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From signaling pathways to clinical trials: mesenchymal stem cells as multimodal regenerative architects in liver cirrhosis therapy

Vida Bozorgi[1,2†], Mahnaz Babaahmadi[3†], Mohammad Salehi[1,2], Jamshid Vafaeimanesh[1,2*] and Ensiyeh Hajizadeh-Saffar[3,4,5*]

Abstract

Liver cirrhosis, a chronic disease distinguished by extensive scarring in the liver, results in liver dysfunction and fatal complications such as portal hypertension and liver cancer. Although early interventions can retard or reverse early injury, advanced stages often call for liver transplantation—a therapy undermined by donor shortage and logistical setbacks. Emerging cell therapies, particularly those based on mesenchymal stem cells (MSCs), offer a novel approach to addressing these clinical needs. MSCs, self-renewing multipotent stromal cells, can differentiate into many cell types, including hepatocyte-like cells. Immune regulation, regenerative signaling, and anti-scarring effects are three mechanisms that underlie their therapeutic promise. MSCs modulate immune cells, suppressing inflammation and promoting tissue healing. MSCs release several growth factors and cytokines, including hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and matrix metalloproteinases (MMPs), which participate in tissue regeneration. Among these, HGF is bivalent, as it supports hepatocyte proliferation while also inhibiting fibrosis and apoptosis, thereby allowing the tissue to repair and protect itself. Recent advances identify extracellular vesicles from MSCs (MSC-EVs) as a cell-free alternative. The vesicles contain bioactive cargo, including microRNAs and proteins, that regulate immune function, inhibit cell death, and facilitate liver repair. Preclinical models of cirrhosis in animals have demonstrated MSC-EVs to enhance liver function, reduce scarring, and improve survival. This review integrates current knowledge of MSC-based therapies, their mechanisms, clinical potential, and challenges associated with their deployment. More than 50 clinical trials are registered or planned to evaluate MSC-based treatments for liver cirrhosis. Preclinical and clinical outcomes are encouraging; however, further work is needed to optimize delivery strategies, confirm safety, and

†Vida Bozorgi and Mahnaz Babaahmadi Co-first author.

*Correspondence:
Jamshid Vafaeimanesh
jvafaeemanesh@yahoo.com
Ensiyeh Hajizadeh-Saffar
en.hajizadeh@royan-rc.ac.ir

Full list of author information is available at the end of the article

facilitate the universal clinical use of this approach. Advances in MSC-guided regenerative medicine have the potential to revolutionize therapy for end-stage liver disease, offering hope where traditional treatments fail.

Keywords Mesenchymal stem cells, Liver cirrhosis, MSC-EVs, MSC

Introduction

Cirrhosis is a chronic liver disease characterized by the progressive replacement of healthy liver tissue with scar tissue, a process known as fibrosis. Liver scarring alters the typical structure of the liver, impairing its essential functions, including detoxification, protein synthesis, and bile production. The condition typically arises as a result of chronic liver injury from factors like chronic alcohol consumption, viral infections (hepatitis B and C being prominent), and non-alcoholic fatty liver disease, often in association with obesity, diabetes, and metabolic syndrome. A second group of causes includes autoimmune diseases, genetic disorders (e.g., hemochromatosis, Wilson's disease), and bile duct diseases like primary biliary cholangitis [1, 2].

Cirrhosis may be asymptomatic in its early stages, a condition referred to as compensated cirrhosis. As the disease evolves, symptoms such as fatigue, jaundice, weight loss, ascites, easy bruising, and mental confusion due to hepatic encephalopathy appear. Severe complications are portal hypertension leading to life-threatening bleeding from esophageal or gastric varices, renal failure, and an increased risk of hepatocellular carcinoma [3–6].

One of the key challenges in the management of cirrhosis is its often irreversible nature, particularly in advanced stages characterized by septal neovascularization and severe portal hypertension, in which structural damage of the liver becomes irreversible. Cirrhosis, if in early stages, can be reversible if the etiologic factor (e.g., viral hepatitis or alcohol use) is addressed early through interventions such as antiviral therapy or extended alcohol abstinence. Reversion of fibrosis, however, is a gradual process that typically takes years to achieve [7, 8]. Early diagnosis, however, remains elusive due to the asymptomatic presentation of early cirrhosis, with therapy delayed until late liver damage has been attained. In cases where reversal is impossible, the clinical practice focuses on arresting disease progression through lifestyle changes (e.g., diet, control of comorbidities) and the management of complications such as ascites, variceal bleeding, and hepatic encephalopathy, which require complex, long-term treatment [9].

Liver transplantation remains the only curative option for end-stage liver disease, and refinements in surgical procedures, immunosuppressive therapy, and postoperative management have significantly enhanced patient survival and quality of life. Its application is, however, limited by persistent constraints, including global donor shortages leading to waitlist times and death, excessive costs (surgery, long-term immunosuppression, and follow-up), and long-term adverse effects of infections, metabolic complications, and malignancies associated with immunosuppressive drugs [10, 11].

In recent decades, newer therapies, including cellular-based therapy (e.g., hepatocyte transplantation, liver organoids from stem cells, or gene-edited cell therapy), have novel promise [12–14]. These strategies aim to regenerate damaged liver tissue, reduce the need for donor organs, and minimize the requirement for immunosuppression. Among these, mesenchymal stem cells (MSCs) therapy has been one of the most promising, wherein its immunomodulatory properties, multipotent differentiation capabilities, and paracrine signaling activities are exploited to manage complex liver pathologies [15, 16].

MSCs produce a range of bioactive molecules, including cytokines, chemokines, and soluble factors, with essential roles in immunomodulation, angiogenesis, and tissue repair. Some of these mediators are indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), prostaglandin E2 (PGE2), interleukin-10 (IL-10), interleukin-6 (IL-6), and human leukocyte Antigen-G (HLA-G). These molecules regulate the function of immune cells, promote the generation of regulatory T cells (Tregs), and influence dendritic cell maturation [17, 18].

Additionally, MSCs release various wound-healing factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor-beta 1 (TGF-β1), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1). Through paracrine signaling, these factors induce cell survival, migration, and extracellular matrix (ECM) deposition, resulting in tissue regeneration and repair [19–21].

Preclinical studies [22–25] and clinical trials [26–30] demonstrated that MSC transplantation significantly improves liver function and is safe and effective in the treatment of liver failure. The evidence accumulating so far identifies stem cell-based therapy as a paradigm-shifting strategy for end-stage liver disease, filling the critical loopholes in existing therapies. This review attempts to fill critical knowledge gaps by incorporating recent advances in cell therapy for cirrhosis, with a special emphasis on MSCs. We uniquely combine molecular signaling pathways and novel clinical combinatorial approaches to guide precision medicine based on MSCs. Our study builds upon the instructive clinical review by Huang et al. [31], as a complementary approach that links

clinical observations with more profound mechanistic knowledge and engineering-based insights. While their review fully complements the clinical trials, our review advances the science in three fundamental dimensions: [1] understanding the mechanism of capture through the breakdown of molecular signaling and bioengineered MSC-derived extracellular vesicles (MSC-EVs) functionalized with ligands for liver targeting (e.g., galactose)—aspects that have been superficially addressed in previous clinical reviews; [2] integration of next-generation tools such as CRISPR-edited CAR-T cells against PDGFR-β + hepatic stellate cells and digital twin simulations to streamline therapies; and [3] rigorous evaluation of scalable solutions, most importantly, the translational gains of allogeneic cell banking in terms of cost reduction, standardized quality control, and avoidance of donor complications—key but underappreciated considerations for real-world feasibility.

This review outlines advances in MSC-based therapies, identifies current challenges, and sets future research priorities to address the unmet clinical needs of end-stage liver disease. By critically appraising the therapeutic mechanisms, clinical efficacy, and translational potential, our findings have the potential to inspire significant progress in the field.

Molecular pathogenesis of hepatic fibrogenesis.

The deregulated wound-healing responses to chronic liver injury predominantly determine the molecular pathogenesis of cirrhotic progression. The key initiators of this disastrous determination are as follows:

1. Reactive oxygen species (ROS) developed in excess by damaged hepatocytes and inflammatory infiltrate cells, such as neutrophils, represent potent signaling molecules that stimulate redox-sensitive transcriptional factors NF-κB and AP-1. Activation of this pathway further results in the increased expression of pro-inflammatory cytokines, such as TNF-α and IL-6, as well as chemokines, which contribute to inflammation- and fibrosis-promoting microenvironment [32].
2. Damage-associated molecular patterns (DAMPs), like high-mobility group box 1 (HMGB1) or fragmented DNA, are released from hepatocytes. Endogenous danger stimuli bind to Toll-like receptor 4(TRL4) with the MyD88 adaptor protein in Kupffer cells. TLR4/MyD88, prompts the protein NF-κB to lead to the generation of pro-inflammatory and pro-fibrotic mediators associated with the disease—such as TGF-β1 and IL-1β, which further link initial cell death to lasting inflammation [33].
3. Inflammasome activation, particularly through the NLRP3/ASC/caspase-1 complex, represents a critical amplification step in the inflammatory response. Triggered by ROS, DAMPs (like extracellular ATP), or crystalline substances, inflammasome assembly leads to the proteolytic activation of caspase-1. Active caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their mature, bioactive forms. The secretion of IL-1β and IL-18 triggers strong sterile inflammation by directly attracting more immune cells and activating hepatic stellate cells (HSCs), thereby solidifying the transformation from injury to fibrosis [34].

The core fibrogenic response centers on the activation and transdifferentiating of quiescent HSCs into collagen-secreting myofibroblasts. A network of interconnected signaling pathways orchestrates this transformation:

1. TGF-β/Smad Signaling:
2. TGF-β1 (released by Kupffer cells, platelets, and injured hepatocytes) binds to TβRII receptors on HSCs, leading to phosphorylation of Smad2/3. The phospho-Smad2/3-Smad4 complex translocates to the nucleus, activating genes encoding α-smooth muscle actin (α-SMA), collagen I and III, and tissue inhibitor of metalloproteinase-1 (TIMP-1) while suppressing matrix metalloproteinases (MMPs).
3. PDGF/ERK Axis:
4. PDGF potently stimulates HSC proliferation through the Ras/Raf/MEK/ERK signaling cascade, thereby accelerating fibrogenesis.
5. Inflammatory-Fibrotic Crosstalk.
6. Pro-inflammatory cytokines TNF-α and IL-1β (secreted by M1 macrophages) activate NF-κB within HSCs, inducing pro-fibrotic gene expression and inhibiting HSC apoptosis. Chemokines such as CCL2 and CXCL8 recruit monocytes, perpetuating the inflammatory response and fibrosis [33, 34].

4.Matrix Remodeling Imbalance:

Activated HSCs overexpress tissue inhibitors of metalloproteinases (TIMPs), which inhibit key matrix-degrading enzymes (MMP-2, MMP-9, MMP-13), thereby preventing ECM degradation and promoting scar accumulation [35, 36].

Collectively, these molecular pathways– chronic injury sensing (ROS/DAMPs), amplified inflammation (inflammasome), dominant pro-fibrotic signaling (TGF-β/Smad), HSC expansion (PDGF/ERK), inflammatory crosstalk (cytokines/chemokines), and impaired matrix degradation (TIMP/MMP imbalance)– which function together to form a self-sustaining fibrogenic microenvironment. In this environment, we observe persistent support of excessive scar tissue formation, which ultimately results in structural damage and functional decay, as seen in cirrhosis (Fig. 1).

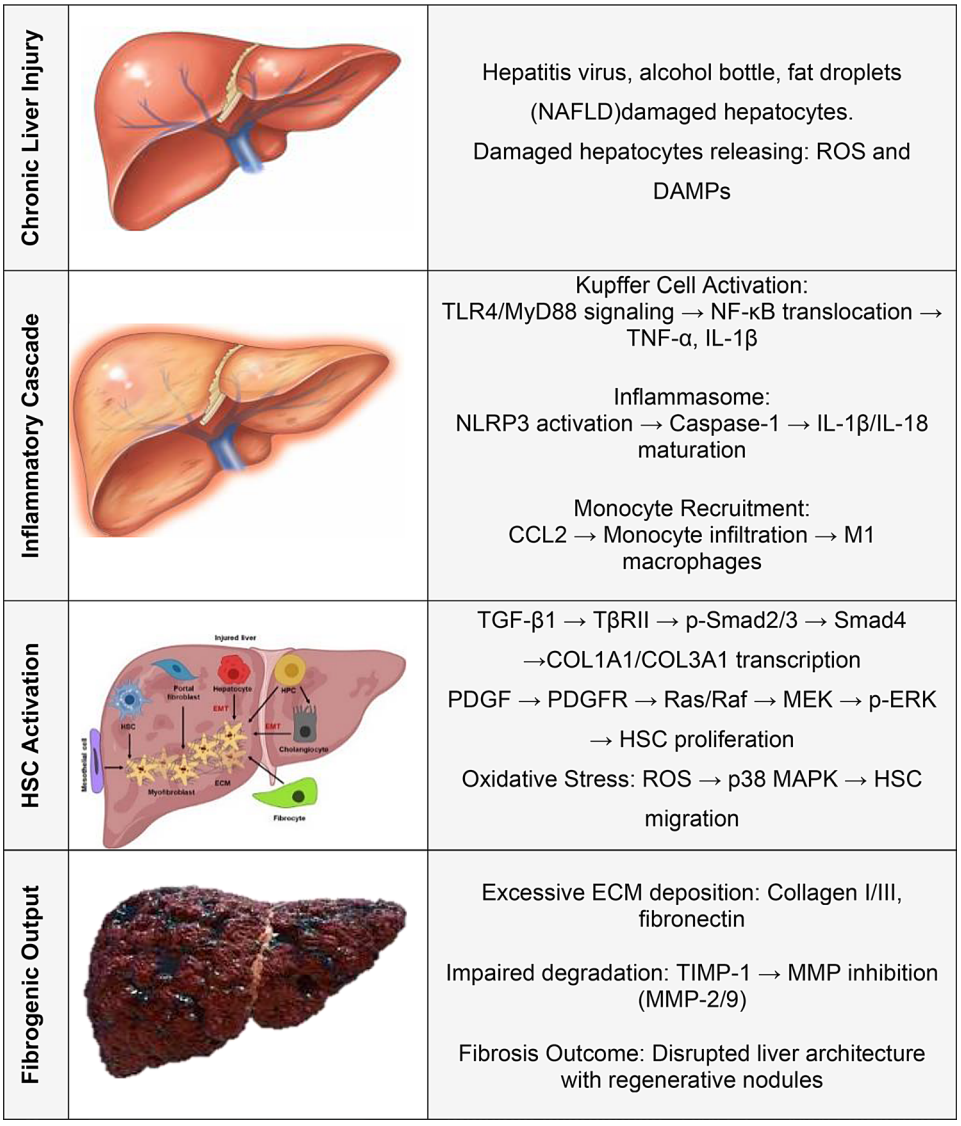

Fig. 1 Molecular mechanisms underpinning hepatic fibrosis. Chronic injury (viral, toxic, metabolic) triggers hepatocyte damage, releasing DAMPs and ROS. These activate Kupffer cells via TLR4/MyD88, driving NF-κB-dependent inflammation and NLRP3 inflammasome formation. Resultant cytokines (TNF-α, IL-1β) and PDGF recruit monocytes and activate HSCs. Quiescent HSCs transdifferentiate into collagen-producing myofibroblasts through TGF-β/Smad signaling (promoting COL1A1/COL3A1 transcription) and PDGF/ERK pathways (inducing proliferation). Impaired ECM degradation results from TIMP-1 overexpression inhibiting MMPs. Self-sustaining fibrogenic loops develop through cytokine cross-talk (e.g., TNF-α → NF-κB → TGF-β). MSC therapies target these pathways (e.g., HGF inhibition of TGF-βR, EV delivery of anti-fibrotic miRNAs). NAFLD: Nonalcoholic Fatty Liver Disease; TLRs: Toll-like receptors; NF-κB: nuclear factor-κB; MyD88: Myeloid differentiation primary response 88; TNF-α: tumor necrosis factor-α; IL-1β: Interleukin-1β; ccl2: C-C motif chemokine ligand 2; TGF-β: Transforming growth factor β; PDGF: Platelet-Derived Growth Factor; ERK: extracellular-signal-regulated kinase; MAPK: mitogen-activated protein kinase; TIMPs: tissue inhibitors of metalloproteinases; MMPs: matrix metalloproteinase; HSC: Hepatic Stellate Cell

Biological basis of mesenchymal stem cells

Mesenchymal stem cells are multi-potential stromal cells found in the majority of tissues, including bone marrow(BM), umbilical cord (UC) blood, fat, and amniotic fluid (AF). The cells possess two distinctive properties: the ability to self-renew in their undifferentiated form and the ability to differentiate into multiple cell lineages [37, 38]. While they were initially discovered to have the ability to generate mesenchymal tissues (bone, cartilage, and fat), newer research has determined their phenomenal plasticity, including their potency to differentiate into hepatocyte-like cells (HLCs)([39, 40] a feature that renders them particularly valuable for liver regeneration therapy. This potential has been documented in numerous studies over the past decade, generating interest in MSCs as a potential alternative to hepatocyte transplantation for the treatment of liver disease.

One of the most significant therapeutic advantages of MSCs is that they are immunologically low and can actively modulate the immune response, making them

suitable for both autologous and allogeneic use [41]. Promising in vitro studies and clinical trials have revealed that they are capable of inducing immunological tolerance. However, current evidence suggests that their significant therapeutic actions are paracrine-mediated rather than via direct differentiation [42, 43].

The combination of their differentiation capacity, immunomodulatory function, and paracrine action renders MSCs a versatile instrument in regenerative medicine. There has been general scientific curiosity in applying them to explore their broader applications in the treatment of complex medical disorders, particularly in diseases where standard therapies are ineffective.

Mechanisms of action: how MSCs modulate liver regeneration and fibrosis

MSC Immunomodulation in cirrhotic liver microenvironments

In liver disease, chronic inflammation is the effect and the cause of tissue damage, perpetuating a pathological process that fuels fibrosis and organ dysfunction [44]. MSCs possess tremendous immunomodulatory capabilities, rendering them well-suited to treat inflammatory liver conditions. Their dynamic interaction with the innate and adaptive immune systems has a global impact, resulting in a generalized anti-inflammatory process that is crucial for breaking chronic liver inflammation and permitting healing to proceed [45].

At the center of innate immune regulation is a triad of powerful mechanisms. First, through IDO, MSCs metabolize tryptophan in the local microenvironment, inducing metabolic stress that tames the ferocity of natural killer (NK) cells and promotes T cell hyperactivation while also fostering regulatory immune cell populations. Simultaneously, MSC-produced PGE2 acts as a molecular switch, converting pro-inflammatory M1 macrophages to their anti-inflammatory M2—a phenotypic shift marked by decreased harmful cytokines, such as TNF-α and IL-6, and increased healing factors, including IL-10 and TGF-β. Completing this natural triad, TNF-α-stimulated gene six protein (TSG-6) is a neutrophil calmer, calming these inflammatory first responders by suppressing their tissue entry, inhibiting oxidative bursts, and preventing pathologic neutrophil extracellular trap formation [46, 47].

The adaptive immune system is modulated equally. MSCs express PD-L1, initiating immune checkpoint signaling pathways to induce T cell anergy and prevent attack on hepatocytes—a process that mimics physiological tolerance mechanisms. Meanwhile, the non-classical HLA-G5 augment Tregs armies while suppressing dendritic cell maturation and effector T cell function, thereby creating a tolerant immunological microenvironment. The anti-inflammatory cytokine IL-10 serves as the chorus to this adaptive regulation, which tends to suppress pathogenic Th1/Th17 responses while promoting regulatory B cell differentiation [48, 49]. This multilayered immunomodulation, encompassing metabolic regulation, cellular reprogramming, and checkpoint regulation, positions MSC therapy as a singularly holistic approach to inflammatory liver disease. From autoimmune hepatitis to alcoholic steatohepatitis, MSCs may restore immune homeostasis, extending beyond symptom suppression.

MSC trophic signaling as a driver of liver regeneration

MSCs secrete a growth factor cocktail comprising two key mediators: HGF and VEGF, which coordinate critical signaling pathways to initiate hepatocyte proliferation, angiogenesis, and tissue repair.

HGF plays a crucial role in liver regeneration by inducing various protective and regenerative pathways within hepatocytes. In the presence of tissue damage in the liver, HGF is a very effective signaling molecule that binds to a tyrosine kinase receptor, mesenchymal-epithelial transition factor (c-MET), on the surface of the hepatocyte. This binding activates two primary signaling pathways. The first of these is the phosphoinositide 3-kinase (PI3K)/Akt pathway, which induces cellular survival by inhibiting apoptosis [50]. The second involves extracellular signal-regulated kinase 1/2 (ERK1/2), a member of the mitogen-activated protein kinase (MAPK) family. MAPK cascades serve as intermediary channels for transferring extracellular messages to intracellular effectors, thereby regulating key cellular functions, including cell growth, cell differentiation, and stress adaptation [50–52]. All the pathways, collectively, collaborate to allow the regeneration and repair of liver tissue. Its capacity to both safeguard mature hepatocytes and induce new cell growth puts it at the forefront of interest in liver repair therapy studies. Recent studies have been examining how to amplify HGF signaling or give HGF-like drugs as a treatment for liver disease where regeneration is impaired.

The liver's complex vascular bed, based upon its distinctive sinusoidal endothelial cells (SECs), is crucial for tissue integrity and regeneration. During liver injury, these fragile vascular networks often collapse, deranging oxygen and nutrient flow to areas that require repair [51]. VEGF secreted by MSCs now emerges as a fundamental mediator of vascular repair in this context. VEGF activates VEGF receptor-2(VEGFR-2) on SECs, promoting their proliferation and migration to areas of injury. This mechanism initiates the reconstruction of liver microvasculature, a prerequisite for the restitution of functional blood flow. Concurrently, VEGF stimulates endothelial nitric oxide synthase (eNOS), thereby elevating the concentration of NO and inducing vasodilation to enhance blood flow [52]. Furthermore, VEGF exerts an anti-apoptotic effect on endothelial cells, promoting facilitating vascular stabilization during tissue repair.

By revascularizing SEC networks, VEGF restores normal perfusion, supplying oxygen, growth factors, and metabolic substrates to regenerating hepatocytes [53]. Vascular regeneration like this is obligatory for energy-requiring repair processes, including DNA replication and cell proliferation, and therefore advances overall liver regeneration.

MSC anti-fibrotic effects in liver fibrosis

Liver fibrosis is an abnormal wound healing process that involves excessive accumulation of ECM components, particularly collagen types I and III [1]. MSCs counteract fibrosis through three mechanisms: paracrine signaling, immunomodulation, and suppression of fibrogenic pathways [54]. A critical mediator, TGF-β1, via Smad-dependent signaling (TGF-β/Smad), activates HSCs and results in ECM overproduction [55]. MSCs disrupt this process by [1] secreting HGF to block TGF-β receptor binding [2], suppressing Smad2/3 signaling (key pro-fibrotic mediators), and [3] enhancing Smad7, a negative protein that arrests TGF-β signaling [56, 57]. These combined effects repress HSC activation and ECM deposition, promoting tissue repair. Additionally, MSCs exert robust matrix-modifying effects through the secretion of MMPs, specifically MMP-2 (gelatinase A) and MMP-9 (gelatinase B), which possess characteristic proteolytic activity towards fibrillar collagens that constitute the fibrotic scar tissue [60]. The enzymes degrade the triple-helical domain of collagen types I and III into smaller fragments that are subsequently phagocytosed by macrophages.

MSC- extracellular vesicles

Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) represent a breakthrough in the field of regenerative medicine, particularly in liver regeneration [58]. These nanosized particles, once viewed as cellular byproducts, are now recognized as active molecular messengers that enable communication between cells [58, 59].

MSC-EVs carry a high-tech load of RNAs, proteins, lipids, and immunomodulatory factors [60]. MicroRNAs (miR)-181 and miR-223 are included among them, serving as precision tools to disrupt pathological processes. Specifically, miR-223 suppresses pro-inflammatory signaling pathways [61], while miR-181 selectively inhibits collagen-producing genes, thereby disassembling the molecular scaffolding of fibrosis [62, 63]. MSC-EVs also carry protective proteins, such as heat shock protein 70 (HSP70) and survivin, which stabilize hepatocytes under inflammatory stress [64]. HSP70 safeguards cellular integrity by suppressing apoptosis [65], while survivin suppresses enzymatic pathways that trigger programmed cell death [66]. This dual cargo not only suppresses inflammation and oxidative damage but also creates a pro-regenerative microenvironment. By inhibiting pathologic immune discourses and guarding vulnerable liver cells, MSC-EVs terminate the cycle of self-reinforcing chronic fibrosis and inflammation. Their simultaneous ability to modulate immune reactions, inhibit apoptosis, and initiate repair places them on the list as a multipurpose therapeutic modality for diseases from alcoholic steatohepatitis to acute liver failure. With advancing research, these vesicles are revolutionizing liver disease treatment, offering a cell-free alternative that leverages the inherent healing potential of MSCs without exposing patients to the risks associated with whole-cell transplantation [62, 67].

MSC efficacy in animal models of liver cirrhosis

Preclinical research involving liver cirrhosis primarily employs three types of animal models: chemically induced (e.g., carbon tetrachloride (CCl_4) and thioacetamide (TAA), surgically induced (e.g., bile duct ligation (BDL), and genetically engineered models.

Subcutaneous or intraperitoneal administration twice a week for 6–8 weeks induces oxidative stress and activates HSCs using the CCl_4 induction schedule. The model resembles numerous characteristics of alcoholic cirrhosis (AC) in humans, including progressive fibrosis. Disadvantages thereof include high individual variation and system toxicity of the drug due to its extensive tissue actions [68, 69]. Through research conducted by Khalil et al., CCl_4-induced experimental models of hepatic fibrosis have shown that BM-MSCs are capable of reversing structural and functional liver injury. Their intervention suppressed the hepatotoxicity of CCl_4, leading to increased levels of liver function biomarkers, such as albumin (Alb), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [70].

A single injection of MSC isolated from Wharton's jelly (WJ-MSCs) administered to TAA-induced liver fibrosis in mice was able to reduce collagen deposition and attenuate fibrotic damage in two weeks. The therapy promoted the expression of regenerative markers, such as HGF and proliferating cell nuclear antigen (PCNA). It suppressed pro-fibrotic signaling pathways, including Smad2, RhoA, and extracellular signal-regulated kinase (ERK). Interestingly, treated mice exhibited lower plasma fibronectin (pFN) levels in liver tissue, suggesting that WJ-MSCs have the potential to promote the regenerative microenvironment by affecting pFN deposition. These findings indicate that WJ-MSCs are a therapeutic regimen of value in combating fibrosis and aiding tissue repair in chronic liver disease [71].

The BDL model, with surgical occlusion of the common bile duct, immediately induces cholestasis, inflammation, and hepatic fibrosis within 2–3 weeks. The model is widely employed to study cholestatic cirrhosis, including

primary biliary cholangitis [69]. In a preclinical study by Jun et al., the transplantation of placenta-derived MSCs (PD-MSCs) in cirrhotic rats induced by BDL elevated C-reactive protein (CRP) levels through exosome-mediated delivery. CRP activation of the Wnt/β-catenin signaling pathway induced liver regeneration by promoting angiogenesis and hepatocyte proliferation. Significantly, PD-MSC-derived exosomal CRP suppressed fibrotic advancement and enhanced vascular and parenchymal repair. These findings elucidate CRP's dual role in liver regeneration and the resolution of fibrosis, highlighting its therapeutic potential for degenerative liver diseases through MSC-based therapies [72].

Table 1 summarizes preclinical studies investigating the efficacy of MSCsin models of liver fibrosis and cirrhosis. Several key patterns emerge from these data:

1. Toxin-induced models (CCl_4, TAA) were the most widely used (8 of 12 studies) and carried similarities to human toxic or metabolic pathologies. Cholestatic (BDL) and immune-mediated (DDC) models also showed notable improvement after MSC therapy, suggesting that these cells are functional across a range of etiologies for cirrhosis.
2. Bone marrow-derived MSCs (BM-MSCs) and umbilical cord-derived MSCs (UC-MSCs) were the most commonly utilized sources. Intravenous (IV) administration was the most common method (7 studies). However, intrasplenic (IS) or intrahepatic arterial (IHA) administration (as seen in the dog study) demonstrated superior results in reducing fibrosis and improving liver function, likely due to direct access to the injured tissue.
3. All the studies showed significant decreases in fibrosis (reduced collagen and α-SMA) and improvements in liver function (decreased ALT/AST and elevated Alb). MSCs mediate their therapeutic action by secreting trophic factors (HGF, VEGF), immune modulation (decreased TNF-α, increased IL-10), and modulation of fibrogenic pathways (decreased TGF-β/Smad, balanced MMP/TIMP).
4. Optimal doses ranged widely (10^5 to 10^7 cells/kg), varying with MSC source and animal species.
5. Only long-term assessments (e.g., the dog model with 12-week follow-up) established.
6. Indocyanine green (ICG) clearance improvement in dogs (Studies 81, 82) represents a direct measurement of hepatic functional recovery and has high clinical relevance. Collectively, these data demonstrate that MSCs exert potent antifibrotic and regenerative effects, irrespective of their source or the cause of fibrosis. However, optimization of the administration route and long-term monitoring are crucial for the successful translation of this approach to human clinical trials.

Clinical translation: safety and efficacy of MSC-based therapies

MSCs have been researched in the past decade as a potential therapeutic intervention for liver disease due to their immunomodulatory activity, antifibrotic effects, and ability to stimulate tissue regeneration.

A randomized controlled study quantified intravenous administration of BM-MSCs in patients with hepatitis B-related acute-on-chronic liver failure (ACLF). Clinical results demonstrated significant enhancements in the model for end-stage liver disease (MELD) scores—a poor prognosticator—coupled with reduced mortality rates compared to the control group. The improvement was linked to reduced systemic inflammation, as indicated by decreased cytokine levels of TNF-α and IL-6. The survival rate of the MSC-treated group was significantly higher at 24 weeks, which was attributed to enhanced hepatic function (e.g., reduction in total bilirubin) and a decrease in severe infections. Notably, the intervention was safe, with no severe adverse events. The findings are promising and reflect the potential of MSC-based therapies as a future strategy for the treatment of HBV-ACLF and other end-stage liver diseases sharing a similar pathophysiology [28]. However, the authors acknowledged several limitations: [1] The 24-week follow-up—though justified by high early mortality in ACLF—was insufficient for comprehensive safety assessment; [2] Varied hospitalization durations impeded accurate adverse event monitoring post-discharge; [3] The open-label design introduced potential bias in outcome interpretation; [4] Single-center recruitment may limit generalizability. Future multicenter studies with extended observation periods are needed to validate these findings.

Clinical trials by Suk et al. (2016) assessed autologous BM-MSC therapy for AC patients. Outcomes exhibited histologic reversal of hepatic fibrosis (confirmed through biopsy) in association with improved liver function, as evidenced by decreases in ascites and hepatic encephalopathy. A comparison between two BM-MSC groups receiving single or double infusions revealed a 25% and 37% reduction in collagen deposition. Notably, a one-time administration of BM-MSC was sufficient to yield structural liver improvement, reflecting sustained therapeutic efficacy. However, the study acknowledged key limitations: [1] The precise mechanism underlying MSC-mediated fibrosis reduction remains incompletely understood; [2] Technical challenges in tracking infused cells hindered mechanistic insights; [3] Phase 3 trials are warranted to confirm efficacy in long-term outcomes like survival.

Table 1 Summary of preclinical studies on MSC therapy for cirrhosis

Animal Model	MSC Source	Dose(cells)	Administration Route	Key Findings	Ref.
Rat (CCl4-induced)	BM-MSC	1×10^6	IV	Reduced fibrosis, improved liver function, anti-inflammatory effects	[83]
Rat (CCl4-induced)	UC-MSCs	1×10^6	IV	↑PDGF and VEGF, ↓ALT and AST normality of histology appearance and accelerate liver regeneration	[84]
Mouse (CCl4-induced)	Flk1 + murine MSCs	1×10^6	IV	Reduced liver damage & collagen deposition ↓ Hepatic hydroxyproline & serum fibrosis markers Improved histologic recovery Low-frequency donor cell engraftment & albumin expression	[85]
Rat (CCl4-induced)	UC-MSCs	1×10^6	IV	↓ALT/AST, ↑synthetic function Reduced fibrosis ↓Collagen deposition MMP-13↑/TIMP-1↓ (ECM remodeling) Histopathological improvement	[56]
Rat (CCl4-induced)	BM-MSC	2×10^6	IV	↓ AST/ALT/ALP ↑ Albumin Anti-inflammatory effect (↓TNF-α) Detoxification enhancement (↓CYP450)	[70]
Rat (TAA-induced)	BM-MSCs	5×10^5	IH	Inhibited Smad3 phosphorylation attenuated hepatic fibrosis in rats	[87]
Canines (CCl4-induced)	Autologous BM-MSCs	4×10^5/Kg	IV	↓ Sirius red-stained fibrosis area (vs. control), ↑ Liver function: Improved ICG clearance No adverse effects observed Successful canine cirrhosis model established	[88]
Canines (CCl4-induced)	Autologous BM-MSCs	4×10^5/Kg	IV or IH	Hepatic artery delivery showed superior efficacy: Greater reduction in ICG vs. vein at 12 weeks Earlier functional improvement (8weeks) Excellent safety profile: No liver infarction (CT-confirmed) No LDH elevation or hypercoagulability Proof-of-concept established for arterial route	[89]
Canine (Chronic Hepatitis)	Allogeneic BM-MSCs	$(2.5\times10^{6)}$ ×3	IV	Clinical improvement: Resolution of vomiting/diarrhea, Improved energy levels ↓ ALT, ↓ ALP, ↑ Albumin	[90]
Rabbit (CCl4-induced)	autologous AD-MSCs	5×10^5/kg	PV	Histological improvement in cirrhotic liver observed one month after MSC transplantation	[91]
Mouse (DDC-induced cholestatic liver injury)	MenSCs	5×10^5	IV	↑ Survival rate (60% → 100%) ↓ Serum markers: AST / ALT /ALP / DBIL&TBIL ↓ Fibrosis area Improved cholestasis & bile duct dilation ↓ Fibrogenic markers: COL1A1, α-SMA, TGF-β1 ↑ β-catenin signaling	[92]
NOD/SCID mice (TAA-induced)	WJ-MSCs	3×10^5	IP	Significant attenuation of liver fibrosis Enhanced expression of hepatocyte growth factor (HGF) and proliferative marker PCNA.	[71]
Rat Cirrhosis (induction method not specified).	UC-MSC + Tan IIA (combination therapy)	2×10^7	IP.	reduced serum ALT and elevated ALB levels promoted hepatocyte differentiation Tan IIA synergistically enhanced UC-MSC efficacy, amplifying anti-fibrotic and regenerative outcomes.	[93]

CCL4: Carbon tetrachloride; BM-MSC: Bone marrow mesenchymal stem cells; IV: Intravenous Injection; IH: intrahepatic;PV: portal vein; IP: Intraperitoneal PDGF: Platelet-derived growth factors; VEGF: Vascular Endothelial Growth Factor; ALT: alanine aminotransferase; AST: aspartate transaminase; HGF: Hepatocyte Growth Factor; UCMSCs: umbilical cord mesenchymal stem cells; MMP: matrix metalloproteinase; TIMP: Tissue inhibitors of metalloproteinase; ECM: Extracellular matrix; ALP: Alkaline Phosphatase; TNF-α: Tumor necrosis factor; CYP450: cytochrome P450; TGF-β:Transforming growth factor beta; ICG: Indocyanine green; CT: Computerized Tomography; LDH: lactate dehydrogenase; AD-MSCs: Adipose-derived-MSCs; DDC: 3,5-diethoxycarbonyl-1,4-dihydrocollidine;MenSCs: Menstrual blood-derived stem cells; DBIL: Direct bilirubin; TBIL: Total bilirubin; COL1A1: Collagen type I α1; NOD/SCID: Nonobese diabetic/severe combined immunodeficiency

These findings indicate that BM-MSC transplantation not only reduces fibrotic tissue but is also associated with measurable clinical improvements, making it a promising adjunct therapy for AC. The study highlights the need for Phase 3 trials to confirm further BM-MSC efficacy in improving long-term outcomes, such as survival rates, and to optimize dosing regimens for patients with severe liver disease [29].

In a pioneering clinical trial, Schache et al. tested the safety and efficacy of BM-MSC therapy for treating

patients with severe acute-on-chronic liver failure (ACLF, Grades 2–3). While prior trial reports had shown that BM-MSC infusions were safe, no survival benefit was identified between the treatment and control groups at 90 days. Of specific interest, one patient completing the full five-dose course demonstrated a truly remarkable improvement in liver function and resolution of ACLF, a testament to the potential of BM-MSC therapy in less severe disease (e.g., ACLD Grade 1). While confirming treatment safety, no survival benefit emerged at 90 days—a result likely influenced by key methodological constraints, including severe disease burden (mean MELD: 38), an underpowered design, late intervention timing, and high early mortality that prevented protocol completion. These findings underscore the challenge of treating critically ill cohorts and highlight the need for Phase 3 trials in earlier disease stages [73].

In research on cirrhosis due to autoimmune disease, researchers found that the combination of MSCs with immunosuppressive treatment (e.g., corticosteroids) was more effective than monotherapy with MSCs alone. This collaborative effort enhanced the speed of fibrosis regression and immune response modulation [30].

Wang et al. demonstrated that MSC transplantation in patients with Primary biliary cholangitis (PBC) led to significant biochemical alterations. The therapy reduced liver injury markers, including ALT, AST, and γ-glutamyltransferase, and lowered immunoglobulin M and CD8 + T cell levels. At the same time, it increased the levels of Tregs (CD4 + CD25 + Foxp3+) and anti-inflammatory cytokine IL-10. These alterations were not just numbers on a lab report; they translated into a tangible improvement in the quality of life of patients, as evidenced by favorable outcomes in PBC-40 questionnaire tests [74]. However, serial histological analysis revealed that immunomodulatory effects were not sustained at 12-month follow-up. The transient nature of cellular responses underscores the need for earlier post-treatment assessment. Confirmation through prospective randomized trials remains essential.

In a meta-analysis conducted by Wang et al., they reviewed 14 clinical trials and reported that the combination of MSC therapy with standard supportive care significantly improved liver function in patients with cirrhosis of various etiologies. This improvement was not only biochemical but also resulted in a reduction in clinical manifestations, demonstrating the efficacy of the combination therapy [75].

Cumulatively, recent clinical trials illustrate the therapeutic potential of MSCs for treating liver cirrhosis. Across studies, reports consistently present evidence of improved liver function, as indicated by reduced MELD scores, normalization of albumin levels, and regression of fibrosis. Biochemical indicators, such as ALT and bilirubin, also showed a notable reduction in accordance with the increased survival rates observed in the treated groups. Mechanistically, these actions are attributed to MSC secretion of trophic factors (e.g., HGF, VEGF), immune modulation through M2 macrophage polarization, and blockade of fibrogenic pathways, such as TGF-β/Smad signaling.

While outcomes varied by MSC source (BM, UC vs. others), administration schedules, and patient stratification, the therapy had a promising safety profile, with minor transient toxicities (e.g., fever, tiredness) in few patients. Also, there were no serious adverse events—tumorigenicity or pulmonary embolism. In general, however, heterogeneity of trial designs, small numbers of studies, and short durations of follow-up do not permit conclusions. The urgency and importance of more extensive, larger, multicenter Phase III studies with controlled protocols are required to validate long-term efficacy, make dosing regimens more rational, and determine which patient subsets will most benefit from such regenerative therapy. The listed clinical studies in Table 2 demonstrate extensive global research into MSC treatment of cirrhosis of the liver with over 50 registered trials across several investigation phases.

These trials have a broad geographic spread, with intense research activity in China, India, Turkey, Iran, South Korea, Japan, the USA, and several European countries. Although approximately 14 studies have been completed, many more are ongoing or newly initiated between 2023 and 2024. These trials employ different MSC sources, with UC-MSCs being the most prevalent, followed by BM-MSCs and autologous MSCs. The innovative strategies include the use of menstrual blood-derived MSCs, which offer a non-invasive and easily accessible source of MSCs, and exosomes derived from MSCs, which are being explored for their potential to deliver therapeutic molecules without the risk of immune rejection, in certain studies. The clinical studies are centered on various etiologies of cirrhosis, including hepatitis, alcohol abuse, and autoimmune liver diseases, with a special emphasis on decompensated cirrhosis. The mode of delivery varies in experimental studies, but it is mainly intravenous infusion, while some studies incorporate hepatic artery injection and portal vein delivery. A notable aspect of the research is the combination of MSC therapy with conventional treatments, immunomodulators, or scaffold materials in some studies, demonstrating a comprehensive approach to treatment enhancement. Table 2 reveal UC-MSCs and BM-MSCs are safe and effective in improving liver function (↓MELD, ↑albumin) and reducing fibrosis, with Phase 3 trials ongoing to confirm survival benefits. We acknowledge the diversity in MSC products and stress the ongoing work to standardize protocols. The extensive global research underscores

Table 2 MSC clinical trials in liver cirrhosis up to 2025-04-25

Location	Start Date	Phase	Intervention	Type of transplantation	NCT Number
India	2013	Phase1|phase2	UC-MSC BM-MSC	Allogeneic Autologous	NCT01877759
Turkey	2016	Phase1|phase2	AD-MSC	Autologous	NCT02705742
India	2012	Phase2	BM-MSC	Allogeneic	NCT01591200
China	2017	NA	MSC	NP	NCT03209986
Singapore	2018	Phase1|phase2	BM-MSC	Autologous	NCT03626090
India	2019	Phase 4	BM-MSC HSC	Autologous	NCT04243681
Japan	2012	NA	AD-MSC	Autologous	NCT01062750
NP	2016	Phase1|phase2	BM-MSC	Autologous	NCT02943889
China	2016	Phase1	UC-MSC	Allogeneic	NCT02652351
China	2014	Phase1|phase2	UC-MSC	Allogeneic	NCT01573923
Turkey	2008	NA	BM-MSC	Autologous	NCT01499459
Japan	2017	Phase1|phase2	AD-MSC	Autologous	NCT03254758
Korea	2009	Phase2	BM-MSC	Autologous	NCT01741090
Iran	2023	Phase2	UCMSC-EV	Allogeneic	NCT05871463
China	2009	Phase1|phase2	UC-MSC	Allogeneic	NCT01233102
China	2019	Phase2	UC-MSC	Allogeneic	NCT03945487
NP	2018	Phase2	UC-MSC	Allogeneic	NCT03529136
Iran	2007	Phase2	BM-MSC	Autologous	NCT00476060
China	2023	Phase1|phase2	UC-MSC	Allogeneic	NCT05948982
Vietnam	2020	Phase1	UC-MSC	Allogeneic	NCT05331872
Japan	2009	Phase1	AD-MSC	Autologous	NCT00913289
China	2010	Phase1|phase2	UC-MSC	Allogeneic	NCT01224327
China	2023	NA	UC-MSC	Allogeneic	NCT06167473
China	2023	Phase1	UC-MSC	Allogeneic	NCT05984303
China	2022	Phase1	UC-MSC	Allogeneic	NCT05227846
Indonesia	2018	Phase1|phase2	UC-MSC	Allogeneic	NCT04357600
China	2020	Phase1|phase2	MSC&Treg	NP	NCT03460795
China	2024	NA	UC-MSC	Allogeneic	NCT06242405
Belgium	2012	Phase1|phase2	MSC	NP	NCT01429038
China	2009	Phase1|phase2	UC-MSC	Allogeneic	NCT01220492
China	2013	Phase3	BM-MSC	Autologous	NCT01854125
China	2011	Phase1	BM-MSC	Allogeneic	NCT01440309
China	2017	NA	MSC	NP	NCT03668145
China	2009	Phase2	BM-MSC	Autologous	NCT00993941
China	2010	Phase2	BM-MSC	Allogeneic	NCT01223664
Turkey	2024	NA	UC-MSC	Allogeneic	NCT06564740
China	2021	NA	UC-MSC	Allogeneic	NCT05106972
Korea	2012	Phase2	BM-MSC	Allogeneic	NCT01875081
Vietnam	2019	Phase1|phase2	UC -MSC	Allogeneic	NCT04522869
Ukraine	2018	Phase3	BM -MSCs	Autologous	NCT05080465
China	2010	Phase1|phase2	UC-MSCs	Allogeneic	NCT01342250
NP	2008	Phase2	BM-MSC	Autologous	NCT00976287
China	2010	Phase1|phase2	MenSC	Allogeneic	NCT01483248
Korea	2021	Phase3	BM-MSC	Autologous	NCT04689152
China	2012	Phase1|phase2	UC-MSC	Allogeneic	NCT01728727
Iran	2010	Phase1	MSC	Autologous	NCT01454336
China	2022	Phase1	UC-MSCs	Allogeneic	NCT05155657
Turkey	2011	NA	BM-MSC	Allogeneic	NCT01378182
China	2021	Phase2	UCMSC	Allogeneic	NCT05121870
China	2024	Phase2	UC-MSC	Allogeneic	NCT05224960
China	2019	Early_phase1	UC-MSC	Allogeneic	NCT05442437
China	2011	Phase1|phase2	UC-MSC	Allogeneic	NCT01662973

Table 2 (continued)

Location	Start Date	Phase	Intervention	Type of transplantation	NCT Number
China	2018	Phase1	UC-MSC	Allogeneic	NCT03826433
Indonesia	2024	Phase1	UC-MSC	Allogeneic	NCT06629909
China	2021	Phase1|phase2	UC-MSC	Allogeneic	NCT05507762
United States	2019	Phase1	BM-MSC	Autologous	NCT03838250
China	2016	Phase1|phase2	UC-MSCs	Allogeneic	NCT02786017

MSCs: Mesenchymal Stem Cells; HCV: Hepatitis C virus; UC-MSCs: Umbilical Cord Mesenchymal Stem Cell; BM: Bone marrow; HSC: Hematopoietic Stem Cell; MenSC: Menstrual blood-derived stem cells; ESLD: End Stage Liver Disease; LC: liver cirrhosis; NA: Not applicable; NP: Not Provided; Treg: regulatory T cells

the potential of MSC therapy as a significant regenerative strategy that can bridge the gap to liver transplantation.

New frontiers in this field include dose optimization studies and the development of new products derived from MSCs, such as MSC-secretome and exosome treatments. This research landscape encompasses both Phase 1, safety-focused, and Phase 2, efficacy-oriented studies, with some of the latter being randomized controlled trials for improved evidence quality. Long-term follow-up studies provide data on the durability of treatment effects, indicating the field's progress towards more substantial clinical evaluation.

Comparative analysis of transplantation approaches in cirrhosis

Clinical evidence suggests that both autologous and allogeneic MSCs can improve MELD scores and reduce liver fibrosis in the management of cirrhosis. Optimal source selection, however, depends critically on disease stage. For patients with compensated cirrhosis, where endogenous cellular function is relatively preserved, autologous transplantation may be preferable. Conversely, allogeneic transplantation often demonstrates superiority in decompensated cirrhosis. Cells derived from healthy donors exhibit more vigorous immunomodulatory activity and more prominent paracrine effects, enabling more effective suppression of systemic inflammation and generally yielding faster therapeutic outcomes. These source-dependent functional differences underscore the need for personalized treatment strategies for cirrhosis [76].

Autologous MSC transplantation offers a significant advantage: a substantial reduction in immunological risks. However, this approach faces important limitations. In patients with advanced cirrhosis, patient-derived stem cells often exhibit premature senescence or functional impairment, severely diminishing their proliferative capacity and therapeutic efficacy. Furthermore, the personalized preparation process, involving isolation, expansion, and quality control, typically takes up to 6 weeks, delaying treatment initiation in urgent cases and incurring high production costs due to its complexity [77].

In contrast, allogeneic transplantation utilizes MSCs from healthy donors. Its primary advantage is immediate access to "off-the-shelf" products, enabling rapid intervention. Sourced from young, healthy individuals, these cells generally possess standardized and higher therapeutic potential, characterized by more vigorous paracrine activity (e.g., secretion of elevated levels of growth factors like VEGF and HGF). Additionally, allogeneic cells enable large-scale production, thereby enhancing their suitability for broader applications. Nevertheless, challenges remain. Although inherently low-immunogenic due to minimal HLA molecule expression, the risk of immune reactions—particularly with repeated infusions, which can lead to the formation of anti-donor antibodies—is not eliminated. This underscores the need for long-term patient monitoring, a responsibility that we, as healthcare professionals, must uphold. Logistical complexities related to cryopreservation, storage, and transportation also exist [29]. Figure 2 compares the approaches of stem cell transplant (autologous vs. allogeneic) among the included clinical trials in Table 2.

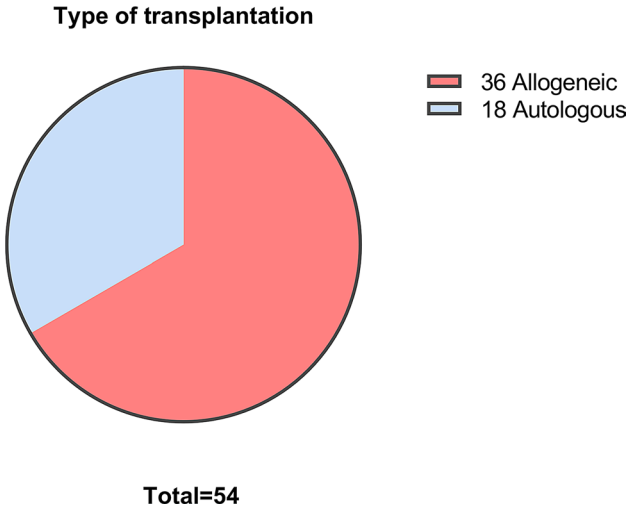

Fig. 2 Comparison of stem cell transplantation approaches (autologous vs. allogeneic) across the included clinical trials

MSC effectiveness by source in cirrhosis management

MSCs from different sources show varying efficacy in treating cirrhosis. BM-MSCs, the most extensively studied, demonstrate moderate to high effectiveness in improving liver function and reducing fibrosis. However,

they face practical limitations due to the invasive harvesting process and reduced yield in patients with cirrhosis. AD-MSCs offer comparable clinical benefits to BM-MSCs, with superior safety and easier harvest via liposuction, making them highly effective for autologous therapy in stable patients [78]. UC/WJ-MSCs emerge as a potentially highly effective source, particularly for allogeneic use. Their potent immunomodulatory properties, rapid proliferation, and 'off-the-shelf' availability enable faster improvements in decompensated cirrhosis and acute liver failure [79]. Other sources, such as dental pulp, remain experimental due to the limited clinical data available. The effectiveness of these treatments is greatly influenced by matching the source to the disease stage: UC/WJ-MSCs excel in urgent advanced cases, while AD-MSCs are optimal for autologous treatment in compensated cirrhosis. Standardization and comparative trials are necessary to optimize protocols and ensure the best outcomes for patients [46]. Figure 3 provides a visual overview of the sources of MSCs used in the clinical trials (Table 2), grouping them (e.g., BM, AT, UC) to demonstrate their relative shares in the studies. This data is highly relevant as it directly impacts the outcomes of the clinical trials, keeping you engaged and interested in the findings.

Figure 4 illustrates the phases of clinical trials (Phase I, II, III, IV or combined phases) and presents a clear contrast of the stages of advancement between the research under study. Phase I trials assess safety in small compensated cirrhosis cohorts. Phase II evaluates efficacy (e.g., improvement in MELD score) in larger groups of early-decompensated patients. Phase III confirms clinical benefits (survival, reduced decompensation events) through large randomized trials. Phase IV monitors post-approval safety. Combined phases (e.g., I/II) accelerate development.

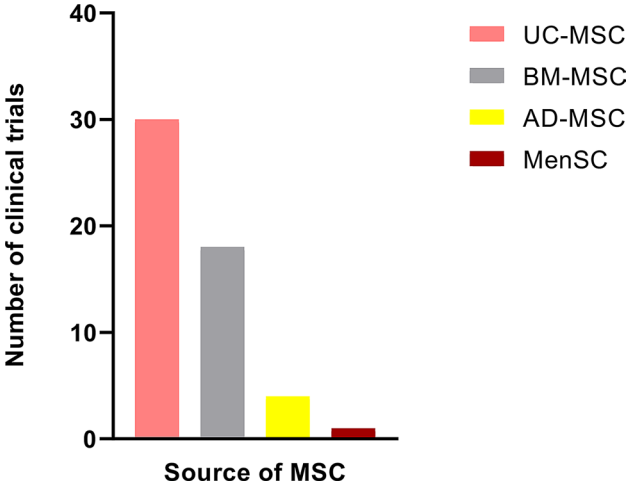

Fig. 3 Distribution of mesenchymal stem cell (MSC) sources (e.g., bone marrow, adipose tissue, umbilical cord) in the analyzed clinical trials

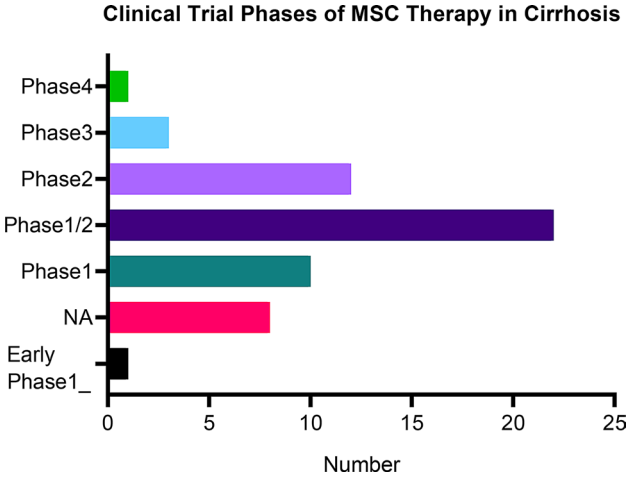

Fig. 4 Clinical trial phases (Phase I, II, III, IV, or combined phases) and their representation in the selected studies

Limitations and challenges of MSC therapy for cirrhosis

Despite the significant disadvantage of the short-term survival of transplanted MSCs in the malignant cirrhotic environment, ongoing research is investigating ways to enhance their resilience and durability. Conditioning MSCs (e.g., hypoxia preconditioning, cytokine treatment) or encapsulating them within protective biomaterials (e.g., hydrogels) are promising strategies being explored [80]. The complexity of the field, with heterogeneity between MSC sources (BM, AT, UC), isolation methods, donor characteristics, and dosing regimens, presents a significant challenge. However, understanding and managing these factors can have a direct impact on cellular potency and clinical outcomes, motivating us to seek innovative solutions. For instance, UC-MSCs often demonstrate superior immunomodulation in viral cirrhosis, while AD-MSCs may excel in metabolic fibrosis. This biological diversity, coupled with methodological disparities in delivery, complicates the translation process. Systemic infusion results in > 80% pulmonary sequestration, whereas localized delivery carries procedural risks, creating inconsistencies that impede cross-trial comparisons and dose standardization [81].

This multifaceted heterogeneity—biological and methodological—translates directly to inconsistent clinical results—furthermore, microenvironment-induced apoptosis, combined with the lack of standardized release criteria, compounds outcome variability. More research and development in this area is needed to establish these criteria. Although MSCs exhibit low immunogenicity, allogeneic transplantation carries risks of immune sensitization or undesirable differentiation (e.g., ectopic tissue formation). Consequently, extended monitoring in clinical trials is essential to rule out tumorigenicity or systemic immunosuppression [82]. Cost remains a

barrier due to intricate production demands. However, the potential of large-scale allogeneic 'off-the-shelf' cell banks and optimized logistics (e.g., cryopreservation, shipping) is immense. These advancements are crucial for democratizing access, particularly in resource-constrained settings, and pave the way for a more accessible and effective MSC therapy in the future.

Future directions

The evolving horizon of MSC-based therapies for cirrhosis reveals strategies at varying developmental stages:

Genetic engineering approach

We categorize these as clinically actionable approaches versus exploratory concepts requiring further validation.

-Clinically Emerging Genetic Engineering.

CRISPR/Cas9 platforms are advancing toward clinical translation to enhance the therapeutic properties of MSCs. Current applications focus on achievable modifications, such as the Overexpression of hepatoprotective factors (HGF, VEGF) or the Knockdown of profibrotic mediators (TGF-β). Evidence-based approaches enhance the targeting of MSCs in fibrotic microenvironments.

-Exploratory Concepts (Preclinical Stage).

Highly innovative technologies, such as base/prime editing, synthetic gene circuits, and autonomous therapeutic release systems, are still in their early stages. Their clinical applicability hinges on extensive safety validation and in vivo efficacy confirmation.

EV-based therapies: translation-ready vs. conceptual

Translation-ready

- - Engineered EVs delivering miRNA cocktails (e.g., miR-122) or antifibrotic agents.
- - Tissue-targeted EVs with galactose/ECM-binding ligands.

Speculative approaches

Concepts like 'Decoy EVs', which act as molecular sponges for cytokines, and hybrid EV-nanoparticle systems show promise but are currently limited to in vitro models. Their potential requires further exploration and scalability studies.

Clinically testable combination therapies

These are immediately actionable strategies with strong preclinical rationale that leverage established clinical modalities such as MSC + antiviral therapy in viral cirrhosis and MSC + β-blockers for portal hypertension.

Precision medicine: current implementation

Biomarker-driven patient stratification and AI-assisted treatment simulation (digital twins) are being integrated into ongoing trials. Liquid biopsies for EV-miR-34a tracking show near-term feasibility.

Localized delivery optimization

Intrahepatic/portal vein delivery and biomaterial scaffolds are undergoing Phase 1/2 testing (e.g., NCT03254758).

CAR-T cell therapy: theoretical potential

Targeting PDGFR-β + stellate cells remains highly speculative due to the risks of liver-specific toxicity and immunosuppressive microenvironments. The evidence represents exploratory biology rather than an imminent clinical pathway.

Conclusion

MSC-based therapies represent a paradigm-shifting frontier in cirrhosis treatment, bridging the gap between palliation and cure. While preclinical models and early-phase clinical trials are promising in terms of safety and efficacy, establishing long-term outcomes requires large-scale randomized controlled trials (RCTs) to be paramount. These trials will also help optimize dosing schedules and standardize formal protocols. Partnerships between academia, industry, and regulators will be essential to achieve translational advancement with scalability and reproducibility in heterogeneous patient cohorts. Meanwhile, patient registering and post-marketing vigilance systems may be given high priority to survey real-world safety and iteratively refine therapeutic strategy. By mitigating the challenges of the moment through technological innovation, biomarker-driven personalization, and rigorous clinical validation, MSC therapies may yet re-engineer the treatment of advanced liver disease, reducing transplant dependency and improving global health outcomes. Although significant challenges remain in clinical translation, the regenerative potential of MSCs suggests a therapeutic strategy for cirrhosis patients, which could enable disease-modifying therapies with further research and development.

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Author contributions

VB and MB designed the study and wrote the manuscript, MS data analyzed, JV and EH reviewed the article. All authors read and approved.

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Author details
[1]Clinical Research Development Center, Qom University of Medical Sciences, Qom, Iran
[2]Qom Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, Iran
[3]Advanced Therapy Medicinal Product Technology Development Center (ATMP-TDC), Royan Institute for Stromal Cell Biology and Technology, ACECR, Banihashem Sq., Banihashem St., Resalat Highway, P.O. Box: 16635-148, Tehran 1665659911, Iran
[4]Department of Stromal Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stromal Cell Biology and Technology, ACECR, Tehran, Iran
[5]Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stromal Cell Biology and Technology, ACECR, Tehran, Iran

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References

1. Sharma B, John S. Hepatic cirrhosis. 2018.
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71.
3. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. Lancet. 2021;398(10308):1359–76.
4. Alberts CJ, Clifford GM, Georges D, Negro F, Lesi OA, Hutin YJ, et al. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. Lancet Gastroenterol Hepatol. 2022;7(8):724–35.
5. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38(3):266–72.
6. Nusrat S, Khan MS, Fazili J, Madhoun MF. Cirrhosis and its complications: evidence based treatment. World J Gastroenterology: WJG. 2014;20(18):5442.
7. Sohrabpour AA, Mohamadnejad M, Malekzadeh R. The reversibility of cirrhosis. Aliment Pharmacol Ther. 2012;36(9):824–32.
8. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. Cells. 2020;9(4):875.
9. Tapper EB, Parikh ND. Diagnosis and management of cirrhosis and its complications: a review. JAMA. 2023;329(18):1589–602.
10. Kim D-S, Yoon Y-I, Kim BK, Choudhury A, Kulkarni A, Park JY, et al. Asian Pacific association for the study of the liver clinical practice guidelines on liver transplantation. Hep Intl. 2024;18(2):299–383.
11. Khalil A, Quaglia A, Gélat P, Saffari N, Rashidi H, Davidson B. New developments and challenges in liver transplantation. J Clin Med. 2023;12(17):5586.
12. Mun SJ, Ryu J-S, Lee M-O, Son YS, Oh SJ, Cho H-S, et al. Generation of expandable human pluripotent stem cell-derived hepatocyte-like liver organoids. J Hepatol. 2019;71(5):970–85.
13. Peng WC, Logan CY, Fish M, Anbarchian T, Aguisanda F, Álvarez-Varela A, et al. Inflammatory cytokine TNFα promotes the long-term expansion of primary hepatocytes in 3D culture. Cell. 2018;175(6):1607–19. e15.
14. Cardinale V, Lanthier N, Baptista PM, Carpino G, Carnevale G, Orlando G, et al. Cell transplantation-based regenerative medicine in liver diseases. Stem Cell Rep. 2023;18(8):1555–72.
15. Joshi M, Patil B, He P, Holgersson Z, Olausson J, Sumitran-Holgersson M. Fetal liver-derived mesenchymal stromal cells augment engraftment of transplanted hepatocytes. Cytotherapy. 2012;14(6):657–69.
16. Wu M-C, Meng Q-H. Current Understanding of mesenchymal stem cells in liver diseases. World J Stem Cells. 2021;13(9):1349.
17. Kulesza A, Paczek L, Burdzinska A. The role of COX-2 and PGE2 in the regulation of Immunomodulation and other functions of mesenchymal stromal cells. Biomedicines. 2023;11(2):445.
18. Liang X, Ding Y, Zhang Y, Tse H-F, Lian Q. Paracrine mechanisms of mesenchymal stem cell-based therapy: current status and perspectives. Cell Transplant. 2014;23(9):1045–59.
19. Ehlen QT, Costello JP, Mirsky NA, Slavin BV, Parra M, Ptashnik A, et al. Treatment of bone defects and nonunion via novel delivery mechanisms, growth factors, and stem cells: A review. ACS Biomaterials Sci Eng. 2024;10(12):7314–36.
20. Hsiao ST-F, Asgari A, Lokmic Z, Sinclair R, Dusting GJ, Lim SY, et al. Comparative analysis of paracrine factor expression in human adult mesenchymal stem cells derived from bone marrow, adipose, and dermal tissue. Stem Cells Dev. 2012;21(12):2189–203.
21. Jiang Z, Liu G, Meng F, Wang W, Hao P, Xiang Y, et al. Paracrine effects of mesenchymal stem cells on the activation of keratocytes. Br J Ophthalmol. 2017;101(11):1583–90.
22. Xagorari A, Siotou E, Yiangou M, Tsolaki E, Bougiouklis D, Sakkas L, et al. Protective effect of mesenchymal stem cell-conditioned medium on hepatic cell apoptosis after acute liver injury. Int J Clin Exp Pathol. 2013;6(5):831.
23. Huang B, Cheng X, Wang H, Huang W, la Ga Hu Z, Wang D, et al. Mesenchymal stem cells and their secreted molecules predominantly ameliorate fulminant hepatic failure and chronic liver fibrosis in mice respectively. J Translational Med. 2016;14:1–12.
24. Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell. 2009;5(1):54–63.
25. Li J, Zhang L, Xin J, Jiang L, Li J, Zhang T, et al. Immediate intraportal transplantation of human bone marrow mesenchymal stem cells prevents death from fulminant hepatic failure in pigs. Hepatology. 2012;56(3):1044–52.
26. Wang L, Li J, Liu H, Li Y, Fu J, Sun Y, et al. A pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. J Gastroenterol Hepatol. 2013;28:85–92.
27. Liu Wh S, Fq R, Ln G, Wq, Wang T, Feng Yx, et al. The multiple functional roles of mesenchymal stem cells in participating in treating liver diseases. J Cell Mol Med. 2015;19(3):511–20.
28. Lin Bl C, Jf Q, Wh W, Kw X, Dy C, Xy, et al. Allogeneic bone marrow–derived mesenchymal stromal cells for hepatitis B virus–related acute-on-chronic liver failure: a randomized controlled trial. Hepatology. 2017;66(1):209–19.
29. Suk KT, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, et al. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: phase 2 trial. Hepatology. 2016;64(6):2185–97.
30. Liang J, Zhang H, Zhao C, Wang D, Ma X, Zhao S, et al. Effects of allogeneic mesenchymal stem cell transplantation in the treatment of liver cirrhosis caused by autoimmune diseases. Int J Rheum Dis. 2017;20(9):1219–26.
31. Huang W-C, Li Y-C, Chen P-X, Ma KS-K, Wang L-T. Mesenchymal stem cell therapy as a game-changer in liver diseases: review of current clinical trials. Stem Cell Res Ther. 2025;16(1):3.
32. de la Conde L, Goicoechea L, Torres S, Garcia-Ruiz C, Fernandez-Checa JC. Role of oxidative stress in liver disorders. Livers. 2022;2(4):283–314.
33. Mihm S. Danger-associated molecular patterns (DAMPs): molecular triggers for sterile inflammation in the liver. Int J Mol Sci. 2018;19(10):3104.
34. Guan Y, Gu Y, Li H, Liang B, Han C, Zhang Y, et al. NLRP3 inflammasome activation mechanism and its role in autoimmune liver disease: role of NLRP3 inflammasome in autoimmune liver disease. Acta Biochim Biophys Sin. 2022;54(11):1577.
35. Di Carlo SE, Peduto L. The perivascular origin of pathological fibroblasts. J Clin Investig. 2018;128(1):54–63.
36. Puche JE, Saiman Y, Friedman SL. Hepatic stellate cells and liver fibrosis. Compr Physiol. 2013;3(4):1473–92.
37. Wu X, Jiang J, Gu Z, Zhang J, Chen Y, Liu X. Mesenchymal stromal cell therapies: Immunomodulatory properties and clinical progress. Stem Cell Res Ther. 2020;11(1):345.
38. Rodríguez-Fuentes DE, Fernández-Garza LE, Samia-Meza JA, Barrera-Barrera SA, Caplan AI, Barrera-Saldaña HA. Mesenchymal stem cells current clinical applications: a systematic review. Arch Med Res. 2021;52(1):93–101.
39. Eom YW, Shim KY, Baik SK. Mesenchymal stem cell therapy for liver fibrosis. Korean J Intern Med. 2015;30(5):580.
40. Hu C, Zhao L, Zhang L, Bao Q, Li L. Mesenchymal stem cell-based cell-free strategies: safe and effective treatments for liver injury. Stem Cell Res Ther. 2020;11:1–12.

41. Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nat Immunol. 2014;15(11):1009–16.
42. Soliman H, Theret M, Scott W, Hill L, Underhill TM, Hinz B, et al. Multipotent stromal cells: one name, multiple identities. Cell Stem Cell. 2021;28(10):1690–707.
43. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14(8):493–507.
44. Possamai LA, Thursz MR, Wendon JA, Antoniades CG. Modulation of monocyte/macrophage function: a therapeutic strategy in the treatment of acute liver failure. J Hepatol. 2014;61(2):439–45.
45. Gazdic M, Markovic BS, Arsenijevic A, Jovicic N, Acovic A, Harrell CR, et al. Crosstalk between mesenchymal stem cells and T regulatory cells is crucially important for the Attenuation of acute liver injury. Liver Transpl. 2018;24(5):687–702.
46. Cao Y, Ji C, Lu L. Mesenchymal stem cell therapy for liver fibrosis/cirrhosis. Annals Translational Med. 2020;8(8):562.
47. Yao L, Hu X, Dai K, Yuan M, Liu P, Zhang Q, et al. Mesenchymal stromal cells: promising treatment for liver cirrhosis. Stem Cell Res Ther. 2022;13(1):308.
48. Lin YC, Chen MC, Huang SW, Chen Y, Ho JHC, Lin FY, et al. Targeting dual immune checkpoints PD-L1 and HLA-G by trispecific T cell engager for treating heterogeneous lung cancer. Adv Sci. 2024;11(41):2309697.
49. Moayedfard Z, Lankarani KB, Alizadeh AA, Nekooeian AA, Dara M, Koohpeyma F, et al. The ameliorative effect of Adipose-Derived mesenchymal stem cells and their exosomes in Non-alcoholic steatohepatitis by simultaneously enhancing autophagic flux and suppressing Endoplasmic reticulum stress. Iranian Journal of Medical Sciences; 2025.
50. Wang M, Zhang J, Gong N. Role of the PI3K/Akt signaling pathway in liver ischemia reperfusion injury: A narrative review. Annals Palliat Med. 2022;11(2):80617–817.
51. Wilkinson AL, Qurashi M, Shetty S. The role of sinusoidal endothelial cells in the axis of inflammation and cancer within the liver. Front Physiol. 2020;11:990.
52. Xia Y-P, Li B, Hylton D, Detmar M, Yancopoulos GD, Rudge JS. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. Blood. 2003;102(1):161–8.
53. Abdulazeem L, Tariq A, Abdalkareem Jasim S. An investigation of vascular endothelial growth factor (VEGFR-1 and VEGFR-2) in burn wound healing. Arch Razi Inst. 2022;77(2):747.
54. Shi Q, Xia Y, Wu M, Pan Y, Wu S, Lin J, et al. Mi-BMSCs alleviate inflammation and fibrosis in CCl4-and TAA-induced liver cirrhosis by inhibiting TGF-β/Smad signaling. Mater Today Bio. 2024;25:100958.
55. Hashim Y, Abdel Baky NA, Kamal MM, Gad A. Aliskiren and Fenofibrate constrict liver fibrosis by means of focusing on TGF-β1/Smad signaling pathway and actuating HGF expression. Azhar Int J Pharm Med Sci. 2021;1(1):73–86.
56. Krstic J, Trivanovic D, Obradovic H, Kukolj T, Bugarski D, Santibanez JF. Regulation of mesenchymal stem cell differentiation by transforming growth factor beta superfamily. Curr Protein Pept Sci. 2018;19(12):1138–54.
57. Qin L, Liu N, Bao C- et al. Yang D-z, Ma G-x, Yi W-h,. Mesenchymal stem cells in fibrotic diseases—the two sides of the same coin. Acta Pharmacologica Sinica. 2023;44(2):268– 87.
58. Zhang J, Lu T, Xiao J, Du C, Chen H, Li R, et al. MSC-derived extracellular vesicles as nanotherapeutics for promoting aged liver regeneration. J Controlled Release. 2023;356:402–15.
59. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373–83.
60. Heydari Z, Peshkova M, Gonen ZB, Coretchi I, Eken A, Yay AH, et al. EVs vs. EVs: MSCs and Tregs as a source of invisible possibilities. J Mol Med. 2023;101(1):51–63.
61. Hou X, Yin S, Ren R, Liu S, Yong L, Liu Y, et al. Myeloid-cell–specific IL-6 signaling promotes MicroRNA-223-enriched exosome production to attenuate NAFLD-associated fibrosis. Hepatology. 2021;74(1):116–32.
62. Chen W, Huang Y, Han J, Yu L, Li Y, Lu Z, et al. Immunomodulatory effects of mesenchymal stromal cells-derived exosome. Immunol Res. 2016;64:831–40.
63. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci. 2020;21(24):9739.
64. Birtwistle L, Chen X-M, Pollock C. Mesenchymal stem cell-derived extracellular vesicles to the rescue of renal injury. Int J Mol Sci. 2021;22(12):6596.
65. Rérole A-L, Jego G, Garrido C. Hsp70: anti-apoptotic and tumorigenic protein. Molecular Chaperones: Methods and Protocols: Springer; 2011. pp. 205–30.
66. Altieri DC. Survivin and IAP proteins in cell-death mechanisms. Biochem J. 2010;430(2):199–205.
67. Alvites R, Branquinho M, Sousa AC, Lopes B, Sousa P, Maurício AC. Mesenchymal stem/stromal cells and their paracrine activity—immunomodulation mechanisms and how to influence the therapeutic potential. Pharmaceutics. 2022;14(2):381.
68. Faccioli LA, Dias ML, Paranhos BA, dos Santos Goldenberg RC. Liver cirrhosis: an overview of experimental models in rodents. Life Sci. 2022;301:120615.
69. Wu S, Wang X, Xing W, Li F, Liang M, Li K, et al. An update on animal models of liver fibrosis. Front Med. 2023;10:1160053.
70. Khalil MR, El-Demerdash RS, Elminshawy HH, Mehanna ET, Mesbah NM, Abo-Elmatty DM. Therapeutic effect of bone marrow mesenchymal stem cells in a rat model of carbon tetrachloride induced liver fibrosis. Biomedical J. 2021;44(5):598–610.
71. Kao Y-H, Lin Y-C, Lee P-H, Lin C-W, Chen P-H, Tai T-S, et al. Infusion of human mesenchymal stem cells improves regenerative niche in thioacetamide-injured mouse liver. Tissue Eng Regenerative Med. 2020;17:671–82.
72. Jun JH, Kim JY, Choi JH, Lim J-Y, Kim K, Kim GJ. Exosomes from Placenta-Derived mesenchymal stem cells are involved in liver regeneration in hepatic failure induced by bile duct ligation. Stem Cells Int. 2020;2020(1):5485738.
73. Schacher FC, Martins Pezzi da Silva A, Silla LMR, Alvares-da-Silva MR. Bone marrow mesenchymal stem cells in Acute-on-Chronic liver failure grades 2 and 3: A phase I-II randomized clinical trial. Can J Gastroenterol Hepatol. 2021;2021(1):3662776.
74. Wang L, Han Q, Chen H, Wang K, Shan G-l, Kong F, et al. Allogeneic bone marrow mesenchymal stem cell transplantation in patients with UDCA-resistant primary biliary cirrhosis. Stem Cells Dev. 2014;23(20):2482–9.
75. Sang W, Lv B, Li K, Lu Y. Therapeutic efficacy and safety of umbilical cord mesenchymal stem cell transplantation for liver cirrhosis in Chinese population: a meta-analysis. Clin Res Hepatol Gastroenterol. 2018;42(3):193–204.
76. Chen B, Pang L, Cao H, Wu D, Wang Y, Tao Y, et al. Autologous stem cell transplantation for patients with viral hepatitis-induced liver cirrhosis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31(10):1283–91.
77. Ma X-R, Tang Y-L, Xuan M, Chang Z, Wang X-Y, Liang X-H. Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials. Gastroenterol Res Pract. 2015;2015(1):908275.
78. Eder C, Schmidt-Bleek K, Geissler S, Sass FA, Maleitzke T, Pumberger M, et al. Mesenchymal stromal cell and bone marrow concentrate therapies for musculoskeletal indications: a concise review of current literature. Mol Biol Rep. 2020;47:4789–814.
79. Hoang DM, Pham PT, Bach TQ, Ngo AT, Nguyen QT, Phan TT, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Therapy. 2022;7(1):272.
80. Hu C, Wu Z, Li L. Pre-treatments enhance the therapeutic effects of mesenchymal stem cells in liver diseases. J Cell Mol Med. 2020;24(1):40–9.
81. Česnik AB, Švajger U. The issue of heterogeneity of MSC-based advanced therapy medicinal products–a review. Front Cell Dev Biology. 2024;12:1400347.
82. Shah K, Shah N, Ghassemi F, Ly C, George T, Lutz C, et al. Alloreactivity of allogeneic mesenchymal stem/stromal cells and other cellular therapies: a concise review. Stem Cells Int. 2022;2022(1):9589600.
83. Zhang Y, Li R, Rong W, Han M, Cui C, Feng Z, et al. Therapeutic effect of hepatocyte growth factor-overexpressing bone marrow-derived mesenchymal stem cells on CCl4-induced hepatocirrhosis. Cell Death Dis. 2018;9(12):1186.
84. Putra A, Antari AD, Kustiyah AR, Intan YSN, Sadyah NAC, Wirawan N, et al. Mesenchymal stem cells accelerate liver regeneration in acute liver failure animal model. Biomedical Res Therapy. 2018;5(11):2802–10.
85. Fang B, Shi M, Liao L, Yang S, Liu Y, Zhao RC. Systemic infusion of FLK1 + mesenchymal stem cells ameliorate carbon tetrachloride-induced liver fibrosis in mice. Transplantation. 2004;78(1):83–8.
86. Zhang G-Z, Sun H-C, Zheng L-B, Guo J-B, Zhang X-L. In vivo hepatic differentiation potential of human umbilical cord-derived mesenchymal stem cells: therapeutic effect on liver fibrosis/cirrhosis. World J Gastroenterol. 2017;23(46):8152.
87. Jang YO, Kim MY, Cho MY, Baik SK, Cho YZ, Kwon SO. Effect of bone marrow-derived mesenchymal stem cells on hepatic fibrosis in a thioacetamide-induced cirrhotic rat model. BMC Gastroenterol. 2014;14:1–12.

88. Matsuda T, Takami T, Sasaki R, Nishimura T, Aibe Y, Paredes BD, et al. A canine liver fibrosis model to develop a therapy for liver cirrhosis using cultured bone marrow–derived cells. Hepatol Commun. 2017;1(7):691–703.
89. Nishimura T, Takami T, Sasaki R, Aibe Y, Matsuda T, Fujisawa K, et al. Liver regeneration therapy through the hepatic artery-infusion of cultured bone marrow cells in a canine liver fibrosis model. PLoS ONE. 2019;14(1):e0210588.
90. Santos L, Viana A, Bernasconi N, Basso P, Krause A. Improvement of clinical and laboratory parameters in a canine with idiopathic chronic hepatitis after transplantation of allogeneic mesenchymal cells derived from bone marrow-case report. Arquivo Brasileiro De Med Veterinária E Zootecnia. 2024;76(4):e13115.
91. Skuratov AG, Osipov BB, Lyzikov AN, Zinovkin DA, Adam IM, Kaplan ML et al. Use of mesenchymal stem cell transplantation as a treatment for liver cirrhosis in animal models. Cureus. 2024;16(10).
92. Yang Y, Chen Y, Zhao Y, Ji F, Zhang L, Tang S, et al. Human menstrual blood-derived stem cell transplantation suppresses liver injury in DDC-induced chronic cholestasis. Stem Cell Res Ther. 2022;13(1):57.
93. Lihua Y, Yun W, Xiaohua W, Yanqing L. Effect of allogeneic umbilical cord mesenchymal stem cell transplantation in a rat model of hepatic cirrhosis. J Tradit Chin Med. 2015;35(1):63–8.

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