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REVIEW

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Efficacy and safety of mesenchymal stem cell therapy in acute on chronic liver failure: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background Acute-on-chronic liver failure has become a serious global health burden, which is characterized by an acute deterioration of liver function, rapidly evolving organ failure, and high short-term mortality in patients with chronic liver disease. The pathogenesis includes extensive hepatic necrosis, which is related to intense systemic inflammation and subsequently causes the inflammatory cytokine storm, resulting in portal hypertension, organ dysfunction, and organ failure. Mesenchymal stem cells can function as seed cells to remodel and repair damaged liver tissues, thus showing potential therapeutic alternatives for patients with chronic liver disease. However, standard treatment protocols for mesenchymal stem cells in acute-on-chronic liver failure patients have not been established.

Methods We conducted a detailed search from PubMed/Medline, Web of Science, EMBASE, and Cochrane Library to find randomized controlled trials published before October 23, 2021. We formulated criteria for the literature screening according to the PICOS principle (Population, Intervention, Comparison, Outcome, Study design). Subsequently, the bias risk assessment tool was used to assess the quality of all enrolled studies. Finally, outcome measurements including the model of end-stage liver disease score, albumin, total bilirubin, coagulation function, and aminotransferase were extracted for statistical analysis.

Results A total of 7 clinical trials were included. The results of enrolled studies indicated that patients with acute-on-chronic liver failure who received mesenchymal stem cells inoculation showed a decreased MELD score in 4 weeks and 24 weeks, compared with counterparts who received conventional treatment. Reciprocally, mesenchymal stem cells inoculation improved the ALB levels in 4 weeks and 24 weeks. For secondary indicators, mesenchymal stem cells treatment significantly reduced INR levels and ALT levels, compared with the control group. Our results showed no significant differences in the incidence of adverse reactions or serious adverse events monitored in patients after mesenchymal stem cells inoculation.

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Conclusion This meta-analysis indicated that mesenchymal stem cell infusion is effective and safe in the treatment of patients with acute-on-chronic liver failure. Without increasing the incidence of adverse events or serious adverse events, MSC treatment improved liver function including a decrease in MELD score and an increase in ALB levels in patients with acute-on-chronic liver failure. However, large-cohort randomized controlled trials with longer follow-up periods are required to further confirm our conclusions.

Keywords Mesenchymal stem cells, Acute-on-chronic liver failure, Efficacy, Safety, Meta-analysis

Introduction

Acute-on-chronic liver failure (ACLF) has been recognized as a distinct severe clinical syndrome based on rapid clinical deterioration in chronic liver disease patients which is characterized by organ failure, high short-term morbidity, mortality (> 15% at 28-d), severe systemic inflammation, immune dysfunction, and healthcare resource utilization [1–6]. Currently, the definitions of ACLF in different international institutes are heterogeneous worldwide, mainly due to differences in patient situation and lack of consistency in medical history, diagnostic criteria, and acute triggering factors [7–9]. Regardless of this heterogeneity, ACLF is commonly defined as acute complications of compensated or even decompensated cirrhosis, which portend a poor prognosis and a great burden to patients [2, 10]. The development of ACLF is mainly caused by precipitating factors, including bacterial infection, severe alcoholic hepatitis, gastrointestinal bleeding, or toxic encephalopathy [7, 11–13]. Clinically, the treatment of ACLF generally is primarily supportive and focuses on reversing organ failure [14]. Liver transplantation is a potentially life-saving strategy for patients with ACLF [7, 15, 16], which is also limited by the supply of organ donors, expensive expenditure, optimal patient selection, and identification of relative contraindications [17–19]. Therefore, it is an urgent need to develop effective nontransplant medical therapies such as cell-based therapies.

Human mesenchymal stem/stromal cells (MSC) are adult stem cells that derive from the mesoderm and can be obtained from a wide range of tissues and organs including but not limited to, adipose tissue (AT), umbilical cord blood (UCB), bone marrow (BM), muscles, salivary glands, umbilical cords (UC), dental pulp, menstrual fluid and amniotic fluid [20–24]. The multipotency property of MSCs has attained global consideration because of their high self-renewal capacity and therapeutic function in tissue regeneration [21, 25–28]. Currently, preclinical studies and clinical trials have demonstrated the efficacy and feasibility of MSC-based therapy in a variety of diseases, such as autoimmune disease [29–31], vascular disease [22], myocardial infarction [32, 33], diabetes [34, 35], hepatic failure [36] and acute graft versus host disease [37, 38]. For example, an animal model study has shown that MSC ameliorated hepatic dysfunction and improved liver regeneration after hepatectomy acute liver failure by paracrine mechanisms [39]. Similarly, clinical trials have demonstrated that MSC transplantation can improve liver function and decrease the incidence of severe infections [40–45]. In conclusion, infusion of MSC is a promising treatment strategy for liver failure patients. Although some meta-analyses of MSC therapy for chronic liver disease had been performed previously, research protocols and evaluation indicators are inconsistent across studies [46–49]. Moreover, few studies have investigated the influence of different factors (treatment window period, cell transfusion, approach, and dosage of MSC infusion) on the therapeutic effects based on randomized controlled trials (RCTs). This meta-analysis included the largest number of clinical trials of MSC therapy for ACLF. As evidence accumulates, we screened and extracted data about MSC for the treatment of ACLF in controlled trials and aim to rigorously discuss the clinical value and safety of MSC transplantation ACLF in this review.

Methods

This meta-analysis was carried out following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and Cochrane, and registered on PROSPERO.

Search strategies

Studies were searched the from their inception dates to October 2024 following four databases: the PubMed, Web of Science, Medline, Embase, and the Cochrane Library databases. A comprehensive search of the literature used “mesenchymal stem cells” and “acute on chronic liver failure” as keywords. The details of search method are presented in the Additional file 2.

Study selection process and data extraction

Two authors (Wenming Lu and Longxiang Yan) determined independently study inclusion based on the screening criteria. Then, the articles were screened by reading titles and abstracts. Articles passed the title and abstract screening were finally included in this study. Any disagreements were settled by discussion or by consulting a third reviewer.

After identifying the enrolled studies, two authors (Wenming Lu and Xingkun Tang) performed the collection of relevant data. The following data were extracted

from the studies: first author, year of publication, experimental location, type of study design, type, source, and dosage of MSCs, number of sample sizes for control and experimental groups, and outcome measures.

Inclusion criteria

The Population, Intervention, Comparison, Outcomes, and Study (PICOS) design model was used to establish the article inclusion criteria:

Population (P) Patients diagnosed with ALCF, regardless of country, region, age, sex, and race.

Intervention (I) The treatment of the disease was MSC.

Comparison (C) MSC intervention groups and the control group.

Outcomes (O) adverse events (AE); model for end-stage liver disease score (MELD); albumin (ALB); alanine aminotransferase (ALT); international normalized ratio (INR); total bilirubin (TBIL) aspartate aminotransferase (AST).

Study design (S) Randomized controlled trials (RCTs) or non-RCTs.

Exclusion criteria

The following types of articles were excluded:

(a) The study did not meet the inclusion criteria; (b) records of meetings, letters, conference abstracts, single-arm experiment, animal experiments, meta-analyses, reviews, and case reports; (c) non-English documents; (d) inability to access full-text information and extract data for research. (e) studies not relevant to this topic were excluded.

Quality assessment

The quality of the included studies was evaluated based on the recommendations of the Cochrane Collaboration using Review Manager (version 5.4). Each study was assessed through seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants, (4) inadequate outcome data, (5) blinding of outcome assessment, (6) selective reporting, (7) other possible bias. Each assessment item was classified as "low risk," "high risk," or "unclear risk". Two authors independently assessed the quality of the literature. In cases of doubt, a third investigator was consulted to reach a consensus decision.

Data extraction

This meta-analysis was performed via Review Manager version 5.0 software. The means and standard deviations (SD) were used for continuous outcomes. The standardized mean difference (SMD) with the 95% confidence interval (CI) for each parameter was calculated to compare the effect the both groups. We also calculated the mean and SD based on the conversion tools for subsequent analyses. For dichotomous data, odds ratios (OR) with 95% CI was used as the effect size through Mantel–Haenszel (M-H) analysis. The I^2 statistic was used to quantify statistical heterogeneity across studies. When $p > 0.1$, $I^2 < 50\%$, indicating lesser heterogeneity among the studies, a fixed-effects model was applied. When $p < 0.1$, $I^2 > 50\%$, the random-effect model was utilized for data analysis. Sensitivity analysis was performed by excluding one study to evaluate the influence of individual studies on the final results. Subgroup analyses were performed to assess potential sources of heterogeneity. $p < 0.05$ was considered significant for all outcomes.

Result

Literature search

In total, 1568 potentially eligible records were obtained from PubMed, Cochrane Library, Web of Science, and Embase databases. After eliminating duplicates, 898 records remained, and the titles and abstracts of these publications were carefully screened. Next, 753 articles were excluded for the following reasons (with no relevant topics, animal experimental models, no English publications, and reviews). Then, 145 full-text articles were assessed for eligibility criteria. Consequently, 7 clinical trials were included in the systematic review and meta-analysis. The detailed process of the literature search is illustrated in Fig. 1.

Study characteristics

A total of 7 studies were included in our systematic review. Five studies recruited patients from China. Only one study came from Brazil. All studies were designed as randomized controlled trials. Of these, four studies used umbilical cord MSCs (UC-MSCs) as infused cells, while the remaining studies were bone marrow MSCs (BM-MSCs). All the studies' sample sizes ranged from 9 to 158 and were published from 2012 to 2021. The main infusion methods were intravenous infusion and hepatic artery injection, in which the total dose ranged from 1×10^6_1×10^8 cells/kg. The etiology of ALCF is mainly HBV. The detailed characteristics of each study are shown in Table 1.

Result of quality assessment

The methodological quality and risk of bias were assessed according to the Cochrane risk of bias tool (Revman5.4). A detailed evaluation of each study was presented in (Figs. 2 and 3). Overall, the risk of bias for the included trials was relatively low.

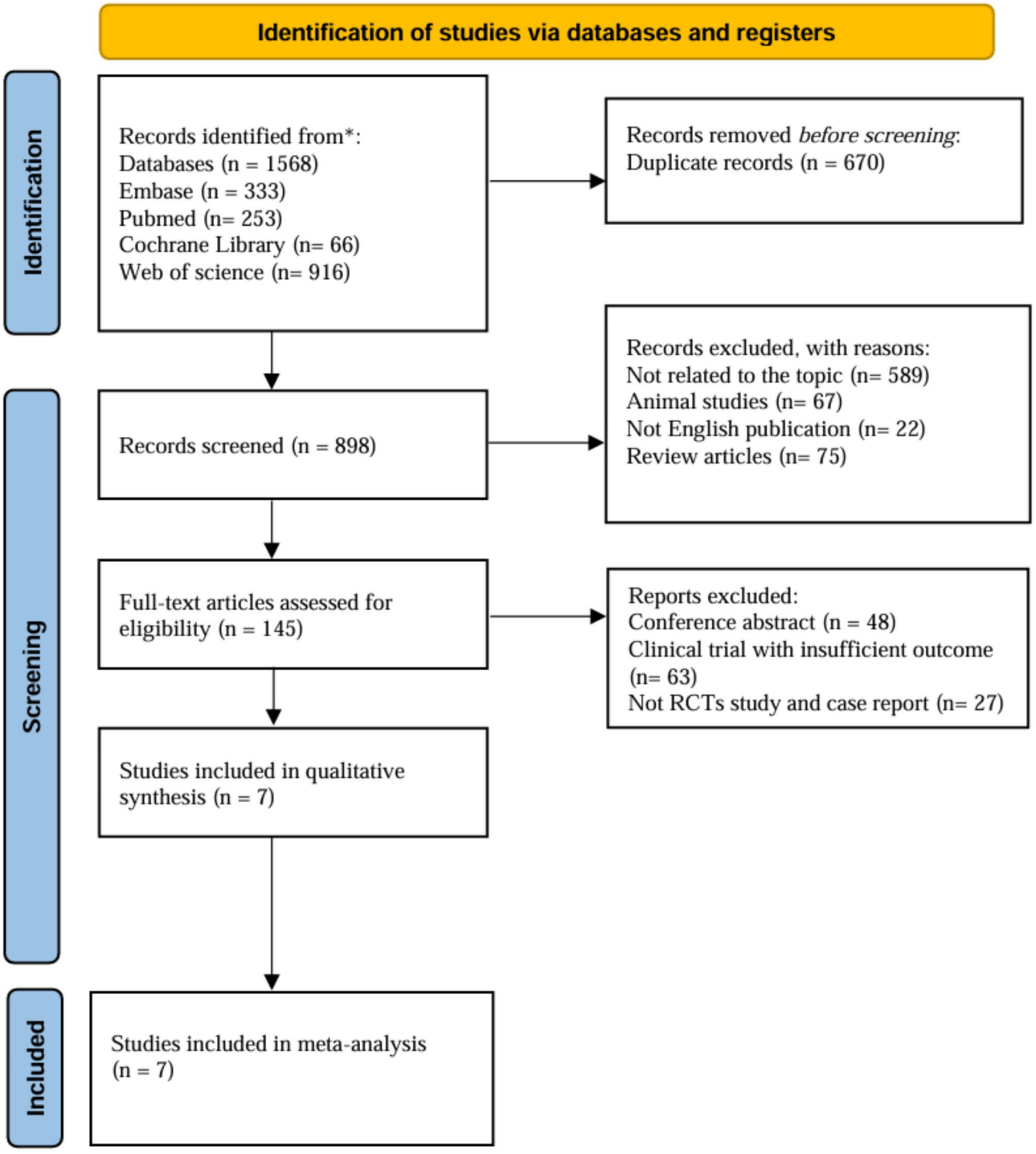

Fig. 1 Flowchart of study selection

Meta-analysis

Seven eligible articles were enrolled for meta-analysis using a random-effects model, with ALB and MELD scores as primary and ALT, TBIL, AST and INR as secondary indicators to measure the effectiveness of MSC for ALCF, and AE as a safety indicator.

Primary indicators

MELD score The MELD score was analyzed in four of the included trials involving 363 patients. Low heterogeneity was detected ($I^2 = 21\%$; Q test $p = 0.28$), and a fixed-effect model was adopted for analysis. The MELD score in patients with ACLF significantly reduced after MSC ther-

Table 1 Summary of clinical studies of mesenchymal stem cells therapy for acute-on-chronic liver failure

Included studies	Country	Design	Age(year)	Patients	Cell type	Total dose/kg body weight (average 50kg/person)	Administration route	Follow up	Main outcome measures	Cause of ACLF
Shi et al (2012)	China	RCT	EG: 24 ± 8.75 CG: 45 ± 9	EG: 24 CG: 19	UC-MSCs	0.5×10^7cells/kg	vein of the arm	1,2,4,8,12,24,36, 48weeks	ALT,TBIL,ALB,CHE,PTA,MELD score	HBV
Xu et al (2019)	China	RCT	EG: 40.67 ± 9.89 CG: 44.97 ± 11.83	EG: 30 CG: 30	UC-MSCs	1×10^6cells/kg	intravenous	30,60,90,180weeks	ALT,TBIL,ALB,MELD score	HBV
Li et al (2016)	China	RCT	EG: 40.67 ± 9.89 CG: 44.97 ± 11.83	EG: 11 CG: 34	UC-MSCs	1×10^8cells/kg	intravenous	4–24 months	HCC incidence, ALT,TBIL,ALB,MELD score	HBV
Lin et al (2013)	China	RCT	EG: 40.04 ± 9.94 CG: 42.78 ± 8.4	EG: 56 CG: 54	UC-MSCs	$1.0–10\times10^8$cells/kg	intravenous	1, 2, 3, 4, 8, 12 and 24 weeks	ALT,TBIL,ALB,MELD score	HBV
Peng et al (2011)	China	RCT	EG: 42.19 ± 9.94 CG: 42.78 ± 8.4	EG: 53 CG: 105	BM-MSCs	UK	hepatic artery	1,2,3,4,12, 24,36,48 weeks	ALT,ALB,TBIL,PT,MELD score	HBV
Schacher et al (2021)	Brazil	RCT	EG: 55.8 ± 12.8 CG: 53.4 ± 14.4	EG: 4 CG: 5	BM-MSCs	1×10^6cells/kg	intravenous	UK	ALT,TBIL,ALB,PT,CRP	HBV
Jia et al (2020)	China	non-RCT	16–60	513	UC-MSCs	1×106cells/kg	intravenous	1, 4, 12, 24	ALT,TBIL,AST	HBV

EG: experimental Croup; CG: control Croup; ACLF: Acute-on-chronic liver failure; RCT: randomized controlled trial; UK: unknown; BM-MSCs: bone marrow mesenchymal stem cells; UC-MSCs: umbilical cord mesenchymal stem cells; MELD: model for end-stage liver disease; ALT: alanine aminotransferase; ALB: albumin; AST: aspartate aminotransferase; TBIL: total bilirubin; INR: international normalized ratio; PT: prothrombin time; HBV: hepatitis B virus

apy (WMD = − 1.78; 95% CI = [− 2.89, − 0.68]; $p = 0.002$) (Fig. 4).

ALB levels Among 7 studies included, the ALB levels were evaluated in 4 studies of 119 patients in the intervention group and 177 patients in the control group. The result of the Cochrane Q-test demonstrated great homogeneity among studies ($I^2 = 78\%$; Q test $p = 0.001$), and the random effects model was adopted as the effect indicator. The forest map results showed a significant improvement in ALB levels between groups (SMD: 0.72; 95% CI [0.10, 1.34]; $p = 0.02$) (Fig. 5).

Subgroup of model for end-stage liver disease

Time subgroup of model for end-stage liver disease We performed a time subgroup analysis for the MELD score to investigate the impact of MSC infusion on the MELD score at various points after infusion. Pooled analysis showed that the MSC group significantly decreased the MELD score (WMD = − 1.78; 95% CI = [− 2.89, − 0.68]; $p = 0.002$; heterogeneity test $p = 0.001$; $I^2 = 78\%$), compared with the control group. Subgroup analysis with fix-effects model showed that the MSC infusion significantly decreased MELD score in 4 weeks (WMD: −2.57; 95%CI= [− 3.55, − 1.59]; $p < 0.00001$), 24 weeks (WMD: −4.12; 95%CI= [− 6.21, − 2.02]; $p = 0.0001$; heterogeneity test $p = 0.64$; $I^2 = 0\%$). However, statistically significant differences were observed between the intervention and control group in 2 weeks (WMD: −1.03; 95%CI= [− 2.07, 0.01]; $p = 0.05$; heterogeneity test $p = 0.72$; $I^2 = 0\%$) (Fig. 6).

Subgroup of albumin levels

Time subgroup of albumin levels We performed a time subgroup analysis for ALB levels to investigate the impact of MSC infusion on ALB levels at various points after infusion. Pooled analysis showed that the MSC group had significantly improved ALB levels (SMD: 0.72; 95% CI [0.10, 1.34]; $p = 0.02$; heterogeneity test $p = 0.001$; $I^2 = 78\%$), compared with the control group. Further subgroup analysis with a random-effects model showed that the MSC group significantly increased ALB levels in 4 weeks (SMD = 0.67; 95%CI = [0.44, 0.91]; $p < 0.00001$), 24 weeks (SMD: 1.54; 95%CI= [0.87, 2.22]; $p < 0.00001$). Whereas, comparisons between both groups showed no statistical differences in 2 weeks (SMD = 0.24; 95%CI = [− 0.73, 1.21]; $p = 0.62$), 12 weeks (SMD = 0.41; 95%CI = [− 1.46, 2.29]; $p = 0.67$; heterogeneity test $p < 0.00001$; $I^2 = 95\%$) and 48 weeks

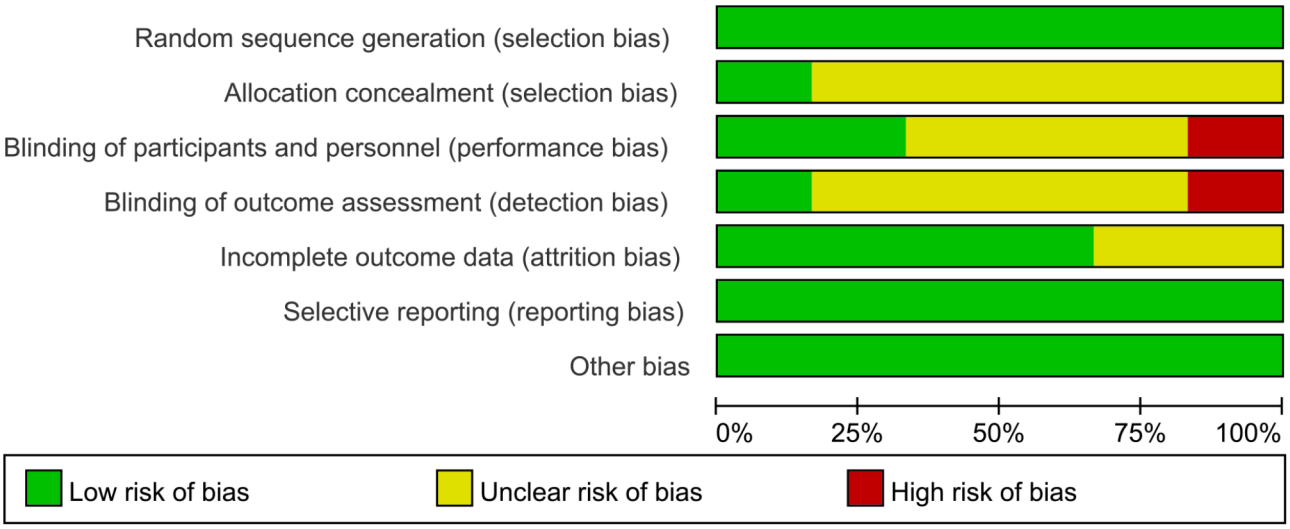

Fig. 2 Risk of bias graph

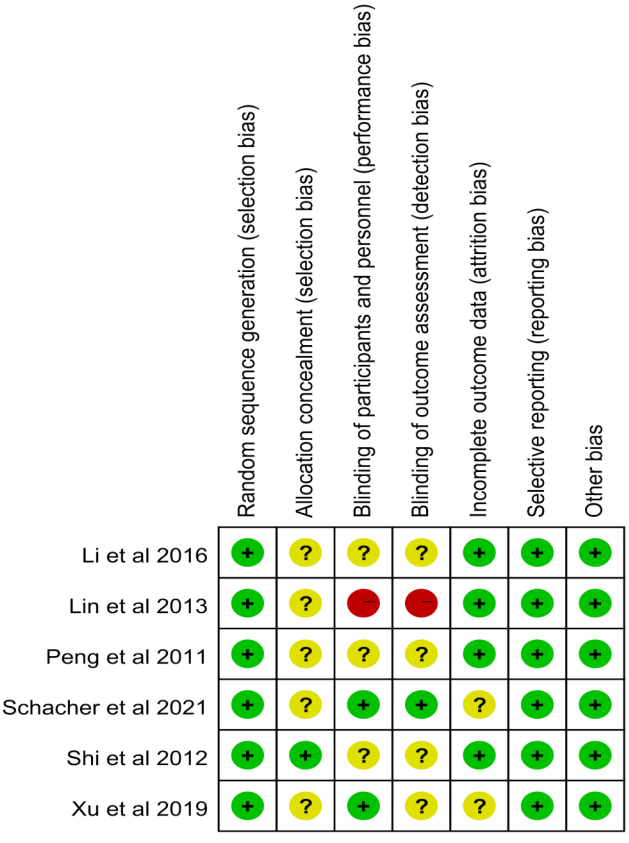

Fig. 3 Risk of bias summary

(SMD = 1.05; 95%CI = [− 0.90, 3.00]; $p = 0.29$; heterogeneity test $p = 0.001$; $I^2 = 90\%$) (Fig. 7).

Secondary indicators

TBIL levels Four studies of all reviewed articles evaluated the therapeutic effects of MSCs on TBIL levels. Similarly, a random-effects model indicated no statistically significant differences were observed (SMD = − 0.01; 95%CI = [− 0.44, 0.42]; $p = 0.97$; heterogeneity test $p = 0.007$; $I^2 = 72\%$) (Additional file 1: Fig. S1A). We carried out a time subgroup analysis to make the conclusions more accurate. A pooled analysis showed that no significant difference was found between the two groups (SMD = − 0.05; 95%CI = [− 0.38, 0.28]; $p = 0.78$; heterogeneity test $p = 0.0009$; $I^2 = 70\%$). Further subgroup analysis showed that patients with ACLF had no a significantly improved TBIL levels by MSC therapy in 4 weeks (SMD = − 0.09; 95%CI = [− 0.57, 0.39]; $p = 0.72$), 12 weeks (SMD = − 0.28; 95%CI = [− 1.05, 0.50]; $p = 0.48$), and 24 weeks (SMD = 0.19; 95%CI = [− 0.63, 1.00]; $p = 0.65$; heterogeneity test $p = 0.10$; $I^2 = 63\%$) (Additional file 1: Fig. S2).

INR levels The INR levels were analyzed in two included trials involving 105 patients. The INR level of the MSC-treated group was significantly lower than control groups (SMD = − 0.01; 95%CI = [− 0.44, 0.42]; $p = 0.97$; heterogeneity test $p = 0.007$; $I^2 = 72\%$) (Additional file 1: Fig. S1B).

AST levels The AST levels were assessed based on 2 RCTs of 105 pregnant women. A fix-effects model demonstrated that compared with the control group, MSC significantly decreased the AST levels (WMD = − 13.71; 95%CI = [− 22.80, − 4.63]; $p = 0.003$; heterogeneity test $p = 0.21$; $I^2 = 36\%$) (Additional file 1: Fig. S1C).

ALT levels Four studies reported the effect of MSC intervention versus the control group on the ALT levels. The pooling results showed that no statistically significant differences were found between the two groups (SMD: −0.11; 95%CI = [− 0.67, 0.46]; $p = 0.71$; heterogene-

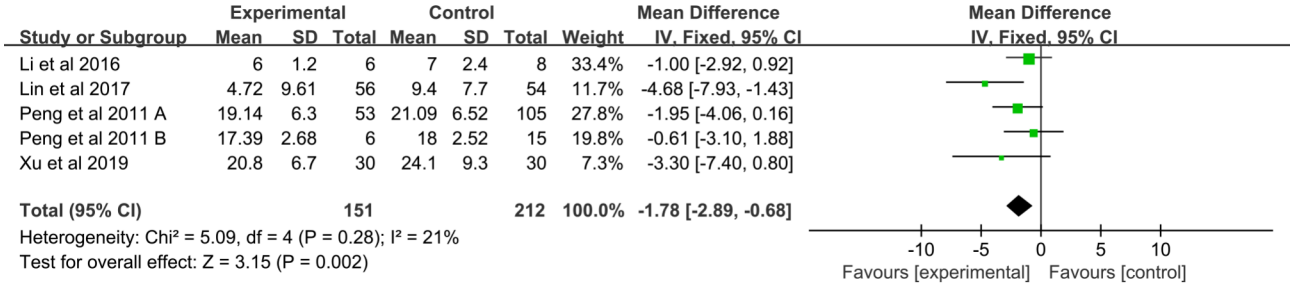

Fig. 4 Pooled results of MELD score

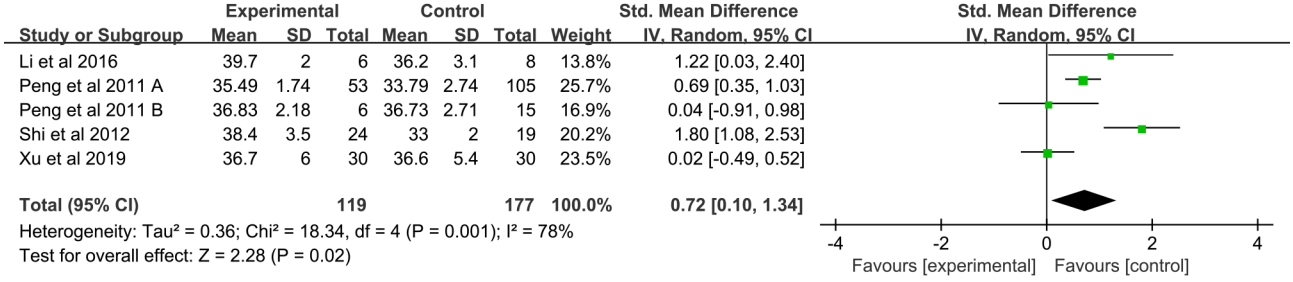

Fig. 5 Pooled results of ALB levels before sensitivity analysis

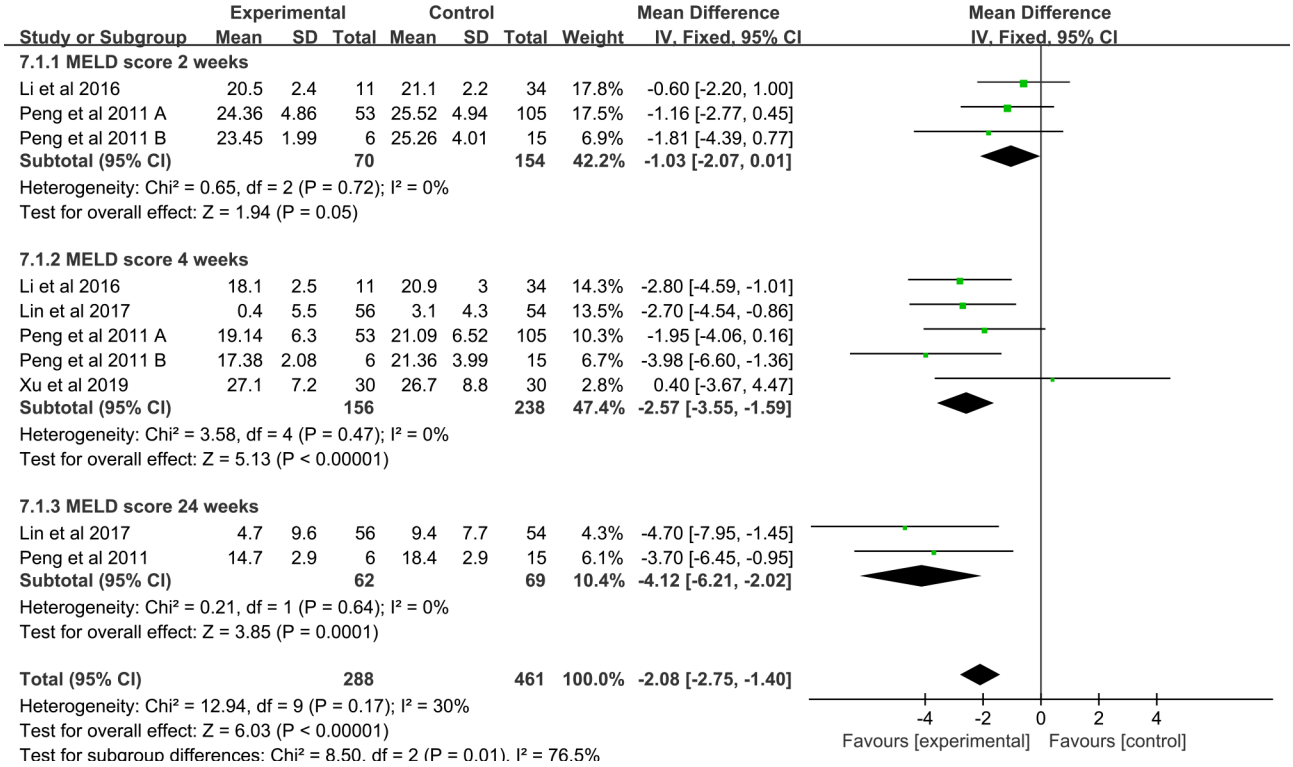

Fig. 6 Time subgroup of MELD score

ity test $p = 0.01$; $I^2 = 74\%$) (Additional file 1: Fig. S1D). We carried out a time subgroup analysis to make the conclusions more accurate. A pooled analysis showed that MSC group were significantly decreased ALT levels (WMD: −9.27; 95% CI [− 13.32, − 5.21]; $p < 0.00001$; heterogeneity test $p = 0.10$; $I^2 = 41\%$), compared with the control group (Fig. 8). Through MSC treatment, the ALT level at 2 weeks (WMD: −13.87; 95% CI [− 20.98, − 6.75]; $p = 0.0001$; heterogeneity test $p = 0.71$; $I^2 = 0\%$) and 4 weeks (WMD: −9.69; 95% CI [− 15.77, − 3.62]; $p = 0.002$) decreased sig-

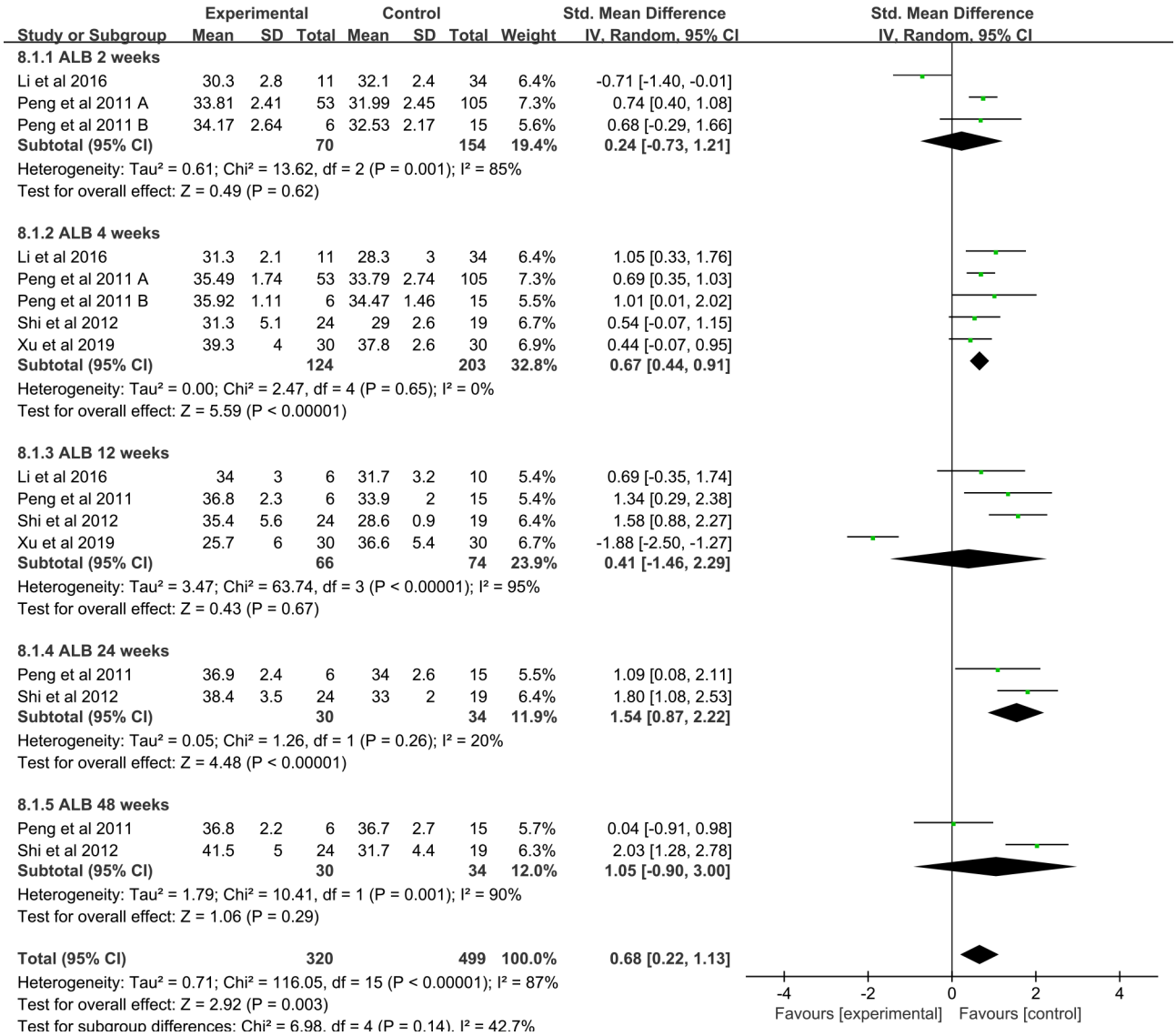

Fig. 7 Time subgroup of ALB levels

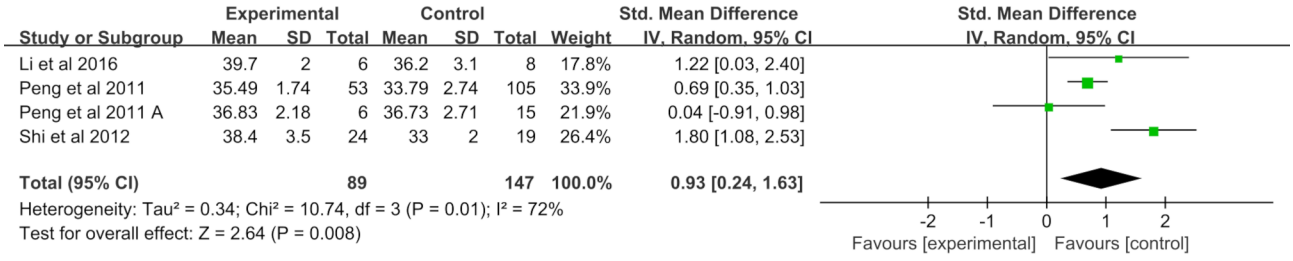

Fig. 8 Pooled results of ALB levels after eliminating heterogeneous

nificantly compared to control group. However, the ALT level after MSC treatment at 12 weeks (WMD: −1.92; 95% CI [− 10.38, − 6.55]; $p = 0.66$; heterogeneity test $p = 0.52$; $I^2 = 0\%$) did not show significant changes (Additional file 1: Fig. S3).

Sensitivity analysis

To test the stability and reliability of the meta-analysis results, we carried out the sensitivity analysis of ALB levels. Forest plots of ALB showed heterogeneity test $p = 0.001$; $I^2 = 78\%$ (Fig. 5). The study performed by XU

et al. in which the combination treatment of plasma exchange and UC-MSCs transplantation, might be the cause of heterogeneity [44]. We found that the result of ALB levels presented lower heterogeneity when the study was removed (SMD = 0.93; 95%CI = [0.24, 1.63]; $p = 0.009$; heterogeneity test $p = 0.01$; $I^2 = 72\%$) (Fig. 8).

Adverse events assessment

Safety should be one of the main concerns following MSC treatment should be safety. We evaluated the side effects that followed treatment. Schacher et al.. reported that the most important adverse events were hypernatremia and gastrointestinal bleeding due to a gastric ulcer [41]. During the plasma exchange process, some patients in both groups experienced an allergic reaction to fresh frozen plasma, resulting in low blood pressure, low respiratory distress, and red, itchy rashes [40]. Xu et al. and Shi et al. indicated that treatment-related complications were treated appropriately and cured within a short period, without impacting the patient's life quality [43, 44].

Descriptive analysis

Peng et al. reported that MSC transplantation could not improve the long-term prognosis of patients with liver failure caused by hepatitis B virus [42]. On the contrary, MSC transplantation improves short-term and long-term hepatic function and improves survival at 3 and 24 months in Hepatitis B Virus Related Acute-on-Chronic Liver Failure [40].

Jia et al. indicated that 4 weeks of UC-MSC treatment gradually improved ALT levels, AST levels, TBIL levels, MELD score. Furthermore, four weeks after UC-MSC therapy, patients who received prolonged treatment with UC-MSCs had a larger reduction in TBIL levels than patients who terminated treatment with UC-MSCs [50].

Discussion

ACLF is a life-threatening clinical syndrome that develops in chronic liver disease patients with compensated and decompensated cirrhosis [51, 52]. Liver transplantation is the ultimately definitive beneficial therapy for ACLF. However, the clinical application is limited by the rapid progression of the disease and the availability of donor organs for severe ACLF patients [7, 53, 54]. Typically, a large number of researches have demonstrated that MSC infusion is a promising treatment strategy for ACLF patients in recent years. For instance, the animal model study showed that human umbilical cord-derived mesenchymal stem cell transplantation improved liver function, and promoted hepatocyte regeneration [55]. Currently, 7 clinical trials were included to conduct a meta-analysis and systematic evaluation of the efficacy and safety of MSC in the treatment of ACLF. Our results suggest that MSC infusion significantly improved liver function in ACLF patients, including reducing MELD score and increasing ALB levels. Remarkably, there were no adverse events reported in the included studies, which indicated the safety of MSC therapy for ACLF. In addition, further analysis based on the following research might provide new perspectives to ensure the availability of MSCs for clinical applications in the future.

Our primary concern is the frequency of MSC therapy. ACLF is a complication of chronic liver diseases, which is characterized by severe acute liver function impairment with hepatic systemic inflammation and consequent multiple-organ failure and portends both a poor prognosis and a great burden to the affected individual [10, 56, 57]. Extending the duration of treatment indeed improves the aforementioned signs and symptoms and increases MSC efficacy in end-stage liver disease [50]. However, it remains unclear about the appropriate time to infuse MSCs to achieve optimal efficacy. For the MELD score, the time subgroup analysis with a random-effects model indicated that compared to the control group, MSC infusion significantly reduced the MELD score at 4 and 24 weeks. However, after two weeks, there was no statistically significant difference between the two groups. Similarly, for ALB levels, the time subgroup analysis showed that the MSC group significantly increased ALB levels in 4 and 24 weeks. This finding is the most up-to-date MSC injection detail compared to previous meta-analyses. Whereas, comparisons between both groups showed no statistical differences in 2 weeks, 12 weeks, and 48 weeks. In addition, MSC transplantation could not improve the long-term prognosis of these patients markedly. Notably, Jia et al. reported that peripheral infusion of UC-MSCs showed good therapeutic effects for HBV-related liver failure and liver cirrhosis, and prolonging the treatment course can increase the curative effect of UC-MSCs for end-stage liver disease [50]. Therefore, our results suggested that 4 or 24 weeks after the infusion is an ideal time point for re-infusion of MSCs. Interestingly, the results are consistent with the findings of Jia et al. [50]. If the frequency of infusion is taken into consideration in future clinical design and application.

According to ClinicalTrials.gov (https://clinicaltrials.gov/), AT, BM, and UC are the three major sources of MSC treatment in more than half of clinical trials [58]. Typically, MSCs can be isolated from multiple tissues, yet different origins of MSCs exert certain differences in proliferation capacity, differentiation ability, and immunomodulatory properties [59–61]. The majority application of BM-MSCs is autologous transplantation, but the cellular differentiation potential of BM-MSCs decreases with generation [62]. Furthermore, in light of their plentiful source and less invasive isolation techniques, AD-MSCs have demonstrated considerable potential in liver regeneration for treating acute or chronic liver injury [63, 64].

Presently, the UC-MSCs were used in 4 of the 7 enrolled studies. Concerning these differences, the properties and qualities of MSC that come from different sources should be carefully evaluated before being employed therapeutically. In other words, while using MSC to treat patients with ACLF, it is critical to take cell types into account. Unfortunately, subgroup analyses of the effectiveness concerning the cell types could not be carried out due to the small number of studies. However, the infusion of human UC-MSCs can alleviate liver fibrosis in both rats and humans [65–67]. Hence, more prospective clinical research is required to examine the advantages of various cell types in ACLF treatment in the future.

Excitingly, MSC-derived exosomes have therapeutic potential for treating chronic liver disease. MSC-derived exosomes prevent cell injection, infection transmission, emboli formation, potential carcinogenesis, and needless differentiation that are linked to MSC transplantation. They also serve as a mediator of intercellular communication between MSC and injured organ regions [68–70]. In recent years, several studies based on animal models showed that MSC-derived exosomes can ameliorate drug-induced acute liver failure and liver fibrosis [71–73]. Thus, we have reason to believe that the transplantation of MSC-derived exosomes may present exciting novel cell-free therapy for the intervention of various liver diseases in the future.

Currently, the effectiveness of MSC in ACLF has been a concern with various transplantation techniques. The delivery route of MSC is mainly via intravenous peripheral vein infusion, hepatic artery infusion, intrasplenic injection, intrahepatic injection, and intraperitoneal injection [74]. Systemic transplantation of cells may lead to an abundance of rapid losses of cells within the capillaries, particularly in the lungs, which creates a short lifespan for remaining MSCs [75]. Intrahepatic injection significantly reduces the number of lung-entrapped MSCs and raises the amounts of cells that are accumulated in the liver [74]. Furthermore, delivery of the MSC by the portal vein or hepatic artery indicates a homing efficacy of less than 5% and 20–30%, respectively [76, 77]. Hepatic artery and vein are preferred infusion routes in 7 enrolled clinical studies. Interestingly, Sang et al.. found that MSC transplantation in the portal vein greatly improved liver function, prevented apoptosis, and increased survival, making it superior to alternative delivery routes for treating acute liver failure (ALF) [78]. Unfortunately, subgroup analysis of infusion routes cannot be carried out to explore statistical results due to a paucity of research. More carefully planned clinical trials are needed to confirm the optimal MSC infusion approaches for treating ACLF, and the pertinent mechanisms should be clearly explained.

MSC are capable of differentiating into specific issue cells, thus replacing the damaged cells [79]. Meanwhile, the fate of MSC is regulated by a range of instructive signals from the microenvironment, which includes numerous biomolecules (both soluble and insoluble) and biomechanical factors [80]. Migration or homing of MSC within the injured tissues is influenced by several factors including culture conditions, the number of infused cells, and the delivery route [18]. Unfortunately, there is currently no uniform cellular dosage guideline for clinical MSC application in ACLF. The majority of clinical trials perform MSC administration based on patient body weight ($0.5\text{-}4 \times 10^6$/kg), while the remaining clinical trials infuse MSC based on cell quantity ($1 \times 10^7\text{-}5 \times 10^8$ cells) [81]. In addition, a study reported that MSC inoculation improved liver function for two years after infusion [82]. Animal experiments reported that multiple injections of MSC may improve the effect of transplantation [83, 84]. In this meta-analysis, subgroup analyses of cell dose could not be carried out due to several limitations. According to the aforementioned study, it is also hypothesized that giving multiple infusions at extended intervals could improve the therapeutic benefits of MSC. Thus, more vigorous and systematic work should be carried out to facilitate the development of standard cellular dosage protocols.

Regarding secondary indicators, the clinical management of liver function status is guided by biochemical indicators such as ALT, AST, TBIL, and INR [85]. Transaminase and TBIL are parameters of the severity of liver damage. Our findings revealed that INR levels and ALT levels in the MSC group were significantly decreased compared with the control group. However, there was no difference in the AST levels and TBIL levels. Similarly, the temporal subgroup analyses of TBIL levels presented that there was no statistical significance between the two groups at any time point. which might be attributed to the limited sample sizes, age and sex ratios of patients, and inconsistent follow-up duration.

How MSC treatment improves liver function is still under investigation. Partially, MSC-mediated immunomodulation is involved. MSCs have exceptional immunosuppressive qualities and reduce systemic inflammation, modulate dendritic cell activity, induce regulatory T cells, reduce proinflammatory cytokine levels (IFN-γ, and IL-4), and inhibit the proliferation and function of numerous immune cells, including T cells, B cells, and natural killer cells [86, 87]. Another explanation is that MSCs are capable of differentiating into Hepatic parenchymal cells and replacing damaged cells [88]. Di Bonzo et al. showed that intravenously injected BM-MSCs may migrate into liver parenchyma in cases of chronic injury [89]. Accordingly, intrasplenic injection was unable to produce stable MSC engraftment in the liver. However,

intrahepatic injection MSCs remain in the liver indefinitely and differentiate into myofibroblasts [90]. Last but not least, it is of great importance to enhance engraftment and prevent undesired differentiation in patients transplanted with MSCs by developing more clinical trials in the future.

Herein, we evaluated the efficacy and safety of MSC in the therapy of ACLF and offered potential directions for clinical application. Of note, this meta-analysis has some limitations. Firstly, the heterogeneity of enrolled studies was detected and there was significant between-study heterogeneity in ALB levels. We performed sensitivity analyses and found the study performed by XU et al., in which the combination treatment of plasma exchange and UC-MSCs transplantation, might be the cause of heterogeneity. On the other hand, subgroup analysis could not be performed to identify the potential factors including cell type for infusion, route of administration, and the frequency of injections that might affect the effectiveness of MSC treatment for ACLF patients. Although the temporal subgroup analyses of MELD levels and ALB levels showed that 4 weeks after the infusion is an ideal time point for re-infusion of MSC, we should be cautious in interpreting this result. Last but not least, the sample size of the included studies was small scale, and long-term follow-up was lacking. Therefore, future multi-center large-scale randomized controlled clinical studies with longer follow-up periods are required to confirm the reliability of the clinical safety and effectiveness of MSC for ACLF.

Conclusion

In conclusion, MSC is safe and effective for treating ACLF. However, it is urgent to establish a standard treatment protocol to create the optimal treatment strategy for improving the efficacy of MSC therapies, which involves sufficient cell number, optimal administration for MSC transplantation, optimal time, and cell sources. Therefore, the protocol for MSC therapy should be further refined, and a large cohort randomized controlled study are required to confirm its efficacy and safety. Besides, MSC-derived exosomes may become a novel direction in ACLF therapy.

Abbreviations

ACLF	Acute-on-chronic liver failure
AEs	Adverse events
ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BM-MSCs	Bone marrow-derived MSCs
CG	Control Croup
EG	Experimental Croup
HBV	Hepatitis B virus
INR	International normalized ratio
MELD	Model for end-stage liver disease
MSC-Exo	MSC-derived exosomes
MSCs	Mesenchymal stem cells
PT	Prothrombin time
RCTs	Randomized controlled trials
TBIL	Total bilirubin
UC-MSCs	Umbilical cord-derived MSCs
UK	Unknown

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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The authors declare that they have not use AI-generated work in this manuscript.

Author contributions

LW: Conceptualization, data curation, methodology, software, visualization, writing original drafts, and writing review editing. YL: Data curation, formal analysis, and writing review editing. WX: Data curation, methodology, software, and visualization. PL: Formal analysis, visualization, and software. LJ: Conceptualization, and formal analysis. TX: Data curation, and visualization. YA: Data curation, and formal analysis. ZZ: Formal analysis, and writing the original draft. LL: Methodology, software, and supervision. YJ: Conceptualization, and supervision. ZL: Conceptualization, formal analysis, and methodology, project administration, resources; supervision, writing original draft, and writing review editing.

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Data availability

The original data contained in this study will be accessible with the publication of this article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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