Annals of Hepatology 30 (2025) 101911

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Letters to the editor

Advancing stem cell therapy in liver failure: Critical insights from meta-analysis

Dear Editor,

We read with great interest the recent meta-analysis by Lin et al. [1], which provides a comprehensive evaluation of stem cell therapy (SCT) for liver failure. This study reinforces the growing body of evidence supporting mesenchymal stem cell (MSC) therapy as a promising adjunct to standard medical treatment (SMT) and plasma exchange (PE). The authors' findings, particularly the enhanced survival outcomes associated with allogeneic MSCs and deep vessel injections, contribute valuable insights to the ongoing development of regenerative medicine strategies in hepatology.

Despite the study's strengths, certain methodological and clinical considerations warrant further discussion. The meta-analysis is based on eight clinical trials, yet there is significant heterogeneity in treatment protocols, including differences in cell sources (autologous vs. allogeneic), delivery routes (deep vs. peripheral vessel), and infusion schedules (single vs. multiple injections). While subgroup analyses were performed, the small sample sizes within each category limit the generalizability of the findings. Additionally, the inclusion of both chronic liver failure (CLF) and acute-on-chronic liver failure (ACLF) cohorts presents a challenge, as these conditions have distinct pathophysiologies that may differentially respond to SCT. Future studies should stratify patient populations more precisely to determine whether SCT exerts uniform benefits across different liver failure phenotypes.

Another key consideration is the mechanism of action underlying SCT efficacy. The authors highlight the immunomodulatory and anti-fibrotic properties of MSCs, but the precise contributions of paracrine signaling, extracellular vesicle (EV) release, and direct hepatocyte differentiation remain incompletely understood. In particular, MSC-derived EVs have emerged as potential mediators of liver regeneration by transferring microRNAs, cytokines, and growth factors to hepatocytes and immune cells [2]. A deeper investigation into these mechanisms may pave the way for cell-free SCT approaches that mitigate concerns related to cell engraftment, immune rejection, and tumorigenicity.

Additionally, while SCT was associated with a modest reduction in MELD scores, its impact on key biochemical markers (ALT, ALB, INR, TBIL) was inconsistent. Given that liver function improvement is a critical determinant of long-term prognosis, future trials should focus on longitudinal biomarker assessment and liver histopathology correlations to better define the true regenerative potential of SCT. Furthermore, the optimal cell dose for liver failure remains unresolved. Some studies suggest a dose-dependent effect, yet the included trials varied widely in their stem cell dosages, ranging from 0.5×10^6 to 1×10^8 cells/kg. Standardized dosing regimens and controlled trials comparing different dose thresholds are essential to optimizing SCT efficacy.

Lastly, the predominance of studies conducted in China and Egypt raises concerns about geographic and ethnic variability in SCT outcomes. Given that genetic factors, dietary habits, and healthcare infrastructure can influence liver disease progression and treatment response, expanding clinical trials to multi-center, international cohorts will be crucial in validating these findings for broader clinical application.

Despite these limitations, Lin et al. provide a valuable synthesis of current evidence supporting SCT as an emerging therapy for liver failure. Addressing standardization of treatment protocols, long-term safety, and mechanistic underpinnings will be critical in translating these findings into routine clinical practice.

Funding

There is no funding for this work.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used AI for language editing and translation of the article.

Author contributions

JW: conceptualization, writing, original draft, formal analysis. YL: review & editing, supervision. All authors contributed and approved the submission.

Declaration of interest

None.

References

[1] Lin S, Gao H, Ma H, Liao Z, Zhang D, Pan J, et al. A comprehensive meta-analysis of stem cell therapy for liver failure: assessing treatment efficacy and modality. Ann Hepatol 2025;30:101586. https://doi.org/10.1016/j.aohep.2024.101586.

[2] Wu R, Fan X, Wang Y, Shen M, Zheng Y, Zhao S, et al. Mesenchymal stem cell-derived extracellular vesicles in liver immunity and therapy. Front Immunol 2022;13:833878. https://doi.org/10.3389/fimmu.2022.833878.

Jinyu Wu
Department of Gastroenterology, West China (Airport) Hospital of Sichuan University (The First People's Hospital of Shuangliu District), Chengdu, Sichuan, China

Yun Liao*
The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

*Corresponding author.
E-mail address: yun-liao@163.com (Y. Liao).

https://doi.org/10.1016/j.aohep.2025.101911