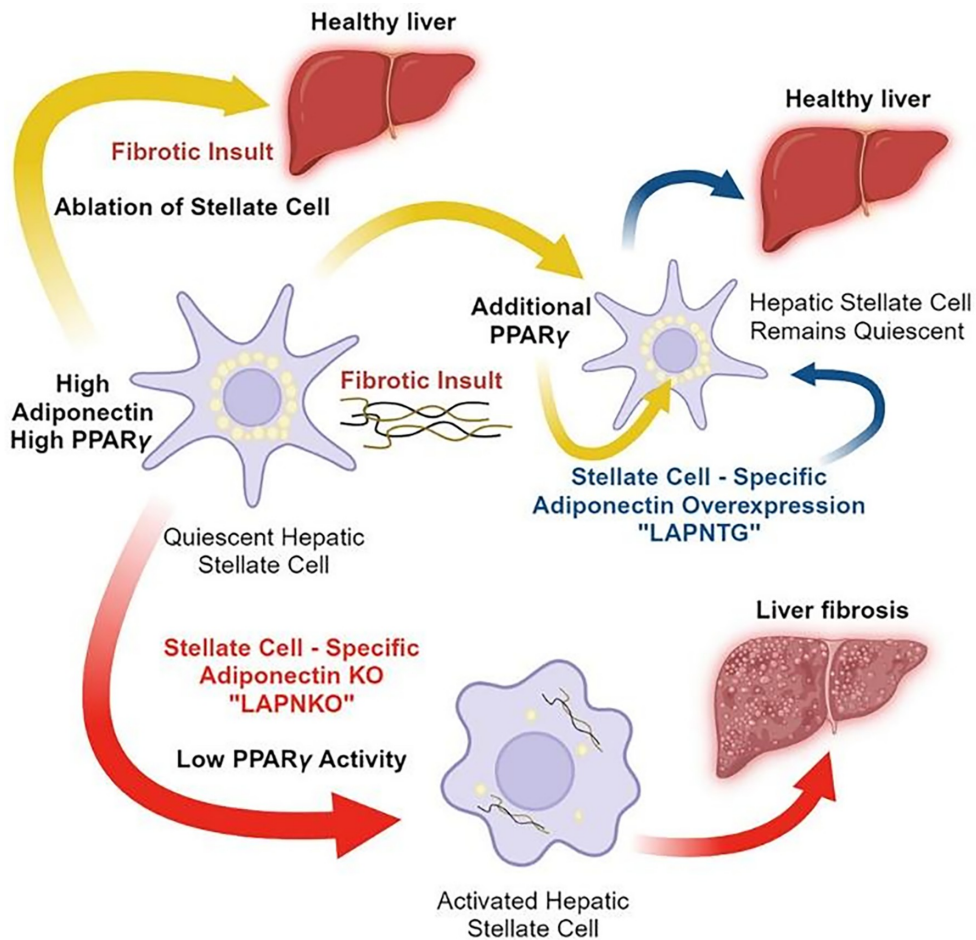


Figure 2.
Activated hepatic stellate cells leading to liver fibrosis [5].

and elevated costs. Over the past decade, a revolution in diagnostic innovation has altered our perception and assessment of liver illness. Currently, clinicians possess a variety of non-invasive, highly accurate, and readily available techniques that facilitate early diagnosis, continuous monitoring, and extensive population screening. These techniques are transforming liver disease from a reactive, late-stage diagnosis to a disorder that can be identified and managed early.

3.1 Transient elastography (FibroScan)

A non-invasive instrument, FibroScan, has emerged as one of the most frequently utilized tools in hepatology clinics globally. It employs vibration-controlled transient elastography (VCTE) to assess liver stiffness, which serves as an indirect but dependable marker of fibrosis as shown in **Figure 3**. This procedure involves positioning a probe on the patient's skin in the right upper quadrant of the abdomen. A non-invasive, low-frequency vibration is transmitted to the liver. The velocity of this wave traversing the tissue is directly proportional to liver stiffness – an increased wave speed signifies a stiffer liver and worse fibrosis.

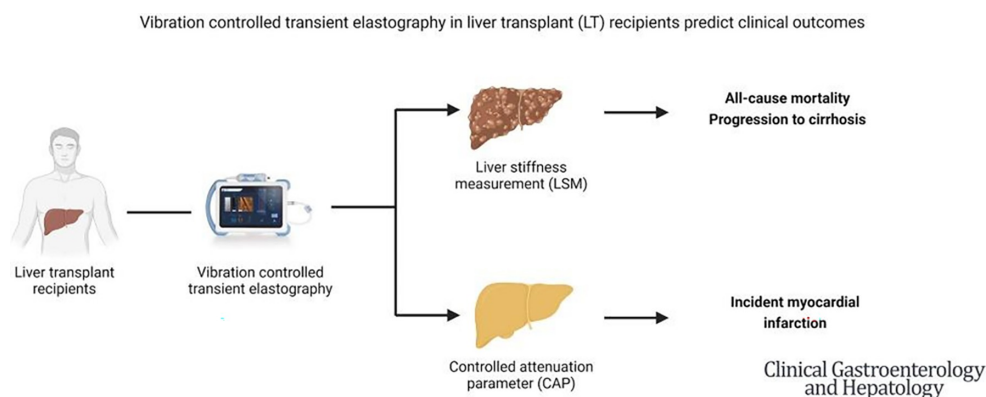


Figure 3.
 VCTE (vibration controlled transient elastography) assessing stiffness of liver [7].

Clinical precision: Meta-analyses demonstrate that FibroScan offers 85% sensitivity and 87% specificity in the diagnosis of cirrhosis. It has 82% sensitivity and 85% specificity in identifying advanced fibrosis [8]. The reason why it represents a paradigm shift is that it is non-invasive. It yields results in under 10 minutes, is portable and replicable, suitable for outpatient or field environments, operable by qualified technicians or nursing personnel, and facilitates mass screening initiatives, particularly among high-risk groups (e.g., diabetics, those with obesity, survivors of viral hepatitis). Countries such as France, South Korea, and Japan have initiated population-wide liver screening via FibroScan, facilitating earlier illness identification by several years.

3.2 Shear-wave elastography (2D-SWE)

Real-time accurate mapping FibroScan delivers a singular assessment of stiffness, whereas 2D Shear-Wave Elastography (2D-SWE) presents a real-time, image-guided representation of liver elasticity [9]. This is particularly advantageous for evaluating uneven or heterogeneous fibrosis distribution, which is prevalent in disorders such as MAFLD or autoimmune hepatitis. In contrast to VCTE, which is conducted without imaging, 2D-SWE is ultrasound-guided. It generates color-coded maps that illustrate stiffness in various liver regions, allowing doctors to more precisely target healthy or diseased areas. Benefits of 2D-SWE exhibits efficacy in individuals with elevated body mass index (BMI) – a prevalent issue in metabolic liver disease. It can be utilized even in the presence of ascites. Unlike FibroScan, it can be used in conventional ultrasound protocols. However, it has some existing constraints dependent on the operator. It necessitates comprehensive training for consistent outcomes, and its performance differs among various equipment brands and software algorithms. Initiatives are in progress to standardize the methodology, encompassing international calibration processes and accreditation standards.

3.3 Magnetic resonance elastography (MRE)

The convergence of imaging and physics MRE integrates the advantages of MRI with the principles of elastography. It depicts liver stiffness via wave propagation

Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation and Death in NAFLD



Figure 4.
MRE (magnetic resonance elastography) assessing the liver fibrosis [10].

physics, generating very detailed cross-sectional images as shown in **Figure 4**. MRE can detect early-stage fibrosis in normal tissue and monitor minor changes over time, rendering it an exceptional instrument for research investigations and intricate diagnostic scenarios.

Its advantages are that it offers maximum diagnostic precision among all non-invasive fibrosis assessments, enhanced reproducibility, and the capability to assess the total liver capacity, thereby minimizing sample error. It is uninfluenced by obesity or ascites. There are a few obstacles to its utilization, including elevated expenses associated with MRI scanners, prolonged examination durations (30–60 minutes), and restricted availability in resource-constrained environments. In academic medical institutes and advanced liver departments, MRE has emerged as the preferred technique for monitoring fibrosis, particularly when biopsy is contraindicated.

3.4 Serological biomarker panels: Diagnosis by blood analysis

In conjunction with advancements in imaging, various blood-based fibrosis assays have become increasingly common. These assays utilize combinations of standard laboratory markers, such as liver enzymes and platelets, or unique fibrosis-related proteins to assess liver scarring. APRI (AST to platelet ratio index) and FIB-4 utilize standard laboratory results; they are cost-effective, readily available, and validated for triage purposes. The Enhanced Liver Fibrosis (ELF) test integrates hyaluronic acid, PIIINP, and TIMP-1. It is sanctioned in Europe and aids in forecasting future fibrosis advancement. There is another test known as Fibro Test/ Fibro Sure. It is a proprietary assay utilizing $\alpha 2$ -macroglobulin, haptoglobin, bilirubin, GGT, and demographic data (age, gender), and it competes with biopsy in some populations.

3.5 Functional testing: Evaluating performance beyond structure

Structural imaging and serology offer significant insights. Liver Maximum Capacity (LiMAx) testing is used to evaluate the performance of the liver. It is a novel technique that evaluates real-time hepatic enzymatic function. The process

involves the administration of ^{13}C -methacetin, a non-toxic chemical processed by hepatic enzymes. The decomposition of this substance liberates tagged carbon dioxide, which is subsequently quantified in the patient's exhalation. Its significance lies in its ability to identify early functional deterioration prior to observable stiffness alterations, aid in pre-transplant risk evaluation, assess graft functionality post-transplant, and is valuable in dynamic clinical settings such as the ICU or ACLF. It is not yet universally embraced, but LiMAx and analogous techniques are progressively utilized in advanced hepatology centers.

4. Artificial intelligence in hepatology

As healthcare evolves into a data-centric field, artificial intelligence and machine learning models are transforming our comprehension of liver disease. These technologies are now integrated into imaging software, electronic health records (EHRs), and consumer health devices, facilitating real-time, precise diagnoses and tailored prognoses.

4.1 AI in imaging interpretation: Beyond the radiologist's eye

Deep learning models, particularly convolutional neural networks (CNNs), have been trained on numerous liver imaging datasets. These models are currently capable of accurately staging fibrosis with radiologist-level precision. They identify early HCC prior to symptom manifestation and precisely quantify hepatic fat and iron content. A recent hybrid model integrated ultrasound-derived stiffness data with serologic indicators, attaining a staging accuracy of 92.5% – a significant progression in cross-modality fusion [11]. A primary problem regarding AI is its “black box” characteristic. To resolve this, explainable AI models now pinpoint image regions or variables that influence a diagnosis, allowing physicians to validate, trust, and perhaps contest AI outcomes.

4.2 Predictive analytics: Seeing the future

Artificial intelligence transcends not only the interpretation of the present, but it also forecasts future developments. ML models such as MELD-Plus and CirrhoPredict evaluate data from laboratory tests, imaging studies, vital signs, and pharmacological treatments to forecast ninety-day mortality, the risk of hepatic decompensation, and the probability of variceal hemorrhage or hepatic encephalopathy. These methods enable the identification of high-risk patients months before the exacerbation of symptoms, allowing for early interventions and reducing emergency visits.

4.3 Precision prognosis with multi-omics

Using extensive datasets from genomics, transcriptomics, proteomics, and metabolomics, AI helps us understand the molecular signature of cirrhosis. High CTGF or PDGF levels indicate aggressive fibrotic activity. Unique miRNA signatures are linked to fibrosis regression during MSC therapy. This enables doctors to classify patients not only by symptoms but also by biology, leading to personalized treatment plans that could significantly improve outcomes.

5. Strategies for medical rehabilitation

5.1 Mesenchymal stem cells (MSCs)

5.1.1 Identification & origin

MSCs are stem cells found in bone marrow, fat, and the umbilical cord, capable of turning into multiple tissue types and significantly affecting the immune system. They can be both autologous and allogeneic. Autologous MSCs, derived from the same patient, lower rejection risks, while allogeneic MSCs, sourced from healthy donors, are available in large quantities for ready application. These MSCs can be used in patients with liver cirrhosis.

5.1.2 Evidence of effectiveness

Clinical trials and studies have shown MSC therapy benefits patients with liver cirrhosis and ACLF, with noted improvements such as:

- Increased survival rates.
- Enhanced liver function reflected in MELD scores.
- Higher albumin levels and lower INR values [12].

MSC treatments also demonstrate a strong safety profile, with no increased risks of tumors or fibrosis. Patients with ACLF treated with MSCs exhibited notable recovery in liver function and survival at 4 and 24 weeks [13].

5.1.3 Action of MSCs in the liver

Once administered, MSCs travel directly to the damaged liver. Their effects stem from a combination of actions: they reduce inflammatory cytokines, which helps alleviate ongoing injury; promote liver cell (hepatocyte) regeneration; and release extracellular vesicles (EVs), small packages carrying microRNAs, growth factors, and anti-fibrotic signals. These EVs provide many of the same benefits as the cells themselves, but without the risk of transplant complications. Animal studies show they can reduce collagen buildup and enhance liver cell regeneration [14].

There are a few delivery methods that are under study, and scientists are still refining what is the best way to administer MSCs. Current delivery options include:

1. *Intravenous (IV)* – easy but less targeted.
2. *Intrahepatic* – injected directly into the liver for precision.
3. *Portal vein infusion* – delivers cells through the main blood supply of the liver for targeted treatment.

Each method has its trade-offs regarding simplicity, effectiveness, and potential risk. Doses typically range from 1 to 5 million cells per kilogram, but the ideal schedule and concentration still require further research.

5.2 MSC-derived extracellular vesicles (EVs)

Instead of using whole cells, researchers are focusing on extracellular vesicles (tiny sacs) secreted by MSCs, filled with healing signals such as proteins, microRNA, and growth factors.

These vesicles can:

- Travel to the damaged areas of the liver.
- Suppress fibrosis-related markers like α -SMA.
- Slow collagen buildup.
- Block TGF- β signaling, a key factor in liver scarring.

5.3 Muse cells

Muse cells is an abbreviation for multi-lineage differentiating stress enduring cells. There are a few inherently robust stem cells located in mesenchymal tissues. In contrast to numerous other stem cells, they possess the ability to develop into various tissue types without necessitating genetic reprogramming. Muse cell therapy in animal models of cirrhosis yields enhanced hepatic function, decreased fibrosis, and incorporation of cells into hepatic tissue. Muse cells, being autologous and not prone to uncontrolled proliferation, exhibit significant potential as an ethical, low-risk, and readily available regenerative solution.

5.4 Therapies utilizing macrophages

Macrophages are a type of immune cell, and they are under investigation for their potential to facilitate liver healing. In the process of healthy regeneration, damaged cells are eliminated, and signals are transmitted to regulate inflammation and facilitate repair. In clinical research, macrophages extracted from a patient's blood are reintroduced into their liver [15]. This modifies the immunological milieu and aids in reducing inflammation. Phase II trials have demonstrated encouraging outcomes without significant adverse effects [16]. Future macrophage therapies may be integrated with MSCs to improve regeneration outcomes by priming the liver for enhanced responsiveness to stem cell signals.

6. Gene editing and nanomedicine

6.1 Gene editing using CRISPR-Cas9

Future therapeutics may harness the benefits of macrophages in conjunction with MSCs to enhance regenerative outcomes, including the preconditioning of the liver with signals from stem cells.

6.1.1 The upcoming major trend

Nanomedicines and genome editing: The emergence of gene editing has considerably enhanced the prospects for treating liver disease. The existing CRISPR-Cas9 method enables researchers to precisely target and alter specific genes responsible for liver damage and fibrosis. In preliminary trials using animal models, CRISPR was employed to excise genes such as TGF-beta and COL1A1, which are significantly implicated in fibrosis [17]. Research has demonstrated the efficacy of this strategy; gene editing resulted in reduced liver scarring and enhanced liver cell functionality. Nonetheless, problems exist in implementing these therapies in practice, as they can cause deletion of the wrong gene, leading to severe side effects.

6.2 Nanoparticles and small interfering RNA (siRNA)

This novel technology pertains to siRNAs. They are synthetic sequences employed to downregulate specific genes implicated in liver fibrosis. They target molecules such as TGF-1, CTGF, and TIMP-1, which contribute to tissue stiffening and hardening, including collagen. siRNAs have demonstrated significant efficacy in mitigating liver scarring in animal studies. Researchers are currently utilizing lipid nanoparticle (LNP) systems as delivery vehicles to ensure that siRNAs reach liver tissue unaltered and safely [18]. A more targeted method of siRNA delivery is known as SORT LNPs, which directs siRNAs specifically to the liver, enhancing precision and safety.

6.3 Current developments in clinical trials

Numerous promising therapies are presently undergoing human trials. BMS-986,263, an siRNA therapy aimed at galectin-3, has demonstrated substantial decreases in liver fibrosis (F2–F3) after one year in a Phase II clinical trial. Revucade (enoxaparin), a drug formerly utilized as an anticoagulant, has surprisingly demonstrated anti-fibrotic properties. It appears to reduce portal pressure and inhibit fibrosis without elevating the risk of hemorrhage. These trials signify a pivotal transition as laboratory findings advance into tangible healthcare implementations.

7. Novel pharmacological treatments

7.1 Antifibrotic agents

The progress in the development of efficacious oral or injectable anti-fibrotic therapies is accelerating rapidly. Various classes of pharmaceuticals are presently in development to target distinct processes implicated in liver fibrosis, with the objective of mitigating the scarring process. Targeted stem cell therapy is given to reduce the risk of liver fibrosis as shown in **Figure 5**.

Prominent agents in development comprise CCR5 antagonists (e.g., leronlimab) [20]. These medications inhibit a receptor that activates HSCs, the principal cells responsible for fibrosis. Preliminary research indicates that these medicines may

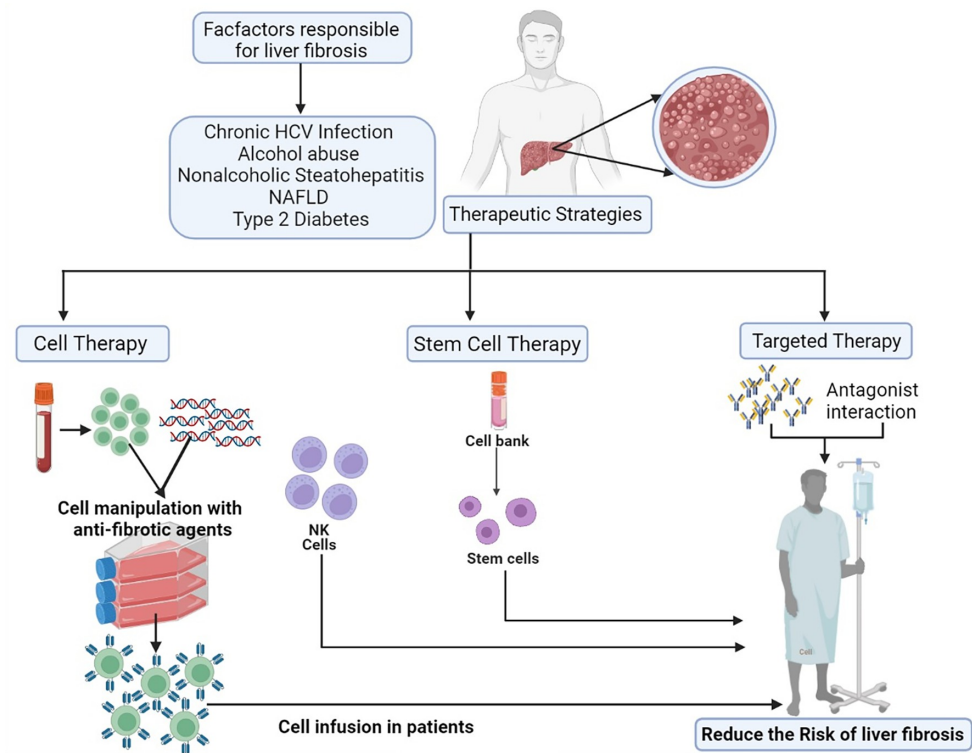


Figure 5.
Targeted stem cell therapy reducing the risk of liver fibrosis [19].

diminish liver stiffness and inflammation. Current Phase II trials are investigating their full potential. Inhibitors of LOXL2 (e.g., simtuzumab) are also in use. They aim to inhibit collagen cross-linking, a vital process in the development of irreversible liver fibrosis. Nonetheless, their efficacy has been somewhat constrained, necessitating the creation of newer iterations with potentially enhanced results. Integrin inhibitors and PDGF antagonists are under investigation to inhibit the activation and proliferation of fibrogenic HSCs. Preclinical models indicate their potential role in future combination medicines to combat liver fibrosis from multiple perspectives.

7.2 Modulators of metabolic enzymes

Metabolic dysfunction is a primary contributor to liver cirrhosis, particularly in conditions such as NASH (non-alcoholic steatohepatitis), now referred to as MASLD; thus, several treatments seek to rectify the metabolic pathways that result in fibrosis. FXR agonists, such as obeticholic acid, are licensed for primary biliary cholangitis and are under investigation for MASLD [21]. These medicines enhance lipid metabolism, augment insulin sensitivity, and diminish fibrosis. Nonetheless, prevalent side effects, including pruritus, have constrained their utilization. PPAR agonists (e.g., elafibranor) demonstrate potential in Phase III trials for cirrhosis associated with MASLD [22]. These medications enhance insulin efficacy, reduce

inflammation, and modulate lipid metabolism, directly addressing the fundamental causes of the condition.

7.3 Combination therapies

Liver fibrosis encompasses various processes that facilitate disease progression, prompting researchers to concentrate on elucidating these pathways. There is an increasing focus on the development of combination therapy utilizing multiple pharmaceuticals. These therapies address many facets of the condition to attain improved results. Preliminary evidence indicates that synergistic effects arise when FXR agonists and CCR5 inhibitors are administered concurrently [23]. Pathophysiology includes metabolic problems and the development of fibrosis. These combination therapies may establish a new norm for individuals with advanced liver disease. Cirrhosis or fibrosis was previously believed to arise from many causes. This section concludes by emphasizing numerous breakthroughs anticipated to influence the future of liver health, including fibrosis repair and regeneration. Innovative therapeutics, including stem cell treatments and gene targeting, are attracting considerable interest. Cirrhosis has demonstrated reversibility using anti-fibrotic medications, which may not only prevent but even reverse the condition. These breakthroughs will facilitate enhanced therapeutic alternatives. Therapies are progressively tailored to each individual's biology, providing optimism for genuine liver regeneration. The future of liver care appears to encompass developments in microbiome therapies. Digital health gadgets facilitate online surveillance and decision-making. The management of liver disease is progressing swiftly, with a focus on patient-centered care being crucial in optimizing these advancements.

8. The gut–liver axis: Where the microbiome meets cirrhosis

8.1 The communication between the gut and the liver

The gut–liver axis facilitates an unimpeded connection between the liver and the gastrointestinal tract. The occurrences in one organ typically influence the other, and this interconnection becomes increasingly significant in instances of cirrhosis. As liver disease progresses, blood circulation is impaired, resulting in a compromised gut barrier. This induces hepatic enlargement and permits deleterious chemicals, including toxins, to infiltrate the bloodstream. Pathogenic bacteria (LPS) generate endotoxins that stimulate immune cells within the organism. The liver activates inflammation by releasing cytokines such as TNF- α and IL-6, which cause fibrosis. As cirrhosis continues, it induces dysbiosis of the microbiome. This results in an imbalance in microbial populations, leading to a reduction of beneficial species. This alteration exacerbates the situation by modifying species populations (e.g., *Bifidobacterium*) and fostering detrimental ones (e.g., *Enterobacteriaceae*), frequently driven by lifestyle modifications. This imbalance leads to diminished liver functions and the potential onset of hepatic encephalopathy. Intestinal bacteria facilitate the liver's conversion of bile acids. Disruption of this mechanism can result in the accumulation of toxic bile acids, which affects both the liver and the body.

9. Microbiome and its advantages and clinical uses

9.1 Insights from microbiome research

Cirrhotic individuals frequently have elevated concentrations of endotoxins and D-lactate in their bloodstream, signifying microbial dysbiosis. Techniques such as 16S rRNA sequencing enhance our comprehension of these alterations and their association with the severity of cirrhosis. The interplay between microbial metabolites, including short-chain fatty acids (SCFAs) and bile acid derivatives, is significant since they affect fibrosis, metabolism, and inflammation by engaging specific receptors in the body. Examining these relationships improves our comprehension of prospective therapies for liver disease.

9.2 Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation (FMT) entails the transfer of healthy stool from a donor to a recipient. Clinical research indicates that FMT may diminish occurrences of hepatic encephalopathy, with enhancements exceeding 30% noted in cognitive function and liver scores. Nonetheless, the issues concerning donor selection and infection risk require resolution.

9.2.1 Symbiotics

They are a combination of prebiotics and probiotics. Probiotics include *Lactobacillus* and *Bifidobacterium*, and they reduce ammonia levels and enhance immunological function. Prebiotics, such as inulin, nourish advantageous gut microbiota and facilitate the synthesis of SCFAs. Synbiotics demonstrate significant potential, as research suggests enhanced cognitive performance and reduced inflammation.

9.2.2 Postbiotics: Utilizing microbial byproducts

Postbiotics, such as butyrate, a SCFA, strengthen the intestinal barrier, reduce hepatic inflammation, and enhance immunological equilibrium. Bile acid metabolites and indole derivatives facilitate gut healing through the activation of immunological responses.

9.3 Precision engineering of the microbiome

Novel therapeutics are aimed at specific pathogenic microorganisms through phage therapy or CRISPR technologies, administered by phages to excise deleterious genes. These treatments provide a method to kill detrimental microorganisms while preserving the integrity of the overall microbiome.

10. Digital health and telehepatology: A new era of liver care

10.1 Wearable devices for trouble detection

Contemporary wearables can detect initial indicators of hepatic decompensation. Decreases in heart rate variability signify illness progression in cirrhosis. Bioimpedance

sensors detect fluid excess (ascites) at an early stage. Activity monitors assess weariness, a prevalent sign of hepatic encephalopathy. These gadgets synchronize with smartphones, delivering real-time notifications to healthcare professionals.

10.2 Reminders for both patients and clinicians

Patients receive daily reminders about diet, fluid consumption, and medications, while physicians oversee changes in weight, exercise, and other metrics. Preliminary research indicates that the analysis of wearable data by specialists results in a 35% reduction in hospital readmissions.

10.3 Implementation of telehealth clinics

Hybrid models are thriving, particularly in neglected regions. Physicians perform consultations over video, while local teams adhere to established norms. Consequently, compliance with recommendations increases from 55% to 92%, while decompensation incidents diminish by 30%.

10.4 Enhanced symptom monitoring

AI chatbots collect patient-reported symptoms. Algorithms detect indicators of deteriorating health or overlooked medications, thus minimizing unnecessary hospital visits and facilitating earlier problem identification.

10.5 Virtual rehabilitation

Home-based health coaching, remote consultations with dietitians, and physiotherapists improve nutrition, physical strength, and overall quality of life while reducing hospitalizations.

11. Health economics: Making liver care sustainable

11.1 Enhanced diagnostics

Improved costs: Implementing FibroScan in primary care has decreased the necessity for costly liver biopsies by 42%, resulting in savings of around \$3,000 per life-year. In the United Kingdom, the integration of imaging and blood tests has diminished specialist referrals by 25%.

11.2 The economics of regenerative therapies

Administering MSC cell treatment (\$15,000) can decrease ICU admissions by 42%, leading to substantial long-term savings. EV treatments provide a more cost-effective and scalable option with streamlined processing.

11.3 Innovative payment methods

Countries are experimenting with innovative financial structures, such as pooled drug programs and value-based pricing, to enhance accessibility to modern therapies.

11.4 Worldwide accessibility and equity

Telehealth systems have facilitated a 20% reduction in inpatient admissions for liver disorders in resource-constrained regions. The collaborations between NGOs and pharmaceutical companies are facilitating the funding of sustainable solutions. Conferences concerning such pharmaceuticals are necessary.

11.5 Ethical considerations in resource distribution

The primary concerns with costly treatments, such as MSC or EVs, pertain to accessibility to these expensive medications. Clinical necessity underpins equitable systems established through subsidies and tiered pricing, ensuring treatment accessibility for all patients.

12. Regulation, equity, patient voices, and future vision in liver cirrhosis care

12.1 Regulation of gene therapies and microbiome-based interventions

Advanced therapeutic medicinal products (ATMPs), such as CRISPR-based modifications and stem cell therapies, are subject to regulation whether utilized in cloning or FMT. Regulations encompass their classification as ATMPs by the European Medicines Agency (EMA) within the European Union and Regulation by the Food and Drug Administration (FDA) in the United States pursuant to Section 351 of the Public Health Service Act. Regulatory standards include comprehensive preclinical evaluations for toxicity, immunogenicity, and biodistribution. Adherence to Good Manufacturing Practice (GMP) standards, essential data metrics from post-marketing surveillance, and safety should be assessed ethically, alongside enduring societal risks. Even basic therapy modalities, such as FMT, necessitate comprehensive donor screening, traceability, and pathogen testing. Stool should not be seen as trash but as a therapeutic substance. Ethical review boards must monitor dual-use risks, particularly if gene editing techniques are employed. Although intended for beneficial applications, gene editing methods may be appropriated and exploited for augmentation, discrimination, or as biosecurity hazards.

13. Health equity: Closing the liver care divide

13.1 The cartography of disparity

Over 75% of deaths attributable to cirrhosis occur in low- and middle-income nations (LMICs), which simultaneously have the least access to diagnostic tools, specialists, or modern therapeutic options. For instance, Sub-Saharan Africa faces deficiencies in immunizations, restricted access to antivirals, and minimal availability of elastography. In South Asia, hospitals lack modern facilities, hepatologists are scarce, and patients sometimes seek treatment only after the onset of serious complications. These discrepancies are not merely logistical; they are ethical in nature. An equitable healthcare system must not allow one's place of birth to determine one's likelihood of survival.

13.2 Practical strategies for fair access

Portable elastography devices can bring diagnostics to remote villages. Training community health workers supports early detection at the local level. Task-shifting models, where local providers follow protocols remotely guided by specialists, help address doctor shortages. Tiered pricing and voluntary licensing for antiviral or regenerative therapies make treatments affordable without hindering innovation. Pilot programs in countries like Nigeria and Pakistan show that these strategies can reduce unmonitored decompensations by 30%, demonstrating that scalable, context-specific models are effective.

13.3 Funding health equity

Interventions for cirrhosis, particularly novel ones, can be costly. Nonetheless, disregarding them incurs far greater expenses. Health economists are currently formulating integrated finance methods that amalgamate investment in the public sector with charitable financing incentives for private innovation. International entities such as the Global Fund, GAVI, and the WHO are expanding their focus to encompass non-communicable diseases, including hepatic disorders. National liver foundations and patient advocacy organizations are advocating for enhanced funding allocations, illustrating how public pressure and policy alignment can facilitate significant change.

14. Patient narratives: Voices from the frontlines

14.1 Mobile liver care in Nigeria

In a rural Nigerian initiative, more than 1,200 individuals were evaluated using handheld FibroScan equipment. Local health workers, trained through a two-week program, documented patient information using smartphones. Hepatologists in Lagos assessed the data through WhatsApp and video chats. It resulted in a 65% improvement in early fibrosis identification, a 20% reduction in hospital admissions over a two-year period, and a 47% increase in patient satisfaction, highlighting enhanced dignity and accessibility. This program illustrated that human-centered digital care can thrive even in resource-constrained environments.

14.2 Mesenchymal stem cells for NASH cirrhosis in the United Kingdom

A Phase II trial in the UK evaluated monthly infusions of allogeneic MSCs for individuals with compensated cirrhosis resulting from MASLD (formerly known as NASH). After 18 months, 30% of patients experienced regression of fibrosis. MELD scores improved from 10.7 to 7.8. Hospital visits decreased, and numerous patients resumed part-time employment. Health economists determined the intervention to be cost-neutral when accounting for averted surgeries and ICU admissions, indicating that regenerative care can be both therapeutic and fiscally prudent.

15. Training a future-ready liver health workforce

15.1 Interdisciplinary training for clinicians and technologists

Contemporary hepatologists must assume multiple roles. They address illnesses, analyze AI findings, administer digital information, and supervise regeneration treatments. Simultaneously, technologists and engineers must develop secure platforms that cater to various populations and comply with evolving rules. This necessitates interdisciplinary education: clinicians must acquire official certification in elastography, MSC treatment, and AI diagnosis. Bioengineers and data scientists must comprehend patient safety, digital ethics, and regulatory frameworks. These clinicians should build a workforce that is prepared for the future. Digital hepatology certification courses are available online, featuring modular, video-based teaching. Combined regional workshops, facilitated by academic institutions and technology companies, mentorship initiatives in which clinicians collaborate with technologists on practical projects, and medical schools can cultivate a workforce that is genuinely prepared for the future.

15.2 Quality assurance and system learning

An effective liver care system necessitates feedback mechanisms that assess successful and unsuccessful practices. Precision and dependability of fibrosis staging instruments (FibroScan, 2D-SWE, MRE) should be evaluated. User interaction using mobile health applications, compliance rates with antiviral or antifibrotic therapies, and rates of hospital readmission following liver decompensation should also be assessed and evaluated. This data drives enhancement because these measurements contribute to national dashboards and global benchmarking databases. Registries furnish data for AI models, enhancing predictive accuracy and informing policy decisions. Each patient visit serves as a data point, contributing to the system's learning process.

16. Conclusion

The future of liver regeneration is highly personalized. MSCs may soon be customized to match a patient's genetic makeup, immune profile, or disease phenotype. Ex vivo gene editing, which corrects a patient's cells in the lab and then reinfuses them, offers safety advantages over in-body editing and opens new therapeutic possibilities. Hydrogel delivery systems embedded with EVs are being designed to gradually release regenerative factors directly into the liver over days or weeks, mimicking natural healing patterns.

These approaches will not only enhance effectiveness but also decrease side effects and dosing frequency, making therapy safer and easier to scale.

Microbiome-based therapies are becoming more precise and programmable. Synthetic bacteriophages can now be designed to target and eliminate harmful gut bacteria specifically. CRISPR-enhanced probiotics might one day be prescribed, like antibiotics, to selectively suppress bacteria that produce ammonia or LPS.

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Conflict of interest

The authors declare no conflicts of interest.

Declarations

We are thankful to all our peers for supporting us in excelling in life and motivating us while completing this chapter.

Acronyms and abbreviations

MAFLD	Metabolic dysfunction-associated fatty liver disease
VCTA	Vibration-controlled transient elastography
APRI	AST to platelet ratio index
ELF	Enhanced liver fibrosis
LiMAx	Liver maximum capacity
CNN	Convolutional neural network
HCC	Hepatocellular carcinoma
XAI	Explainable artificial intelligence
CTGF	Connective tissue growth factor
PDGF	Platelet-derived growth factor
MSC	Mesenchymal stem cells
ACLF	Acute-on-chronic liver failure
MELD	Model for end-stage liver disease
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats-associated protein 9
MASLD	Metabolic dysfunction-associated steatotic liver disease
PPAR	Peroxisome proliferator-activated receptor
FMT	Fecal microbiota transplantation
ATMP	Advanced therapy medicinal products

Appendices and nomenclature

Fibrosis: Excessive accumulation of extracellular matrix proteins leads to fibrosis in liver tissue.

Hepatic stellate cells (HSCs): Resident cells in the liver that become activated in response to liver injury. They are crucial for fibrogenesis.

Lipotoxicity: Cellular injury caused by the accumulation of lipid derivatives within hepatocytes is common in MAFLD.

Epithelial-to-mesenchymal transition (EMT): A process that renders epithelial cells fibrogenic, resulting in scarring.

Senescence-associated secretory phenotype (SASP): Pro-inflammatory traits of senescent cells that exacerbate fibrosis.

Dysbiosis of the microbiome: A dysbiosis in the gut microbiota exacerbates hepatic inflammation and cirrhosis.

Extracellular vesicles (EVs): Diminutive vesicles released by cells that transport proteins, RNAs, and signaling molecules essential for tissue repair.

Fecal microbiota transplantation (FMT): A therapeutic procedure that introduces healthy fecal bacteria into a patient to restore their gut microbiota.

Gene editing (CRISPR-Cas9) is a genome-editing tool that allows for precise modifications to DNA sequences, thereby rectifying genetic diseases.

Peroxisome proliferator-activated receptor (PPAR): A nuclear protein that regulates genes involved in fat storage and glucose metabolism.

Explainable artificial intelligence (XAI) refers to a category of AI designed to facilitate comprehensible and trustworthy decision-making processes for humans.

MELD score serves as a technique to evaluate the severity of chronic liver disease and establish its transplantation priority.

Advanced therapy medicinal products (ATMPs) encompass innovative treatments such as gene therapy, somatic cell therapy, and products derived from tissue engineering.

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Chapter 4

Perspective Chapter: The Future of Liver Transplantation

Eleni Avramidou and Georgios Tsoulfas

Abstract

Liver transplantation (LT) has evolved significantly since its inception in 1963, transitioning from an experimental procedure to a life-saving intervention for patients with end-stage liver disease and selected liver cancers. Through these years, advances in surgical techniques, graft preservation, and postoperative care have resulted in 1-year survival rates exceeding 90%. Despite the increase in 1 year graft function, issues like organ shortage and long-term complications remain major challenges. This chapter explores cutting-edge innovations that aim to improve LT outcomes and address these limitations. Recent developments in precision medicine, artificial intelligence (AI), and other technological breakthroughs have enhanced all stages of LT, from organ allocation to post-operation management. Other major improvements include advancements in the field of immunosuppression protocols, with studies now supporting drug minimization and withdrawal in selected patients. Innovations in the field of diagnosis aim to improve sensitivity and specificity, while also focusing on the development of non-invasive diagnostic methods with clinical applicability. Furthermore, the usage of marginal grafts has led to emerging preservation technologies, such as normothermic and hypothermic machine perfusion. Collectively, these innovations mark a transformative era for LT, moving toward safer, more personalized, and sustainable transplantation practices.

Keywords: liver transplantation, immunosuppression, artificial intelligence, machine perfusion, transplantomics, robotic surgery, xenotransplantation

1. Introduction

Since 1963, when the first liver transplantation (LT) was performed, LT has evolved from an experimental procedure into a standardized and life-saving intervention for patients with end-stage liver failure or specific liver cancer cases [1, 2]. Advancements in the preservation of the liver graft, surgical techniques, and post-operative management of the recipient have resulted in an increased 1-year survival rate that reaches 90%, with median survival also improving [3]. The broad application of LT in the majority of patients with end-stage-liver failure has resulted in a shortage of organs, an issue that living donor LT, split LT, and the use of marginal grafts have sought to address [4, 5]. Ongoing LT research in the field of precision medicine, artificial intelligence, and other

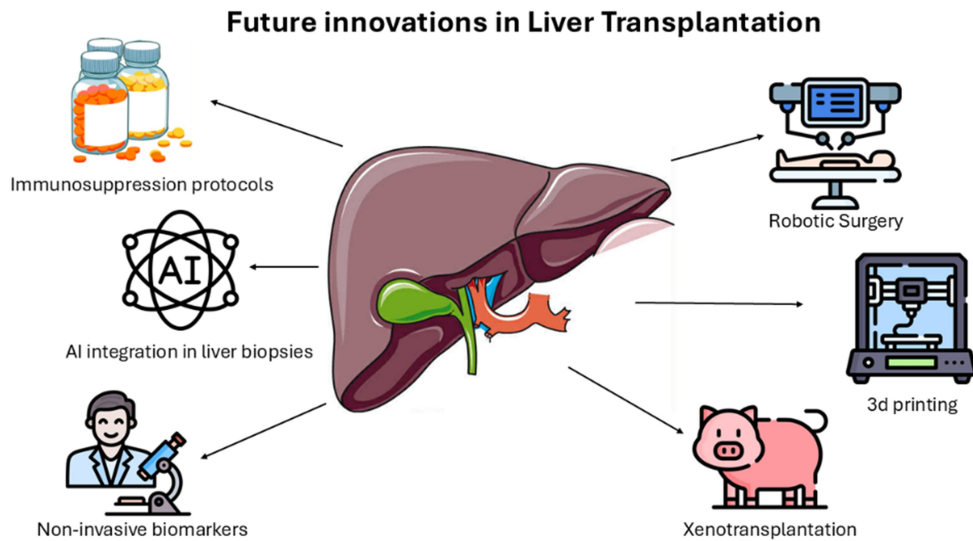


Figure 1.
Innovations in liver transplantation.

technological breakthroughs has the potential to revolutionize LT clinical practice, resulting in increased survival rates and improved management of short-term complications and early allograft dysfunction, ultimately leading to enhanced post-operative recovery of the recipient.

The aim of this chapter is to explore recent innovations in the field of LT and make valuable suggestions regarding the improvement of LT outcomes in the future. **Figure 1** illustrates some of the applications that have the potential to revolutionize the field of LT.

This figure has been designed using resources from Flaticon.com and Servier Medical Art templates.

2. Immunosuppression

Calcineurin inhibitors, like tacrolimus and cyclosporin, are considered the “gold-standard” regarding immunosuppression post-LT [6]. Since their introduction in 1989, these medications have had a positive impact on postoperative survival [7]. Nowadays, immunosuppressive protocols are rapidly changing, with most of the schemes including more than one category of medication, such as corticosteroids, mycophenolate mofetil, or mammalian target of rapamycin inhibitors (mTORi) [7]. Despite the success of these medications in the prevention or management of rejection-related graft loss, they result in long-term complications like cardiovascular events, malignancies, or chronic kidney diseases [8]. Recent studies in the field of personalized medicine are focused on strategies facilitating the reduction or discontinuation of immunosuppression with protocols tailored to individual patient risk profiles [9, 10].

Another interesting observation is that the liver is considered a tolerogenic organ, meaning that the risk for rejection-related graft loss is increased compared to other solid

organ transplantations [11, 12]. This observation is related to the complicated and not fully understood liver immune system, which holds a pivotal role in maintaining tolerance against the immune system of the LT recipient. Particularly, the liver microenvironment consists of an increased vascular density and interactions between liver cells (parenchymal and immune cells) that regulate both innate and adaptive immunity and can promote antigen-specific tolerance [13]. Moreover, the tolerance of the liver derives from the moderate surface MHCII with little costimulatory CD80/CD86 and immunosuppressive factor expression it presents [12]. The tolerogenic physiology of the liver can explain the feasibility of immunosuppression withdrawal in specific cases of LT recipients [14].

3. Organ allocation

The aim of organ allocation systems and algorithms is to efficiently prioritize patients with the highest need for a transplant, while also accounting for factors like compatibility. Currently, the Model for End-Stage Liver Disease (MELD) score, a liver function assessment based on lab values, is used internationally for organ allocation in LT [15]. Additionally, criteria such as the Milan criteria are used for cancer patient cases that are on the waiting list for LT [16]. Despite the efficiency of this allocation system, the MELD score still contains certain limitations, such as geographical location and the cause of liver disease [17]. For this reason, variations like MELD-Na, which also take into consideration hyponatremia, as well as regional share 35 and national share 15 policies, acknowledge the geographical location of potential donors [18–20].

Artificial intelligence (AI) applications have emerged as a crucial method for conducting objective, efficient, and comprehensive patient evaluations and subsequent organ allocation [21]. Machine learning (ML)-based algorithms have been developed that can predict the mortality of patients on the liver transplant list after the 90-day existing mark [22, 23]. Additionally, neural network (NN) algorithms combine parameters included in the MELD score (bilirubin, serum creatinine, and INR) with additional clinical characteristics, including ascites and hepatic encephalopathy, demonstrating superior performance over the MELD score [23]. Lastly, random forest models using more than 1000 variables can now predict waitlist dropout among LT waiting list patients with HCC [24].

4. Preservation of the liver graft

Despite the 1-year survival of LT recipients being above 90% when the liver graft derives from lower-risk donors and donations after brain death (DBD), donations after cardiac death (DCD) and grafts deriving from higher-risk donors result in lower 1-year survival rates [25]. This is a result of ischemia-reperfusion injury caused by the accumulation of metabolic products [26].

In order to optimize the LT outcomes where marginal grafts are used, several machine perfusion technologies and strategies have been developed. These include normothermic machine perfusion (NMP), hypothermic oxygenated machine perfusion (HOPE), controlled oxygenated rewarming, and normothermic regional perfusion [27]. Despite the differences in these technologies, their function is based

on the usage of a membrane oxygenator to deliver oxygen and remove carbon dioxide, a pump, which can provide continuous or pulsatile flow, a heater-cooler unit, a reservoir, and infusion pumps [28]. Some of the emerging potential benefits of machine perfusion compared to static cold storage in LT include the non-invasive assessment of graft viability, the management of steatotic grafts, and better preservation of biliary structure [29].

5. Novel diagnostic tools

The effective graft assessment remains one of the cornerstones of LT that, apart from complications, can also predict its short and long-term function. Currently, liver biopsies remain the gold standard in liver graft evaluation, with liver function tests (LFT) and the indocyanine green (ICG) clearance test being some commonly used non-invasive diagnostic tests [30–32].

5.1 AI and liver biopsies

Liver graft biopsies have great specificity and sensitivity, however, they can be challenging for less experienced pathologists, leading to misdiagnoses. For this reason, various AI algorithms have been developed that can accurately detect and quantify steatosis, a condition strongly associated with early allograft dysfunction (EAD), in liver graft biopsies [33–38].

Despite the reliability of biopsies for steatosis evaluation, they remain an invasive procedure, with minor and major complications occurring in some cases. Some of the most common minor complications after liver graft biopsy include localized pain and mild, transient hypotension due to a vasovagal reaction [39]. Hemorrhage, although rare, is the most serious complication and can be localized, subcapsular, or intraperitoneal [39]. AI integration provides non-invasive diagnostic options that can effectively evaluate the quality of the liver graft based on smartphone images [40, 41]. The sensitivity and specificity of these methods reach 95% and 81%, respectively, and thus they suggest that the AI-based analysis of intraoperative smartphone images can provide a non-invasive and reliable method for steatosis evaluation, particularly when combined with an eyepiece adaptor to assess for microvascular steatosis [40, 41].

5.2 Novel biomarkers for non-invasive liver graft evaluation

Currently, there is a strong interest in studies that investigate the potential of non-invasive biomarkers for the evaluation of liver grafts. Particularly, a correlation has been found between various proteomics and metabolomics detected in the perfusate of the liver graft and biological fluids, such as serum or plasma, of the recipient [42]. Some of the pathways that were found to be enriched in patients with LT complications or dysfunction include triglyceride and glycerophospholipid metabolism, neutrophil degranulation, and the MET-related signaling pathway [42, 43].

These diagnostic approaches have successfully been applied in the diagnosis of complications, such as rejection, but also for the prediction of allograft dysfunction, thus having a pivotal role in personalized medicine in the field of LT [44].

6. Technological advancements

6.1 Minimally invasive surgery

Minimally invasive surgery (MIS) has been a viable option in the field of LT since the first laparoscopic living donor liver resection in 2002 [45]. MIS offers multiple advantages to liver donors, including less postoperative pain, shorter hospitalization, and decreased blood loss compared to the conventional open approach [46]. Even though MIS techniques have been widely used in Hepato-pancreato-biliary (HPB) surgery and donor surgery over the last several years, their applications in liver transplant recipient surgery remain minimal, with most advancements occurring only in the past five years [46]. The first successful pure laparoscopic LT was reported by Suh et al. in 2021, while Broering et al. were the first to successfully accomplish a fully robotic LT in 2023 [47, 48].

Despite being technically more difficult and having a steep learning curve, there are several advantages of MIS applications in LT for both the donor and the recipient. Regarding the recipient's surgery, the main advantages of the minimally invasive approach are those that minimize the inflammatory response. Particularly, the minimally invasive approach results in control of tissue damage as a trigger of the innate systemic inflammatory response, reduction in hospital stay, and thus a lower risk of infectious complications and decreased possibility of wound infection due to smaller incisions [49–51]. These advantages, in combination with shorter hospitalization time and faster recovery for the liver living donor, explain the expanding applications of MIS in the field of LT.

6.2 3D bioprinting and regenerative medicine

3D bioprinting is a field of science where principles of regenerative medicine are combined with novel technologies. It has great applications in the field of organ construction since it can control the spatial arrangement of cells and the microenvironment around them, while also being able to develop a vascular system imprinted onto these tissues [52]. Liver tissue models with embedded human-induced hepatocells that expressed excellent liver functions have been successfully bioprinted [53]. Based on this innovation, 3D bioprinting has the potential to facilitate research in LT, such as in vivo personalized drug testing and the investigation of the pathophysiology of liver diseases [54]. Additionally, 3D printing can also be implemented in education, enriching anatomy lessons for medical students and young doctors [55]. Lastly, constant optimization of 3D bioprinting technologies, in combination with the efficient usage of recipient cells through cutting-edge cytology research, may address the increasing demand for LT and alleviate the organ shortage crisis.

6.3 Xenotransplantation

Shortage of donors remains a main challenge in the field of solid organ transplantation, resulting in research into alternative types of organ donors, such as pigs. Porcine hearts and kidneys have been successfully transplanted into both living and brain-dead individuals, while recently, successful gene-modified liver transplantation has also been reported [56, 57].

Initial efforts in liver xenotransplantation were reported in the 1960s when allotransplant pioneer, Thomas Starzl, performed three chimpanzee and one baboon liver transplants in humans, which resulted in relatively short-term successful outcomes [58, 59]. Through research, pigs were identified as better candidates for liver xenotransplantation because of their similarity in size, anatomy, and physiology. In 2024, a genetically engineered pig liver was transplanted into a 71-year-old living male patient with an unresectable large liver tumor, resulting in sufficient short-term outcomes [60]. Additionally, more recently, in 2025, a genetically engineered porcine liver was transplanted into a brain-dead human, and strict monitoring suggested good graft function, hemodynamic stability, and control of immune and inflammatory responses with regular immunosuppression protocols [61].

7. Conclusion

LT is a field of expanding research, from immunosuppression protocols to translational research and technological advancements. Technologies that have clinical applicability, such as AI and 3D bioprinting, can potentially revolutionize the field of LT in the future, resulting in better organ allocation and management of the shortage of liver grafts. Continued research and collaboration are essential to translate these breakthroughs into routine clinical practice, with the ultimate goal of improving access, survival, and quality of life for LT recipients worldwide.

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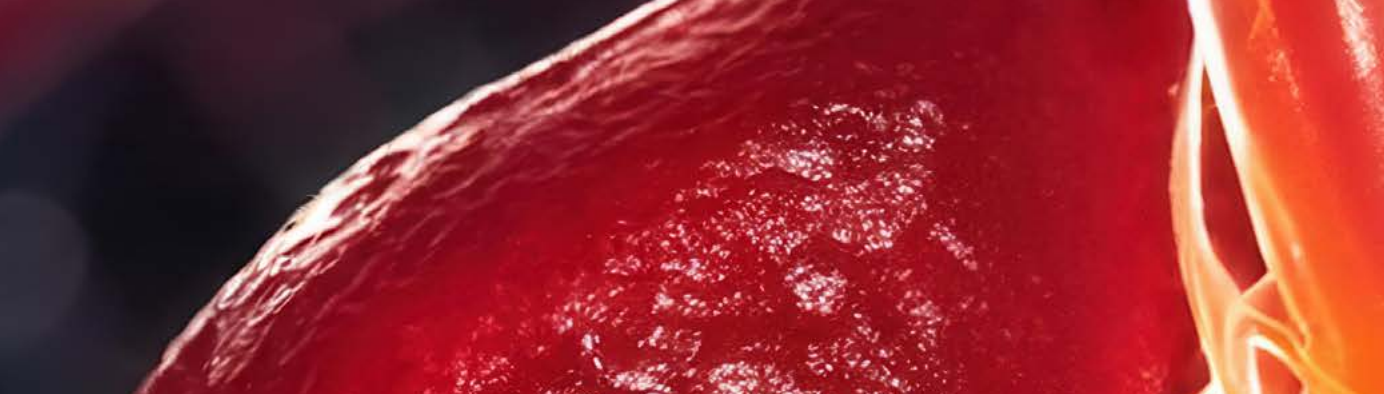
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Liver cirrhosis and its complications affect millions of patients of all ages around the globe and present treating physicians with perplexing problems, given the variety of etiologies and the critical nature of hepatic physiology. This book will be a collection of chapters offering distilled knowledge from leading experts worldwide on the management of patients with cirrhosis, including the critical element of how the evolving technological revolution will change this in the future.

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