

Translating Molecular Heterogeneity into Precision Medicine for Advanced Liver Disease

Tamer A. Addissouky^{1,2,3,4,*}

¹Medical Laboratories Techniques Department, College of Technology and Health Sciences, AL-Mustaqbal University, 51001, Hillah, Babylon, Iraq

²Department of Biochemistry, Science Faculty, Menoufia University, Menoufia, Egypt

³New burg El-Arab Hospital, Ministry of Health, Alexandria, Egypt

⁴American Society for Clinical Pathology (ASCP), Chicago, USA

*Correspondence should be addressed to Tamer A. Addissouky, tedesoky@gmail.com; tedesoky@science.menofia.edu.eg

Received date: July 22, 2024, **Accepted date:** August 27, 2024

Citation: Addissouky TA, Translating Molecular Heterogeneity into Precision Medicine for Advanced Liver Disease. Arch Gastroenterol Res. 2024;5(1):47-58.

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Abstract

Background: Liver fibrosis arises from chronic hepatic injury and involves the accumulation of extracellular matrix proteins. Fibrosis progression ultimately leads to cirrhosis, characterized by architectural distortion and complications. Molecular profiling has identified prognostic transcriptomic subtypes, but management remains limited for advanced disease.

Methods: We conducted a systematic review of the literature to identify recent advances in characterizing liver cirrhosis subtypes and emerging therapies. Electronic databases were searched using relevant terms, and studies published between 2020-2023 involving human subjects were included.

Results: We identified three transcriptomic subtypes (inflammatory, proliferative, cholangiocyte-associated) associated with varying prognoses. Genetic variants like PNPLA3 and HLA alleles influence disease risk. Novel antifibrotic agents targeting hepatic stellate cells and molecular drivers showed promising preclinical efficacy. Observational studies reported association of agents like Obet cholic acid and vitamin E with histologic benefits in early fibrosis.

Conclusion: While addressing etiologies remains key, limitations persist for established cirrhosis without approved antifibrotics. Priorities include developing noninvasive diagnostics, studying early interventions, and validating antifibrotic pipelines informed by molecular subclassification. Precision therapies may help curb advancing cirrhosis worldwide.

Keywords: Liver cirrhosis, Molecular subtypes, Transcriptomics, Genetic variants, Antifibrotic therapies

Background

Liver fibrosis refers to the accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. It is part of the wound-healing response to chronic hepatic injury [1]. Major causes of liver fibrosis include chronic hepatitis B and C infection, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD) [2]. Fibrosis initiates with an acute or chronic liver injury that activates hepatic stellate cells [3]. Activated stellate cells are the major collagen-producing cells in the liver. The activated

stellate cells produce cytokines and other growth factors that further stimulate fibrogenesis and matrix production [4]. As fibrosis progresses, it causes distortion of the hepatic architecture due to formation of fibrous septage and nodules, resulting in cirrhosis [5].

Cirrhosis represents the advanced stages of liver fibrosis. It is characterized by disruption of the hepatic architecture and vasculature leading to portal hypertension, as well as reduced hepatocellular function [6]. Cirrhosis has various etiologies including chronic viral hepatitis, alcohol abuse, autoimmune

diseases, and metabolic syndromes [7]. Not all causes of hepatic fibrosis progress to cirrhosis. For example, fibrosis caused by hepatitis C virus can remain stable or regress with treatment [8]. In contrast, ongoing liver injury from hepatitis B virus or metabolic diseases often continue to stimulate fibrogenesis leading to cirrhosis. There are several scoring systems for evaluating the degree of fibrosis and cirrhosis based on liver biopsy specimens. Semi-quantitative scores include the METAVIR and Ishak scoring systems [9].

These evaluate fibrosis progression on a 5-point scale from F0 (no fibrosis) to F4 (cirrhosis). Quantitative non-invasive methods are now available to estimate liver fibrosis, such as elastography, serum biomarker panels, and imaging techniques [10]. These have good accuracy for diagnosing cirrhosis but remain limited for lesser degrees of fibrosis [11]. Nonalcoholic fatty liver disease (NAFLD) refers to fat accumulation in the liver that is not due to excessive alcohol use or other secondary causes. It has become the most common chronic liver disease worldwide, affecting around 25% of the global population [12]. NAFLD represents a spectrum of disease ranging from isolated steatosis to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma. NAFLD is strongly associated with obesity, insulin resistance, and other features of metabolic syndrome [13].

The pathogenesis is related to multiple factors including excess dietary fat, adipose tissue dysfunction, altered gut microbiota, and genetic predisposition. These factors lead to an excess influx of free fatty acids to the liver, increased lipogenesis, and reduced fatty acid oxidation within hepatocytes. This results in fat accumulation within liver cells [14]. Hepatic steatosis makes the liver more vulnerable to injury from oxidative stress, inflammatory cytokines, and other insults. This can precipitate development of NASH, fibrosis, and cirrhosis [15]. MAFLD (metabolic-dysfunction-associated fatty liver disease) a recent term encompassing NAFLD associated with metabolic dysfunction regardless of obesity, highlights NAFLD incidence independently in non-obese individuals with insulin resistance and dyslipidemia [16].

MASLD (metabolic-dysfunction-associated steatohepatitis) refers to the MAFLD subtype developing steatohepatitis, fibrosis, and cirrhosis, previously termed nonalcoholic steatohepatitis (NASH), capturing metabolic dysfunction's role in progressive disease. Natural histories remain undefined, estimating 10-25% of MAFLD individuals developing MASLD/fibrosis and 10-25% of MASLD progressing to cirrhosis over 10-20 years, conferring elevated HCC risk. MAFLD is projected to become the leading transplantation indication next decade. No FDA-approved MAFLD/MASLD therapies exist [17]. Lifestyle modifications involving diet, exercise, weight loss remain cornerstones [18,19]. Various agents investigate improving steatosis, inflammation, fibrosis including vitamin E, pioglitazone, GLP-1 agonists, FXR agonists. Transplantation alone definitively treats end-stage MASLD disease [20-22].

This review comprehensively surveys recent advances in characterizing transcriptomic and genetic cirrhosis subtypes, highlights emerging antifibrotic therapies tailored to pathogenesis, and outlines key future directions needed to curb the global impact of end-stage liver disease.

Clinical Phenotypes of Liver Cirrhosis

Compensated vs decompensated cirrhosis

Cirrhosis has traditionally been categorized into compensated versus decompensated based on absence/presence of complications. Compensated cirrhosis involves asymptomatic portal hypertension and synthetic dysfunction without overt clinical issues [23]. Contrastingly, decompensated cirrhosis features ascites, variceal bleeding, hepatic encephalopathy and/or jaundice. Patients with compensated cirrhosis have better outcomes and lower mortality versus decompensated disease [24,25]. 5-year survival exceeds 80% for compensated cirrhosis versus 50% post-decompensation. Individuals with compensated disease also experience less progression, with ~5% annual decompensation risk. Decompensation marks a pivotal prognostic shift necessitating transplantation consideration [26].

Etiology-specific phenotypes

The clinical features and course of cirrhosis can vary substantially depending on the underlying etiology [27]. Alcoholic liver disease cirrhosis typically emerges following years of excessive ethanol intake, often defined as >60-80 g/day for males and >20 g/day for females. Patients may experience alcoholic hepatitis previously. Clinical hallmarks involve hepatomegaly, elevated AST/ALT, macrocytic anemia, coagulation abnormalities, and heightened HCC risk [28]. Abstinence prevents worsening and enables regression. Nonalcoholic cirrhosis is associated with obesity and metabolic dysregulation. The liver may be normal-sized with mild-moderate AST/ALT elevations, hyperlipidemia, and insulin resistance, conferring increased cardiovascular risk alongside hepatic complications [29]. Chronic viral hepatitis B and C importantly induce cirrhosis globally. Successful antiviral therapy mitigates progression pre-cirrhosis (hepatitis C) [30]. Stable hepatitis B involves minimal replication and inflammation. Autoimmune liver disease-associated cirrhosis evolves over many years, potentially with other autoimmune conditions. Inflammation reduction and fibrosis progression rates vary with treatment including ursodeoxycholic acid for specific etiologies [31].

Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) refers to acute worsening of liver function in patients with preexisting chronic liver disease or cirrhosis. ACLF commonly arises from infection, acute hepatitis flare, or alcohol exposure in sensitized patients. This insult against chronic injury culminates in

severe dysfunction via exaggerated inflammation/cytokines, microcirculatory disturbances, limited regeneration and extrahepatic organ failure. Robust diagnostic/prognostic criteria incorporate clinical, laboratory and organ failure assessments. Pathophysiology involves precipitant, chronic injury and immunological elements [32].

Molecular Subtypes of Liver Cirrhosis

Recent research efforts have focused on better characterizing the molecular heterogeneity underlying the cirrhosis syndrome. Molecular profiling approaches including transcriptomics, proteomics, and metabolomics have identified distinct cirrhosis subtypes with potential relevance to pathogenesis, prognosis, and treatment responses [33].

Figure 1 provides an overview of the diverse extracellular factors that can promote or inhibit hepatic stellate cell (HSC) activation, a key step in liver fibrogenesis. Stimulation of

Kupffer cells, endothelial cells, platelets, and leukocytes results in release of pro-fibro genic mediators like TGFβ, PDGF, IL-33, and M-CSF. Changes in extracellular matrix (ECM) composition, microbial products, hepatitis viruses, lipids, and toxins also trigger signaling cascades leading to HSC activation. In contrast, molecules such as nitric oxide, interferon γ, and MMPs exhibit anti-fibrotic effects. Activated HSCs are characterized by proliferation, contractility, inflammatory signaling, and increased ECM production. Elucidating these complex extracellular interactions is crucial for identifying potential targets to selectively attenuate HSC activation and liver fibrosis progression [34].

Transcriptomic subtypes

Several studies have now leveraged mRNA expression profiling to define transcriptomic subtypes in cirrhosis. As depicted in Table 1, key features of the transcriptomic subtypes are:

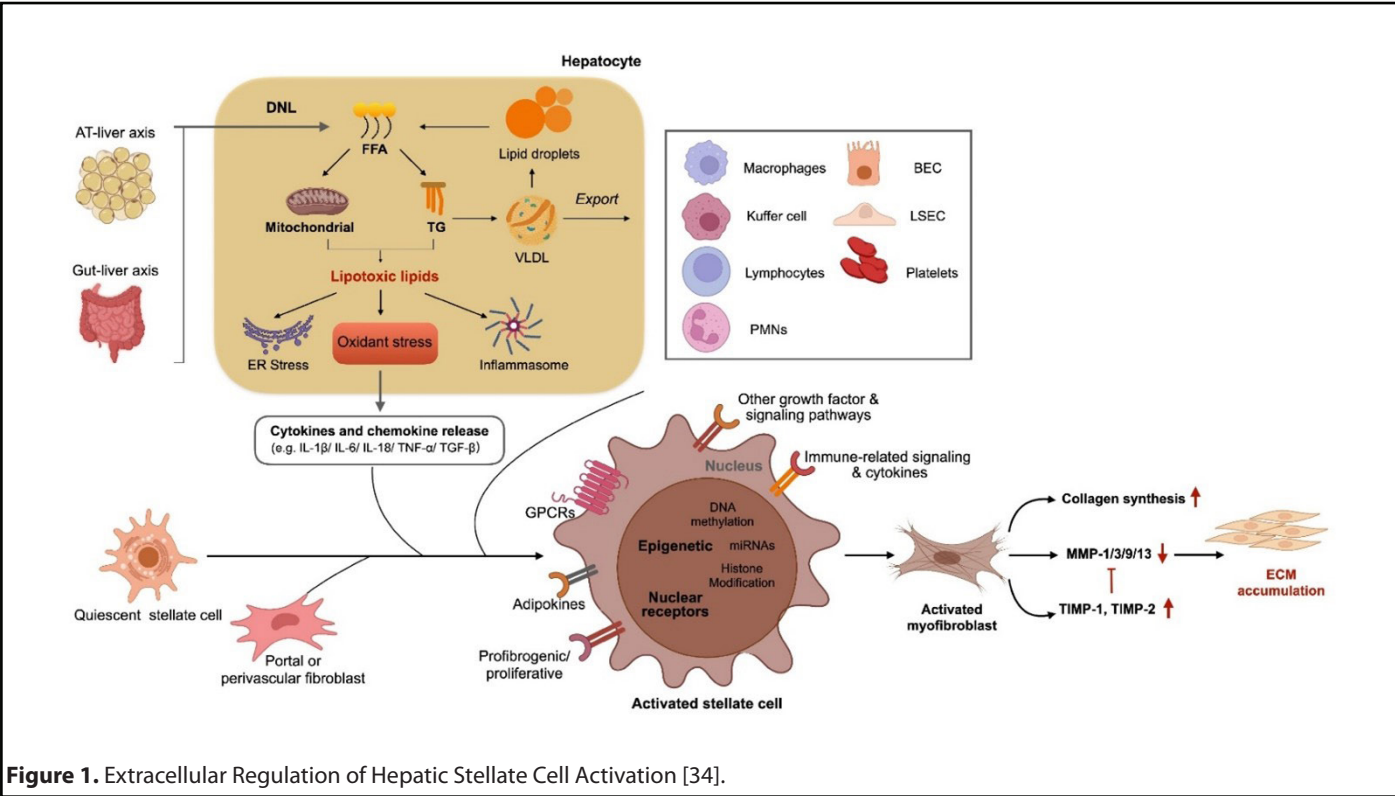


Figure 1. Extracellular Regulation of Hepatic Stellate Cell Activation [34].

Table 1. Summarizing the key molecular subtypes of liver cirrhosis.		
Subtype	Molecular Features	Clinical Associations
Inflammatory	Increased expression of macrophage activation genes (CCL2, CCL8,VCAN), acute phase response genes (SAA2, CRP)	Elevated serum inflammatory markers, advanced fibrosis, worse transplant-free survival
Proliferative	Upregulation of cell cycle progression and proliferation genes (PCNA, MCM2, ASPM), DNA replication and nucleotide metabolism genes	Increased hepatic regeneration markers, improved transplant-free survival
Cholangiocyte-associated	Overexpression of biliary and epithelial genes (KRT19, KRT7, EpCAM)	Higher serum alkaline phosphatase, increased bile ductular proliferation, mixed clinical outcomes

Inflammatory: This subtype demonstrates increased expression of genes linked to macrophage activation and chemotaxis, such as CCL2, CCL8, and VCAN. There is also upregulation of acute phase response genes like SAA2 and CRP. Patients show elevated serum inflammatory markers, more advanced fibrosis, and worse transplant-free survival [35].

Proliferative: The proliferative subtype exhibits induction of genes promoting cell cycle progression and proliferation, like PCNA, MCM2, and ASPM. Genes involved in DNA replication and nucleotide metabolism are also enriched. Patients show increased hepatic regeneration markers and improved transplant-free survival [36].

Cholangiocyte-associated: The cholangiocyte-associated subtype is distinguished by overexpression of biliary and epithelial genes including KRT19, KRT7, and EpCAM. Patients display higher serum alkaline phosphatase, increased histologic bile ductular proliferation, and mixed clinical outcomes [37].

Proteomic and metabolomics subtypes

A proteomics analysis of HCC patients with hepatitis C-related cirrhosis identified a subset with increased oncogenic proteins that correlated with greater cancer risk. Metabolomic studies demonstrate cirrhosis-associated alterations in bile acids, fatty acids, tryptophan, and other metabolites that differ by etiology.

Integrative multi-omics: The ultimate goal is to develop multi- platform integrative models that combine clinical, histologic, and diverse molecular data to derive optimized subtypes. One analysis incorporating transcriptomic and proteomic profiles with clinical parameters revealed five cirrhosis subtypes with escalating mortality risk. Another study defined four subtypes using clinical variables, mRNA and miRNA expression, serum markers, and gut microbiota profiles [38].

Genetic variants linked to liver disease subtypes

In addition to molecular subtypes, there are also genetic variants that predispose individuals to develop certain liver disease etiologies or influence disease phenotypes as depicted in **Table 2**. Several key examples are highlighted below:

NAFLD-related variants: Nonalcoholic fatty liver disease (NAFLD) has a substantial heritable component. Multiple genetic variants have now been implicated in NAFLD susceptibility and disease severity. Three of the most replicated are:

PNPLA3: This encodes adiponutrin, which functions in lipid metabolism. The I148M variant confers robust association with hepatic fat content, inflammation, and fibrosis in NAFLD. It is common in Hispanics, a group vulnerable to aggressive NAFLD. PNPLA3 likely promotes disease by limiting triglyceride hydrolysis [39].

TM6SF2: This variant is linked to altered very low-density lipoprotein secretion. TM6SF2 E167K substitution is associated with greater steatosis but lower NASH risk. Individuals with this variant appear prone to fatty liver accumulation without substantial inflammation [40].

MBOAT7: Variants near MBOAT7 correlate with lower inflammation and fibrosis in NAFLD. MBOAT7 regulates phosphatidylinositols implicated in fatty acid trafficking. The protective genotype may mitigate lipid-induced injury [41].

Autoimmune disease HLA alleles: Human leukocyte antigen (HLA) genes encoding major histocompatibility complex proteins are strongly associated with autoimmune conditions. Specific HLA alleles can predispose individuals to autoimmune liver diseases or modify disease course. Examples include:

Table 2. Summarizing key genetic variants associated with liver disease subtypes.		
Variant	Associated Liver Disease	Functional Impact
PNPLA3 I148M	Nonalcoholic fatty liver disease (NAFLD)	Promotes hepatic fat accumulation, inflammation, and fibrosis by limiting triglyceride hydrolysis
TM6SF2 E167K	NAFLD	Linked to increased hepatic steatosis but lower NASH risk, potentially due to altered VLDL secretion
MBOAT7 variants	NAFLD	Protective against inflammation and fibrosis, possibly by regulating fatty acid trafficking
HLA-DR8, HLA-DPB1*0301	Primary biliary cholangitis (PBC)	Increased disease risk and activity, potentially due to aberrant antigen presentation
HLA-DRB10301, HLA-DRB10401	Autoimmune hepatitis	Genetic susceptibility through dysregulated autoantigen presentation and self-tolerance
HLA-B8, HLA-DRB1*0301	Primary sclerosing cholangitis (PSC)	Predispose to immune targeting of biliary epithelium and cholangitis

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease marked by immune-mediated destruction of small intrahepatic bile ducts. Genetic susceptibility plays a key role, with multiple HLA allele associations reported. HLA-DR8 occurs more frequently in PBC patients and correlates with higher disease activity and anti-mitochondrial antibody levels. Positivity for HLA-DPB1 alleles, especially HLA-DPB1*0301, also confers increased risk. The associations emphasize the importance of aberrant antigen presentation via MHC class II molecules in PBC immunopathology. However, the implicated autoantigens remain unclear. Ongoing characterization of PBC HLA genetics may enable risk profiling, improve diagnostic accuracy, and inform the development of antigen-specific immunotherapies. However, significant research is still needed to fully define the HLA associations and interactions with non-HLA genetic loci [42].

Autoimmune hepatitis demonstrates strong associations with particular HLA haplotypes. Genetic risk factors include HLA-DR3 and HLA-DR4, especially HLA-DRB1*0301 and HLA-DRB1*0401 alleles. The HLA-DRB1*0401 haplotype confers increased susceptibility among North American and Northern European populations. Meanwhile, HLA-DRB1*0301 occurrence is elevated in autoimmune hepatitis patients in Southern Europe. The HLA associations highlight the importance of aberrant antigen presentation in disease pathogenesis. Ongoing studies aim to further define the roles of HLA alleles and additional genetic loci in breaking self-tolerance to trigger hepatocyte autoimmunity [43].

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammatory stricturing of the bile ducts. The pathogenesis involves aberrant immune targeting of biliary epithelium resulting in fibro-obliterative cholangitis. Genetic risk factors include strong associations with particular HLA alleles [44,45]. HLA-B8 positivity is found in up to 80% of PSC patients compared to 20-30% of controls. HLA-DRB1*0301 also confers susceptibility, present in 40% of PSC cases. Additional HLA-DR, HLA-DQ, and HLA-DP variants have demonstrated associations. The HLA links highlight the likely role of abnormal antigen presentation in PSC immunopathology, triggering loss of self-tolerance. However, the mechanisms require further elucidation. HLA genotyping may allow risk stratification and even prediction of disease course. Ultimately, better understanding PSC genetics and immunology is key for developing improved diagnostics, monitoring, and therapies. Emerging genomic approaches will help elucidate complex HLA interactions to provide biological insights and enable personalized management [46].

Other disease-associated variants: Additional genetic polymorphisms linked to specific cirrhosis subtypes continue to emerge, such as HFE C282Y in hereditary hemochromatosis and IFN- λ 4 in hepatitis C infection. For most variants, the functional mechanisms mediating disease susceptibility

remain to be elucidated. Furthermore, replication across diverse populations is necessary to firmly establish disease associations [47,48].

Current Therapeutic Options for Cirrhosis

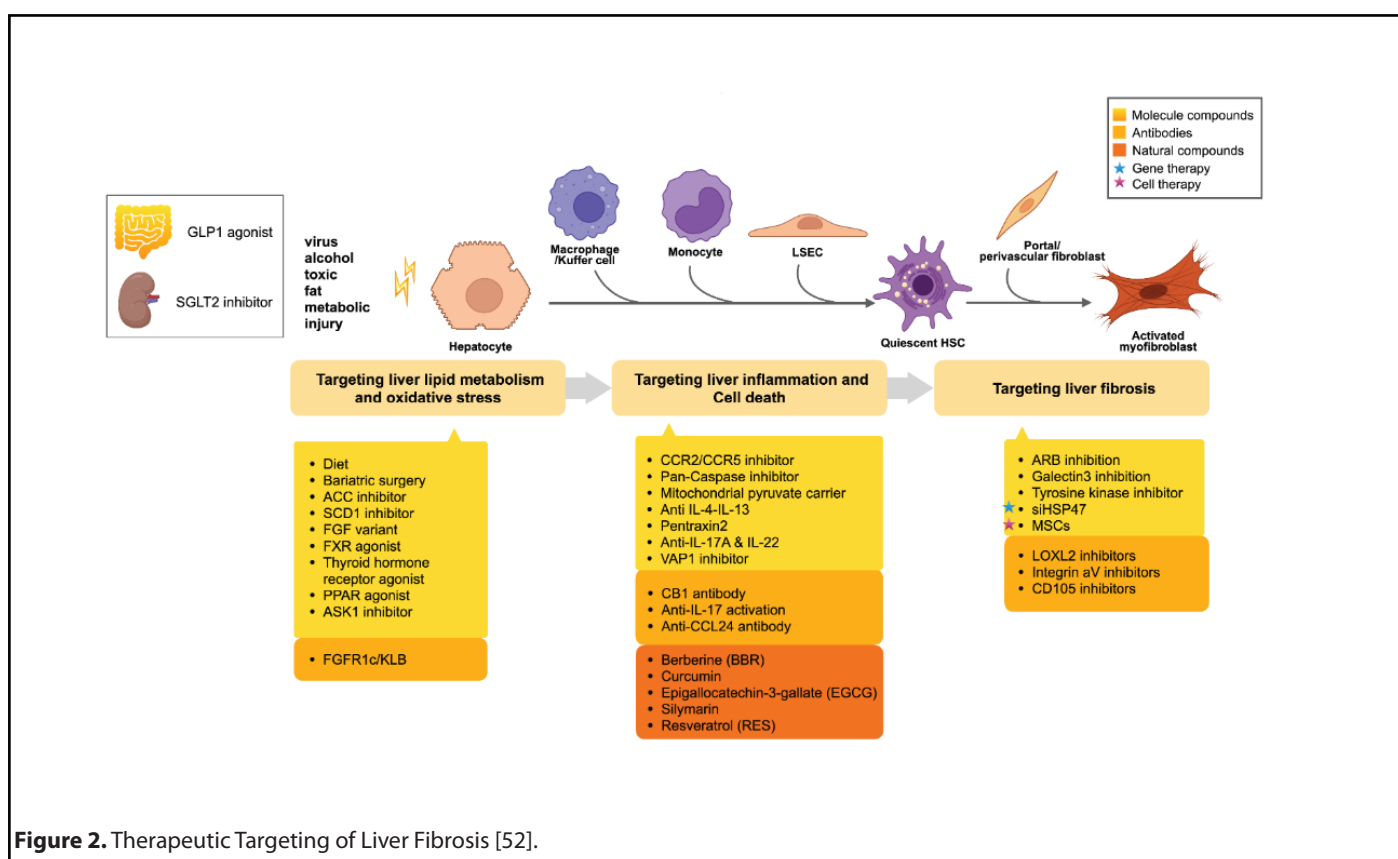
There is no cure for cirrhosis aside from liver transplantation. However, a number of treatments are available to address underlying causes, alleviate symptoms, slow progression, and reduce complications. Current pharmacologic treatments for liver fibrosis target various mechanisms including lipid metabolism, oxidative stress, inflammation, and direct antifibrotic pathways [49-51]. Agents in development include ACC inhibitors, SCD1 inhibitors, FGF agonists, thyroid hormone receptor agonists, FXR agonists, PPAR agonists, and GLP-1 receptor agonists. Natural compounds like berberine and silymarin have also shown potential benefits. Monoclonal antibody therapies blocking profibrotic mediators are emerging. However, no antifibrotics are yet FDA-approved, reflecting challenges demonstrating efficacy in clinical trials using suboptimal endpoints. Combination therapies synergistically targeting multiple pathways may overcome limitations of single agents. Optimization of trial design and endpoints is critical to validate the expanding pipeline of novel antifibrotics as illustrated in **Figure 2** [52].

Addressing underlying causes

Abstinence from alcohol and avoidance of environmental hepatotoxins can halt additional liver damage in alcoholic and toxic cirrhosis, permitting fibrosis regression over months to years. Weight loss exceeding 5-10% through dietary and lifestyle changes in nonalcoholic fatty liver disease can enhance steatosis, inflammation and potentially prevent or delay cirrhosis progression. Highly effective antiviral therapies treat chronic hepatitis B and C before cirrhosis, eliminating future complication risk. In early cirrhosis, antivirals may stabilize disease. Immunosuppressants including corticosteroids and azathioprine manage autoimmune hepatitis and primary biliary cholangitis, potentially reducing symptoms, inflammation, and progression [53-55].

Current anti-fibrotic therapies for cirrhosis

Along with addressing underlying causes, there is growing interest in using anti-fibrotic therapies targeting hepatic stellate cell activation and extracellular matrix accumulation driving cirrhosis progression. Vitamin E antioxidant compounds, which have shown some histologic improvement in early-stage NASH fibrosis but unclear role in advanced disease [56]. RCTs are needed to evaluate anti-fibrotics for cirrhosis. Few have been performed. Vitamin E showed efficacy in early NASH fibrosis in PIVENS. Pentoxifylline reduced fibrosis in some studies. Obeticholic acid improved NASH histology including fibrosis in phase 3 REGENERATE trial. However, larger RCTs of these agents specifically in cirrhosis are still required



to determine if they can halt progression or potentially reverse end-stage disease. Pentoxifylline phosphodiesterase inhibitor, which may inhibit stellate cells and decrease TNF production, with some studies showing improved NASH fibrosis but larger trials still needed [57,58].

Obeticholic acid farnesoid X receptor agonist, which showed histologic improvement including fibrosis in advanced NASH in phase 3 REGENERATE trial and was approved in 2021 for NASH fibrosis stage F2-F3, although further analysis in cirrhosis still needed [59,60].

Other novel agents

Various additional anti-fibrotic agents are in earlier stages of development, such as LOXL2 inhibitors, galectins, apoptosis signal-regulating kinase 1 inhibitors, and cytokine/chemokine targeting drugs. Most remain in phase 2 trials for NASH, with potential for expanded study in other fibrosis etiologies if proven safe and effective [61]. While current anti-fibrotics have demonstrated some efficacy in small trials, largely for early-stage NASH, major limitations persist. Most studies are underpowered with inconsistent endpoints. Many agents have problematic safety profiles or only transient effects. Well-designed robust trials with clinically meaningful endpoints are still lacking, especially in advanced fibrosis and cirrhosis. Anti-fibrotic regimens with sustained efficacy and safety have yet to be defined [62].

Latest innovations in liver transplantation and the role of AI

Liver transplantation remains the only definitive treatment for end-stage liver disease. Survival rates continue to improve with advances in organ preservation, surgical techniques, immunosuppression, and post-transplant care.

Organ perfusion and preservation: Novel perfusion systems allow *ex vivo* maintenance and assessment of donor livers to optimize viability and expand the usable donor pool. Normothermic regional perfusion can resuscitate marginal organs. Machine perfusion at subnormothermic temperatures better preserves organs during storage and transport. Perfusion paired with computational flow modeling enables evaluation of graft function [63].

Minimally invasive surgery: Recent advances in minimally invasive surgery have increased use of laparoscopic and robotic procedures for hepatobiliary operations. Consensus conferences like PAM have promoted safe minimally invasive liver resection (MILR) by better defining anatomy and recommending indocyanine green (ICG) to visualize portal regions during MILR. Glissonean approach and ICG-guided dissection along intersegmental planes enables precise MILR. Robotic MILR is emerging but needs improved ICG imaging and devices [64-66].

Immunosuppression strategies: Newer immunosuppressive protocols aim to minimize toxicity while preventing organ rejection. Options include steroid-free regimens and early elimination of calcineurin inhibitors. Costimulatory blockade agents, lymphodepletion, and stem cell transplantation facilitate minimization of immunosuppression. Chimeric antigen receptor T cell therapy is being explored to induce tolerance to donor antigens [67-70].

Post-transplant care: After liver transplantation, diligent post-transplant care is crucial for patient and graft survival. Immunosuppression is maintained to prevent rejection but requires monitoring for complications like infections [71-75]. Other considerations include managing cardiovascular risks, bone health, and screening for recurrent liver diseases in the allograft. Prompt diagnosis and treatment of graft dysfunction from rejection, viruses, or biliary issues is warranted. Multidisciplinary care optimizes outcomes by addressing adherence, lifestyle factors, and quality of life [76].

Roles of artificial intelligence: Artificial intelligence (AI) has emerging applications throughout the organ transplantation timeline aimed at improving patient outcomes. Machine learning can help predict post-transplant survival to inform waitlist prioritization and donor-recipient matching decisions. Computer vision techniques enable automated assessment of donor graft quality through analysis of steatosis on histological images [77].

AI-powered image guidance systems can assist surgeons with procedural planning and intraoperative visualization of anatomy. Deep learning approaches that integrate gene expression and biomarker data may allow individualized optimization of immunosuppression regimens. Transplant monitoring apps can leverage AI for early detection of rejection and other complications by recognizing patterns in biometric data. While AI holds promise to increase access to transplantation and enhance outcomes through synthesis of diverse data sources, real-world utility requires further validation. Moreover, thoughtful development and regulation of these technologies will be crucial to ensure AI solutions improve equity and align with patient interests [78-80].

Challenges and Future Directions for Cirrhosis Therapies

While progress has been made, management of cirrhosis faces considerable limitations and uncertainties. Key remaining challenges along with promising future directions are highlighted below:

Limitations of current therapies

Despite advances in managing cirrhosis complications, therapeutic options remain inadequate for halting fibrosis progression. No antifibrotic agents are approved for treating

the underlying liver scarring in cirrhosis. Current therapies like steroids and immunosuppressants are limited by substantial adverse effects. Meanwhile, clinical trials of investigational antifibrotics have faced challenges demonstrating efficacy, partially due to variability in endpoint selection. Surrogate markers of histological fibrosis reduction may not capture clinically meaningful outcomes. Suboptimal trial design also contributes, including heterogeneous patient populations and short duration. The lack of reliable noninvasive biomarkers for staging fibrosis is another barrier. Moving forward, optimizing clinical trial endpoints and validation of emerging imaging and serum biomarkers could accelerate antifibrotic drug development [81-83].

Promise of emerging therapies

To overcome limitations of current options, research is focused on exploring novel targets and technologies.

Antifibrotic and anti-inflammatory monoclonal antibodies: Targeted antibody-based therapies hold promise to potentially inhibit fibrogenic effectors and proinflammatory pathways while exhibiting high specificity and favorable safety. For example, phase 2 and 3 trials are underway assessing agents against LOXL2, CSF-1R, CCR2/CCR5, IL-17, VEGF, and other targets. Monoclonal antibodies engineered to preferentially localize fibrotic liver tissue could further enhance therapeutic index [84].

Cell therapy approaches: Cell-based treatments aim to attenuate fibrosis progression as well as augment liver regeneration. Mesenchymal stem cells derived from bone marrow and umbilical cord decrease collagen deposition in animal models via paracrine mechanisms and are now being tested in clinical trials. Hepatic stellate cell targeted therapies are also under investigation to selectively induce stellate apoptosis or restore quiescence [85-87].

Molecular targeting of fibrogenic pathways: Novel small molecules and oligonucleotides allow precise targeting of molecular drivers in fibrosis pathogenesis. Examples in development include tyrosine kinase inhibitors, Hedgehog pathway antagonists, PDGF inhibitors, and antisense oligonucleotides against proteins such as HSP47. Genome editing using CRISPR could also enable direct manipulation of fibrogenic genes. Beyond new drugs, emerging device-based therapies may also provide options to manage portal hypertension and promote liver regeneration. These include micro-stent shunts to lower portal pressure as well as implantable flow modulation devices to increase hepatic perfusion [88].

Need for biomarkers: Validated biomarkers are urgently needed to noninvasively diagnose fibrosis, predict outcomes, and assess therapeutic responses. This would enhance management across the spectrum of chronic liver disease

before end-stage cirrhosis develops. Key priorities include alternative noninvasive fibrosis staging methods to increase screening and monitoring, like serum markers FIB-4 and ELF, and imaging techniques such as transient elastography. There remains a dearth of molecular indicators to contemporaneously monitor treatment efficacy. Proteomics, metabolomics, and microRNA profiling are investigating pharmacodynamic markers of antifibrotic drug activity. Defining surrogate endpoints could expedite drug development. Response markers specific to etiology and molecular subclass are required [89,90].

Focus on preventing progression

While advancing cirrhosis treatments is crucial, greater emphasis on preventing fibrosis progression starting from early disease stages may provide greatest impact. Increased screening in high-risk groups permits earlier detection, such as ongoing efforts to screen diabetics for advanced NAFLD fibrosis requiring accessibility and validated biomarkers [91-94]. Realization of early intervention requires advances in screening, diagnosis, and treatment. Principles conveying fibrosis results from modifiable lifestyle factors must disseminate. Public health initiatives and engaging patients as research partners in longitudinal self-monitoring are key [95].

Conclusions

Liver cirrhosis represents a growing global health burden with substantial morbidity and mortality. While diverse etiologies underlie cirrhosis development, common pathogenic mechanisms converge on hepatic stellate cell activation, inflammation, and extracellular matrix accumulation. Molecular profiling approaches have now identified transcriptomic subtypes - inflammatory, proliferative, and cholangiocyte-associated - that may enable personalized management. Genetic variants also influence disease phenotypes, with polymorphisms in PNPLA3, TM6SF2, and HLA alleles among those linked to cirrhosis risk and outcomes. Currently, cornerstones of cirrhosis care include addressing underlying causes when possible and managing major complications that arise in decompensated disease. However, therapeutic limitations persist, as no antifibrotics are approved for established cirrhosis. Key priorities moving forward are developing robust noninvasive biomarkers for screening and prognostication, studying interventions in early-stage disease, and advancing novel antifibrotic therapies informed by molecular subtyping. Ultimately, a precision medicine approach may curb the rising morbidity and mortality of advanced liver cirrhosis worldwide.

Recommendations

Expand research on emerging antifibrotic therapies including monoclonal antibodies, cell-based approaches, and molecular targeting of pathogenic pathways. Rigorously designed, well-

powered clinical trials with clinically meaningful endpoints are needed to validate these novel agents, especially in advanced fibrosis and cirrhosis.

Develop and validate noninvasive biomarkers using proteomics, metabolomics, and microRNA profiling to enable better screening, prognosis, and assessment of treatment response. Surrogate markers specific to disease stage and molecular subtype could accelerate drug development.

Focus efforts on early detection and intervention, including increased screening in high-risk populations, to prevent progression from early fibrosis to end-stage cirrhosis. Public health initiatives can raise awareness and engage patients in longitudinal monitoring.

Further characterize molecular subtypes across diverse cirrhosis etiologies using multi-omics integration. Validate subtypes prospectively for clinical utility in prognosis and treatment selection.

Expand research on genetic polymorphisms that influence cirrhosis susceptibility and outcomes. Elucidate functional mechanisms and interactions with environmental factors. Incorporate genetics for personalized risk stratification.

Support multidisciplinary collaboration to advance new tools and therapies from bench to bedside. Patient involvement as research partners will also be key to ensuring innovations address unmet needs.

List of Abbreviations

MAFLD: Metabolic Dysfunction Associated Fatty Liver Disease; MASLD: Metabolic Dysfunction Associated Steatohepatitis; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; ACLF: Acute on Chronic Liver Failure; HLA: Human Leukocyte Antigen; MRI : Magnetic Resonance Imaging; ELF: Enhanced Liver Fibrosis Test; FIB-4: Fibrosis-4 Index; TIPS: Transjugular Intrahepatic Portosystemic Shunt; MELD: Model for End Stage Liver Disease; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; HSC: Hepatic Stellate Cell; ECM: Extracellular Matrix; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis; MILR: Minimally Invasive Liver Resection; ICG: Indocyanine Green; AI: Artificial Intelligence

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data is available, and sharing is available as well as publication.

Competing interests

The authors hereby declare that they have no competing interests.

Funding

The corresponding author supplied all study materials. There was no further funding for this study.

Authors' contributions

The author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

Acknowledgments

The author thanks all the researchers who have made great efforts in their studies. Moreover, we are grateful to the editors, reviewers, and readers of this journal.

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