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Letters to the editor

Future directions of stem cell therapy for liver failure: Insights from a meta-analysis

Dear Editor,

We appreciate Professor Liao and his colleague's thoughtful and constructive comments on our recent meta-analysis of stem cell therapy (SCT) for liver failure [1]. We are grateful for the opportunity to engage in further discussion regarding our findings and the points raised by the readers.

We acknowledge the concerns about the heterogeneity in treatment protocols across the studies included in our meta-analysis. As Professor Liao and his colleague rightly pointed out, variations in cell sources (autologous vs. allogeneic), delivery routes (deep vs. peripheral vessels), and infusion schedules (single vs. multiple injections) limit the generalizability of our conclusions. Although subgroup analyses were conducted, we agree that larger sample sizes in each category would help clarify the impact of these variations. This limitation was mentioned in our original paper. We recommend that future trials standardize protocols or conduct more targeted subgroup analyses to draw definitive conclusions.

Regarding the inclusion of both chronic liver failure (CLF) and acute-on-chronic liver failure (ACLF) cohorts, we recognize the challenge of combining these distinct patient populations. The differing pathophysiologies of CLF and ACLF may influence the response to SCT. However, this is an inherent limitation of meta-analysis, as patient selection cannot be strictly controlled. We fully agree that more granular stratification in future studies is essential. More precise patient categorization would allow for a better understanding of whether SCT's benefits vary across different liver failure subtypes.

On the mechanism of SCT in liver failure, we agree that further research into the role of MSC-derived extracellular vesicles (Evs) is crucial. MSC-EVs represent a safer, cell-free SCT strategies with greater efficacy and improved immunotolerance compared to SCT alone. Despite the many potential advantages of natural MSC-EVs, several limitations, such as heterogeneity, low yield, and rapid in vivo elimination, constrain their clinical translation, potentially affecting their therapeutic efficacy. Therefore, researchers are designing engineering strategies to improve MSC-EV therapeutic efficacy and yield in vivo [2,3]. However, as a clinical literature-based analysis, our study primarily focused on the practical clinical applications of SCT.

We acknowledge the letter's concern regarding the inconsistent impact of SCT on biochemical markers such as Alanine aminotransferase, Albumin, International Normalized Ratio, and Total Bilirubin. As previously noted, the limitations of meta-analysis result in heterogeneity across the cohorts, which may lead to inconsistent effects of SCT on biochemical indices. However, we observed that SCT consistently improves the Model for End-Stage Liver Disease (MELD) score across studies. The MELD score has demonstrated consistent reliability in assessing liver disease severity in diverse clinical settings, supported by long-term validation studies [4]. Furthermore, a reduction in the MELD score is associated with better patient outcomes, which supports the primary findings of our study. We agree that these biomarkers are crucial for assessing liver function and prognosis, and future studies should adopt a more rigorous, longitudinal approach to biomarker assessment and histopathology correlation to further understand the regenerative potential of SCT.

Finally, the geographic and ethnic variability mentioned in the letter is an important consideration. As our study primarily included data from China and Egypt, we acknowledge that cultural, genetic, and healthcare infrastructure factors may influence SCT outcomes. Expanding future studies to include multi-center, international cohorts will be crucial for verifying the broader applicability of our findings.

We sincerely appreciate Professor Liao and his colleague's feedback and agree that addressing these issues will be vital for advancing the clinical application of SCT in liver failure. We hope that, despite its limitations, our work contributes to the growing body of evidence on SCT's potential and encourages further research to optimize and standardize treatment protocols.

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Authors' contributions

SL and HG designed the study, contributed to the conceptual framework, and drafted the manuscript. YZ reviewed and approved the final manuscript. All authors contributed and approved the submission.

Declaration of interest

None.

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