META-ANALYSIS

Effectiveness and Safety of Stem Cell Therapy in Liver Cirrhosis: A Meta-Analysis of Randomized Controlled Trials

Xingfen Zhang, MM; Dingcheng Zheng, MM; Lirong He, BM; Wei Li, BM; Wenhong Zhou, PhD; Zhongqiang Pang, MM; Qinzhi Deng, MM

ABSTRACT

Objective • In recent years, stem cell transplantation (SCT) has been applied to the clinical treatment of patients with cirrhosis. The specialist clinic of the SCT clinic provides regular and effective interventions for cirrhosis, helping to improve patient management and compliance. The aim of this study was to determine the efficacy and safety of SCT in the treatment of cirrhosis.

Methods • This systematic review adhered to the guidelines outlined in the PRISMA statement. The National Library of Medicin (MEDLINE), Excerpt Medica Database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials.gov databases were searched to screen liver cirrhosis-related articles with stem cell therapy from 2000 to 2022. The articles were then filtered and extracted for clinical outcomes including MELD score, Child-Pugh score, platelets, creatinine, bilirubin, albumin, international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), α fetoprotein (AFP), prothrombin time (PT). The data were normalized and analyzed using the standardized mean difference (SMD) and 95% confidence interval (CI).

Results • A total of 1209 articles were searched, and from these, ten studies were selected for analysis regarding the association between SCT and the clinical outcomes of liver cirrhosis. The findings revealed that SCT therapy, in comparison to conventional treatment, resulted in a reduction in MELD score and INR after 1 month, a decrease in Child-Pugh score at 3 months, an increase in platelet count at 3 months, and an elevation in ALB levels after 1 month. However, no significant beneficial effects were observed on creatinine, bilirubin, PT, ALT, AST, GGT, ALP, and ASP levels.

Conclusion • This study suggested that SCT therapy could elevate the ALB levels and alleviate the MELD score and INR, short-term decreasing the Chile-Pugh score and increasing the platelet levels. It could be a potential therapeutic alternative for patients with cirrhosis. (*Altern Ther Health Med.* 2024;30(6):246-253).

Xingfen Zhang, MM, Associate Chief Physician; **Wei Li, BM**, Attending doctor; **Wenhong Zhou, PhD,** Chief physician; **Zhongqiang Pang**, **MM**, Attending doctor; **Qinzhi Deng, MM,** Chief physician; Department of Liver Disease, Ningbo No.2 Hospital, Ningbo, China. **Dingcheng Zheng, MM,** Associate Chief Physician; General Surgery Department, Ningbo No.2 Hospital, Ningbo, China. **Lirong He, BM,** Laboratory technician; Department of Experimental Medical Science, Ningbo No.2 Hospital, Ningbo, China.

Corresponding author: Qinzhi Deng, MM
E-mail: dqznbey@126.com

INTRODUCTION

Liver disease is one of the most common diseases in the world, which has the characteristics of a low cure rate, high cost, rapid metastasis, and high mortality in clinical practice.[1] In the early stage of liver disease, persistent inflammation can lead to liver fibrosis and the accumulation of scar tissue, which will develop into irreversible cirrhosis if not treated in time.[2] At present, liver cirrhosis is the 14th most common cause of death in the world, and its incidence and mortality are increasing year by year.[3,4] Liver transplantation is an effective treatment for decompensated cirrhosis, but limited donor sources and immune rejection have affected the wide application of liver transplantation.[5]

Stem cells are a class of cells with self-renewal, efficient proliferation, and multi-directional differentiation into multiple cell lineages. They have been used in the treatment of many diseases including central nervous system diseases, diabetes, and tumors.[6] The use of stem cell-based therapy to repair damaged liver tissue is one of the new treatments.[7] At present, there are many basic and clinical studies demonstrating that stem cells have a good therapeutic effect on liver cirrhosis.[8] For example, human menstrual blood

mesenchymal stem cells can improve liver fibrosis in mice by acting on stellate cells.[9] Umbilical cord mesenchymal stem cell transplantation (SCT) can effectively improve liver function and prolong life in patients with decompensated cirrhosis.[10] Therefore, SCT is expected to become one of the treatment methods for liver diseases such as cirrhosis.[11]

However, it is worth noting that in recent years, there have also been studies that have questioned the effectiveness and safety of SCT in the treatment of liver diseases such as cirrhosis. A multicenter, randomized controlled trial showed that SCT could not improve liver dysfunction or fibrosis, and may also increase the risk of adverse events in patients.[12] Another study suggests that the treatment of autologous stem cells is ineffective in patients with decompensated cirrhosis.[13] In addition, Moore et al.[14] systematically reviewed various clinical studies of autologous SCT for liver disease and found that there is no clear evidence that autologous SCT benefits patients with cirrhosis. Therefore, there are still many problems to be solved in the treatment of liver cirrhosis with SCT, such as the risk of teratoma after transplantation.[15]

With the progress of liver transplantation technology and the use of new immunosuppressants, the survival rate and quality of life of liver transplant recipients have been significantly improved. Various types of stem cells play a role in liver regeneration in their own unique patterns, and the mechanism may be "cell fusion" or "transdifferentiation." Hematopoietic stem cells as a potential source of cells may play a role in liver regeneration or reconstruction therapy. Edge population cells not only serve as an appropriate cell population for liver stem cell therapy, but also provide an ongoing link between liver - and bone-marrow-derived stem cells. Small hepatocyte-like progenitors have the potential to differentiate into hepatocyte parenchymal cells. Before stem cells can be used in the clinical treatment of liver diseases, there are still a series of unclear issues that need to be further studied.

For further verification, the effectiveness and safety of stem cell therapy on clinical liver cirrhosis patients were systematically reviewed and evaluated through meta-analysis. Ten studies were filtered from databases and met the inclusion criteria, several clinical outcomes including the MELD score, Child-Pugh score, platelets, creatinine, bilirubin, albumin, INR, ALT, AST, GGT, ALP, AFP, and PT levels were extracted from studies and normalized to analysis. MELD is a system that mainly uses serum bilirubin, prothrombin time international standardized ratio and serum creatinine to evaluate end-stage liver disease. Its application in predicting end-stage liver disease mortality and liver transplantation has gradually matured, and its application scope has begun to expand to severe hepatitis and liver cancer. Child-Pugh score is one of the most commonly used methods to evaluate liver reserve function in patients with cirrhosis, and has important prognostic value for patients with cirrhosis. A higher score indicates poorer liver reserve function.The results of this study suggest serval clinical outcomes associated with a single infusion of stem cell therapy and provide a comprehensive evaluation perspective on stem cell therapy with liver cirrhosis.

METHODS

Literature search strategy

This systematic review followed the guidelines specified in the PRISMA statement.The search encompassed literature on liver cirrhosis and stem cell transplantation published between April 2000 and April 2022. Multiple electronic databases, such as PubMed and Web of Science, were queried using the specified keyword criteria: [(liver OR liver cirrhosis) AND (stem cells OR stem cell transplantation)]. Additionally, the reference lists of identified articles were manually examined to identify any potentially relevant publications.

Inclusion and exclusion criteria

Two authors (Xingfen Zhang and Wei Li) independently reviewed the titles and abstracts of each screened publication to decide whether the articles met the inclusion criteria as follows: (1) all patients diagnosed with liver cirrhosis. (2) received either SCT therapy or standard therapy. (3) at least one of the following outcomes was investigated: MELD score, Child-Pugh score, platelets, creatinine, bilirubin, albumin, international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), α fetoprotein (AFP), prothrombin time (PT) (4) two-arm study design with randomized controlled or observational. The excluded criteria were as follow: (1) involved patients diagnosed with other diseases; (2) inappropriate controls; (3) lacked data on key variables.

Data extraction and quality assessment

The information on articles included publication date, authors, study type, stem cell type, the number of transplants, sample size, race, country, clinical outcomes type, and clinical outcomes data were extracted and recorded by two authors (Xingfen Zhang and Wei Li) independently. The extracted data was revised by supervisor author Qinzhi Deng. The quality of included publications was reviewed and evaluated following the Newcastle–Ottawa Scale (NOS) by two authors Qinzhi Deng and Wenhong Zhou independently, and Qinzhi Deng rejudged the scale to make a consensus between all reviewers if any difference occurred.

Statistical analysis

Meta-analysis was performed using the Revman5.4 software provided by the Cochrane Collaboration. The bivariate adoption rate difference (RD) and its 95%CI, and the mean difference (WMD) and its 95%CI were used for continuity variables. χ^2 test was used to evaluate the heterogeneity among the trials. The test level α was set at 0.1, and the degree of heterogeneity was expressed. If $P > .10$ and $I^2 < 0\%$, there was statistical homogeneity between the studies, and the fixed-effect model was used to combine the effect size. Qualitative causes (sensitivity analysis, subgroup analysis) can only be combined with random effects models if no heterogeneous causes can be found. For high heterogeneity ($I^2 \geq 70\%$), for moderate heterogeneity ($50\% \leq I^2 < 70\%$), the causes of heterogeneity must be analyzed

Table 1. Clinical characteristics of the included studies in this meta-analysis

Year	Author	Country	Disease etiology	Stem cell type	Dosage	Times of treatment	Administration route	Patient number		Median age		Sex ratio (Male/Female)		Follow-up time
								Control	SCT	Control	SCT	Control	SCT	
2018	Newsome et al.[12]	UK	Mix	$CD133^+$ PBSC	$0.2 X 10^6$ / kg	Once	intravenous infusion	27	28	52	56.5	48%	79%	12 months
2018	Ke et al.[20]	China	HBV	UC-MSC	$3 - 4 \times 10^7$	Three	intravenous infusion	46	46	47.1	46.8	63%	59%	18 months
2016	Suk et al.[16]	Korea	Alcohol	BM-MSC	5×10^7	Once	hepatic artery infusion	18	18	53.7	53.1	94%	83%	6 months
2013	Mohamadnejad et al.[13]	Iran	Decompensated	BM-MSC	$7 - 9 \times 10^8$	Two	portal vein infusion	9	10	46.2	42.9	56%	70%	12 months
2015	Sharma et al.[21]	India	Decompensated	$CD34^+$ PBSC	NA	Once	hepatic artery infusion	17	18	47.4	48.9	87%	73%	3 months
2015	Zekri et al.[22]	Egypt	HCV	BM-MSC	0.5×10^8	Once	intravenous infusion	30	30	49.4	49.6	87%	83%	12 months
2015	Cai et al.[23]	China	HBV	PBSC	$2 - 4 \times 10^7$	Once	hepatic artery infusion	28	23	50.8	51.5	61%	61%	12 months
2014	Li et al.[24]	China	HBV	BM-MSC	$1.6 - 3.2 \times 10^{10}$	Once	hepatic artery infusion	37	40	50.4	51.6	89%	93%	1 months
2012	Lin et al.[25]	China	Mix	UC-MSC	$0.5 - 1 \times 10^8$	Three	intravenous infusion	16	38	48	47	94%	89%	12 months
2012	EI-Ansary et al.[26]	Egypt	HCV	BM-MSC	$1 X 10^7$ / kg	Once	intravenous infusion	10	15	51.6	48	80%	73%	6 months

(sensitivity analysis, subgroup analysis). When the causes of heterogeneity cannot be found, it is recommended to abandon Meta and change to qualitative systematic evaluation. Data from the Juna clinical trials could not be pooled and only descriptive analysis was performed.

RESULTS

Literature Search

A comprehensive search was conducted in PubMed, Embase, and the Cochrane Library, resulting in the identification of 1209 articles. After reviewing the titles and abstracts, 370 studies were deemed irrelevant and excluded. Subsequently, 27 studies were considered potentially eligible and underwent further evaluation. Among these, 18 studies were excluded due to various reasons, including their focus on other topics (n = 2), their design as reviews or meta-analyses (n = 6), or their classification as single-arm studies (n = 10). Ultimately, a total of 10 studies were selected for inclusion in the final meta-analysis. No additional studies were obtained through manual searches of reference lists. The flow diagram of the study selection process is presented in Figure 1.

Clinical characters

The present meta-analysis incorporates ten studies conducted between 2012 and 2018, originating from diverse countries such as China (n = 4), Egypt (n = 2), Korea (n = 1), India (n = 1), Iran (n = 1), and the UK (n = 1). These studies examine the clinical characteristics of liver cirrhosis, with specific pathologies including HBV-related (n = 3), HCV-related (n = 2), decompensated (n = 2), alcohol-related (n = 1), and mixed (n = 2). The analysis encompasses a total of 504 patients, with 238 receiving conventional therapy and 266 receiving SCT. The stem cells were derived from BM-MSC (n = 5), PBSC (n = 3), and UC-MSC (n = 2), and eight studies involved autologous transplants while two studies involved allogeneic transplants. The stem cells were administered via intravenous (n = 5), hepatic artery (n = 4), and portal vein (n = 1) routes. Single infusions were conducted in seven studies, one study involved twice infusions, and two studies involved three infusions (one infusion per month). The dosage of transplanted stem cells varied greatly, ranging from 2×10^7 to 3.2×10^{10} cells. See table 1

MELD score

The analysis was conducted using five studies that assessed the efficacy of the Model for End-stage Liver Disease

Figure 1. The screening strategy and the included article number of this study.

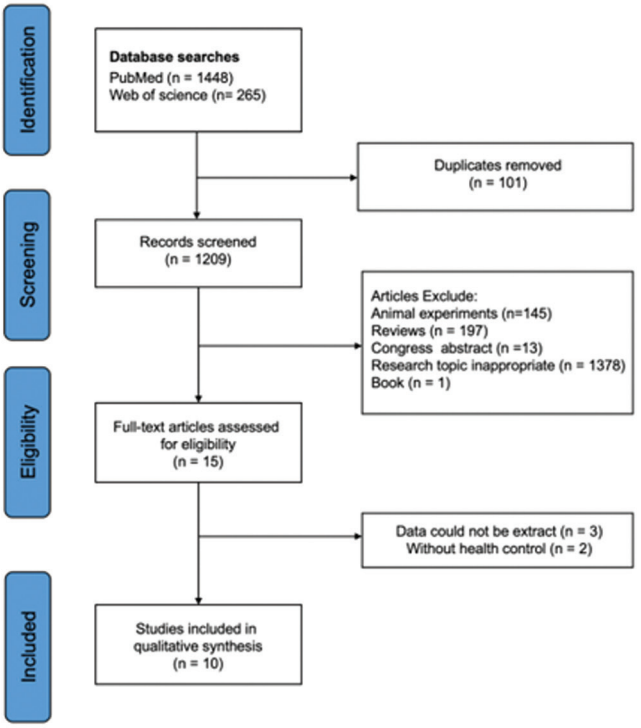


Figure 2. Forest plot of the effects comparison of SCT therapy on MELD score within 1 month, 3 months, and 6 months.

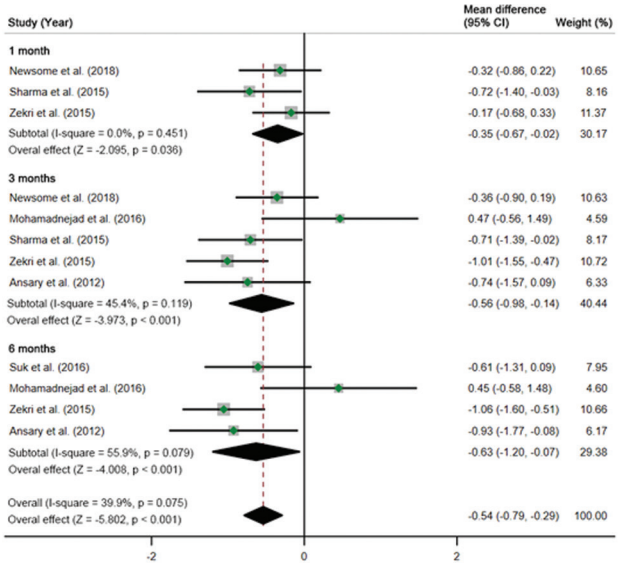


Figure 3. Forest plot of the effects comparison of SCT therapy on Child-Pugh score within 1 month and 3 months.

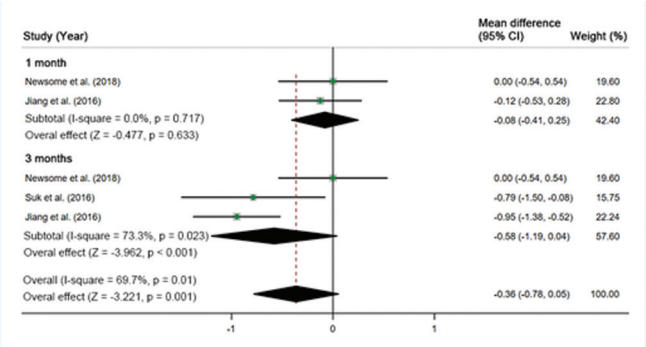


Figure 4. Forest plot of the effects comparison of SCT therapy on platelets within 1 month and 3 months.

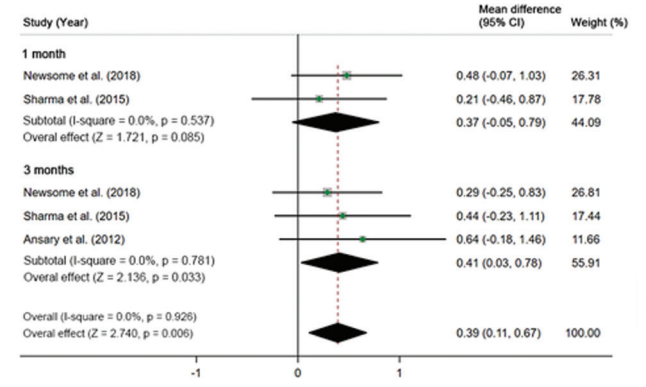
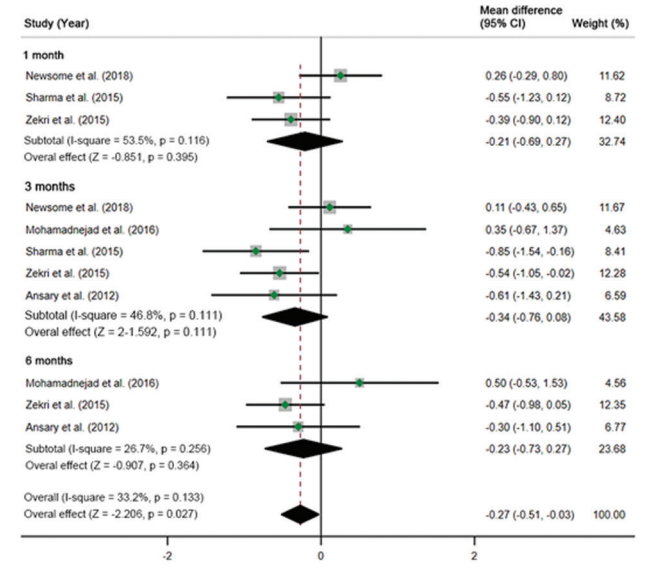


Figure 5. Forest plot of the effects comparison of SCT therapy on creatinine levels within 1 month, 3 months, and 6 months.



(MELD) Score in patients with liver cirrhosis at 1, 3, and 6-month intervals. Specifically, data pertaining to the MELD score were reported in three studies at the 1-month mark, five studies at the 3-month mark, and four studies at the 6-month mark. The results showed that the group receiving stem cell transplant therapy had a lower MELD score compared to the control group at 1 month (SMD: -0.35, 95% CI: -0.67 to -0.02, $P = .036$), 3 months (SMD: -0.56, 95% CI: -0.98 to -0.14, $P < .001$), and 6 months (SMD: -0.63, 95% CI: -1.20 to -0.07, $P = .029$). Mild heterogeneity was observed in the MELD score at 3 months ($I^2 = 45.4\%$, $P = .119$) and 6 months ($I^2 = 55.9\%$, $P = .079$) . See Figure 2.

Child-Pugh score

The analysis comprised of two studies aimed at evaluating the Child-Pugh score in liver cirrhosis patients following one month of treatment, and an additional three studies focused on assessing the score after three months of treatment. The results indicated that there was no significant difference between the stem cell therapy (SCT) group and the control group in terms of the Child-Pugh score after 1 month (SMD: -0.08, 95% CI: -0.41 to 0.25, $P = .633$). However, the SCT treatment was found to be associated with a lower Child-Pugh score compared to the control group within 3 months (SMD: -0.58, 95% CI: -1.19 to -0.04, $P < .001$). There was substantial heterogeneity in the Child-Pugh score after 3 months ($I^2 = 73.3\%$, $P = .023$). See Figure 3.

Platelets

Two studies conducted within a one-month timeframe and three studies conducted within a three-month timeframe examined the disparity in platelet counts among liver cirrhosis patients undergoing stem cell therapy (SCT) treatment versus those receiving traditional therapy. The analysis results showed that there was no significant difference between the SCT group and the control group in terms of platelet numbers at 1 month (SMD: 0.37, 95% CI: -0.05 to 0.79, $P = .085$). However, an increase in platelet numbers was observed after 3 months of treatment (SMD: 0.41, 95% CI: 0.03 to 0.78, $P = .033$). The platelet numbers at 1 month ($I^2 = 0.0\%$, $P = .537$) and 3 months ($I^2 = 0.0\%$, $P = .781$) showed low heterogeneity.See Figure 4.

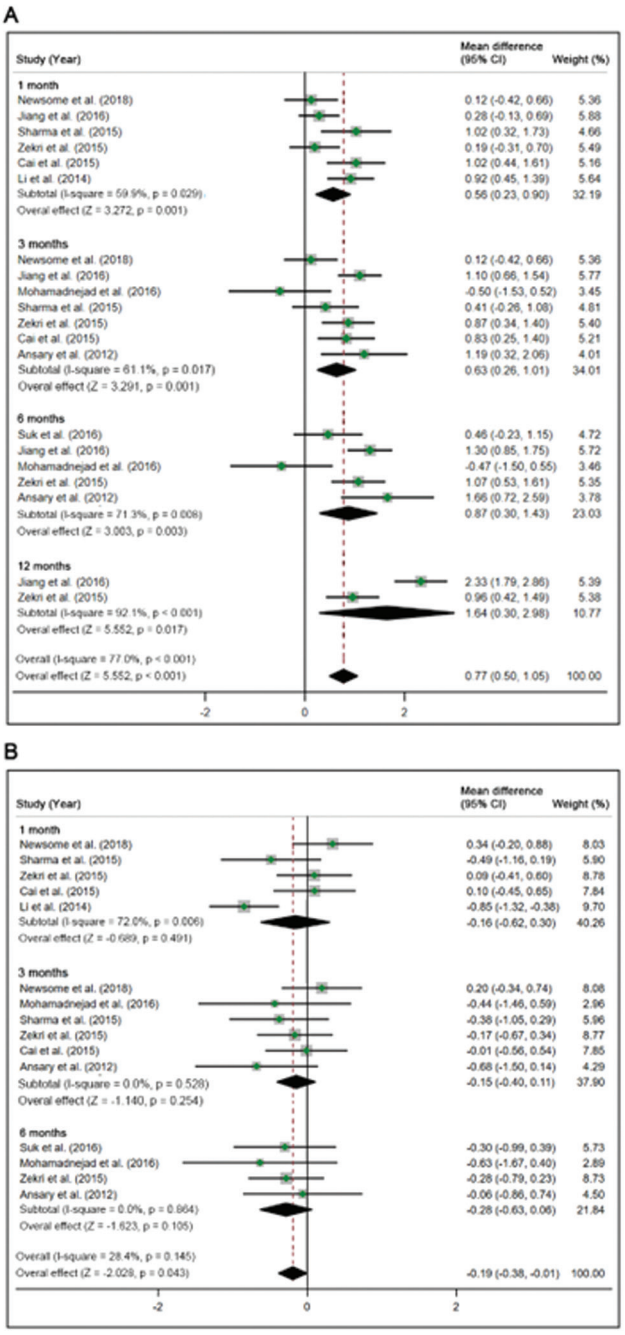
Creatinine levels

The creatinine levels of patients with liver cirrhosis were documented in a total of five studies. Among these, three studies were included in the analysis comparing the treatment group receiving SCT with the control group after one month, five studies were included after three months, and three studies were included after six months. The results showed no significant change in creatinine levels after 1 month of SCT treatment (SMD: -0.21, 95% CI: -0.69 to 0.27, $P = .395$), 3 months (SMD: -0.34, 95% CI: -0.76 to 0.08, $P = .111$), and 6 months (SMD: -0.23, 95% CI: -0.73 to 0.27, $P = .364$). There was mild heterogeneity in the creatinine levels at 3 months ($I^2 = 46.8\%$, $P = .111$). See Figure 5.

Metabolic function (ALB and BR)

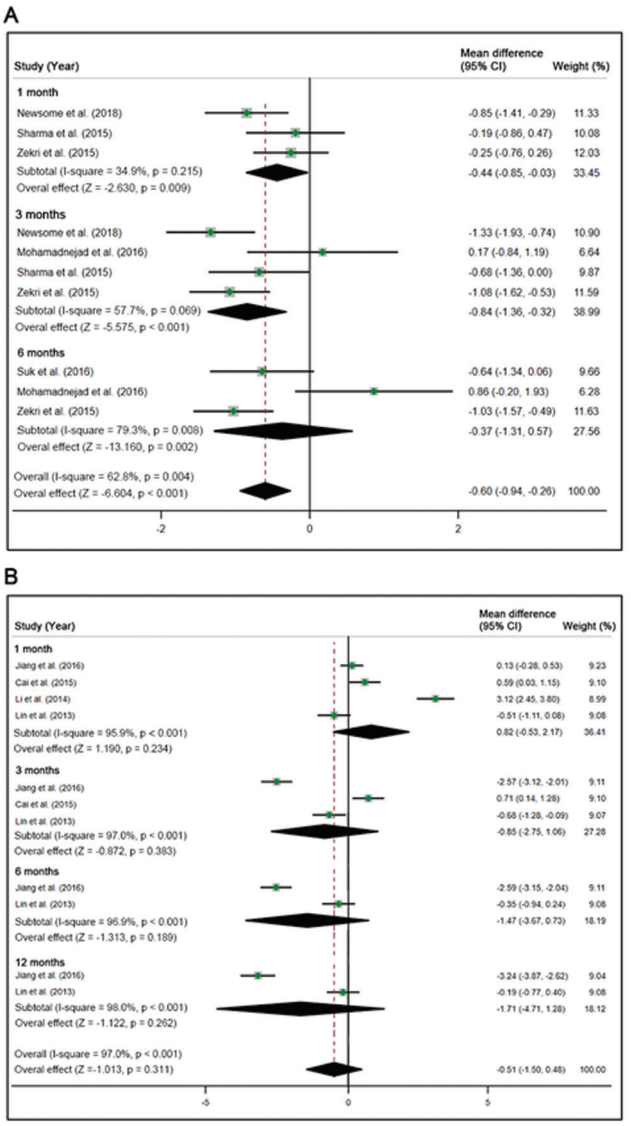
Nine studies were analyzed to determine the impact of SCT therapy on albumin (ALB) levels, while eight studies were analyzed for bilirubin (BR) levels. The results showed that SCT

Figure 6. Forest plot of the effects comparison of SCT therapy on ALB and BR levels within 1 month, 3 months, and 6 months.



therapy led to elevated ALB levels compared to traditional therapy at 1 month (SMD: 0.56, 95% CI: 0.23 to 0.27, $P = .001$), 3 months (SMD: 0.63, 95% CI: 0.26 to 1.01, $P = .001$), 6 months (SMD: 0.87, 95% CI: 0.30 to 1.43, $P = .003$), and 12 months (SMD: 1.64, 95% CI: 0.30 to 2.98, $P = .017$). Significant heterogeneity was observed in all time points (1 month: $I^2 = 59.9\%$, $P = 0.029$; 3 months: $I^2 = 61.1\%$, $P = 0.017$; 6 months: $I^2 = 71.3\%$, $P = .008$; 12 months: $I^2 = 92.1\%$, $P = .017$). For BR levels, there was no significant difference between the SCT group and the control group at 1 month (SMD: -0.16, 95% CI: -0.62 to 0.30, $P = .491$), 3 months (SMD: -0.15, 95% CI: -0.40 to 0.11, $P = .254$), and 6 months (SMD: -0.28, 95% CI: -0.63 to 0.06, $P = .105$). Substantial heterogeneity was observed in BR levels at 1 month ($I^2 = 72.0\%$, $P = .006$). See Figure 6.

Figure 7. Forest plot of the effects comparison of SCT therapy on INR levels within 1 month, 3 months, and 6 months, and PT within 1 month, 3 months, 6 months and 12 months.



Blood coagulation function (INR and PT)

The results of liver cirrhosis patients receiving SCT therapy and conventional therapy in terms of their international normalized ratio (INR) and prothrombin time (PT) were reported in five and four studies, respectively. The patients treated with SCT showed significantly lower INR levels compared to conventional therapy at 1 month (SMD: -0.44, 95% CI: -0.85 to -0.03, $P = .009$), 3 months (SMD: -0.84, 95% CI: -1.36 to -0.32, $P < .001$), and 6 months (SMD: -0.37, 95% CI: -1.31 to 0.57, $P = .002$). Mild heterogeneity was present among the included studies for INR levels at 1 month ($I^2 = 34.9\%$, $P = .215$) and 3 months ($I^2 = 57.7\%$, $P =$

Figure 8. Forest plot of the effects comparison of SCT therapy on ALT and AST levels within 1 month, 3 months, and 6 months.

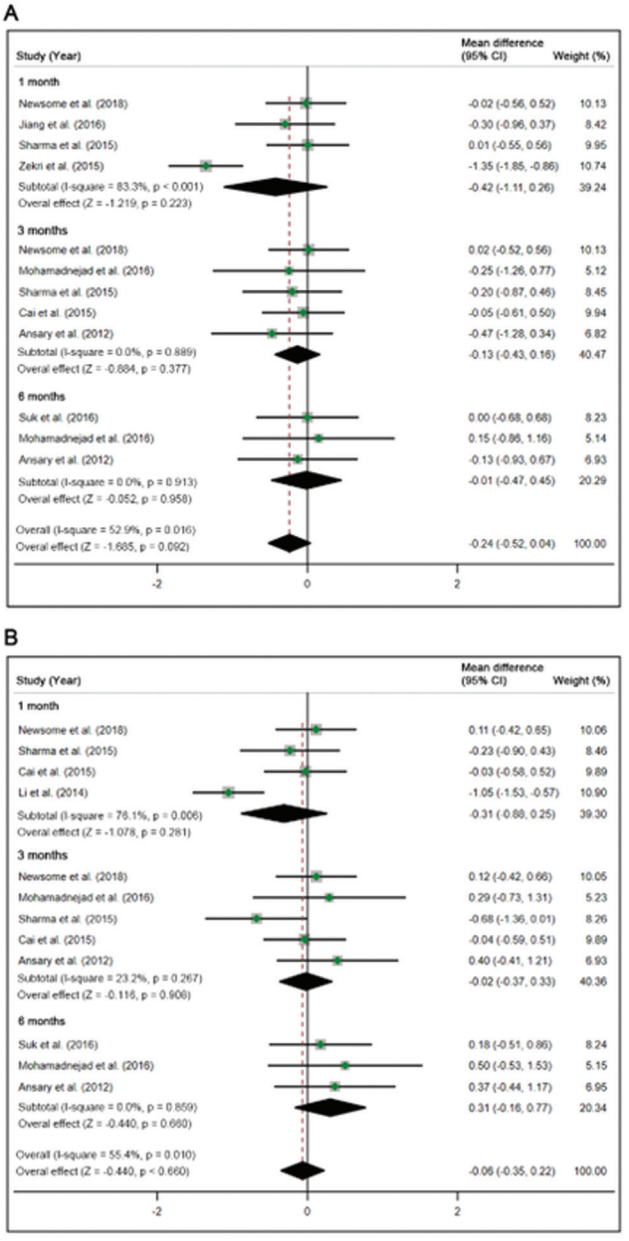
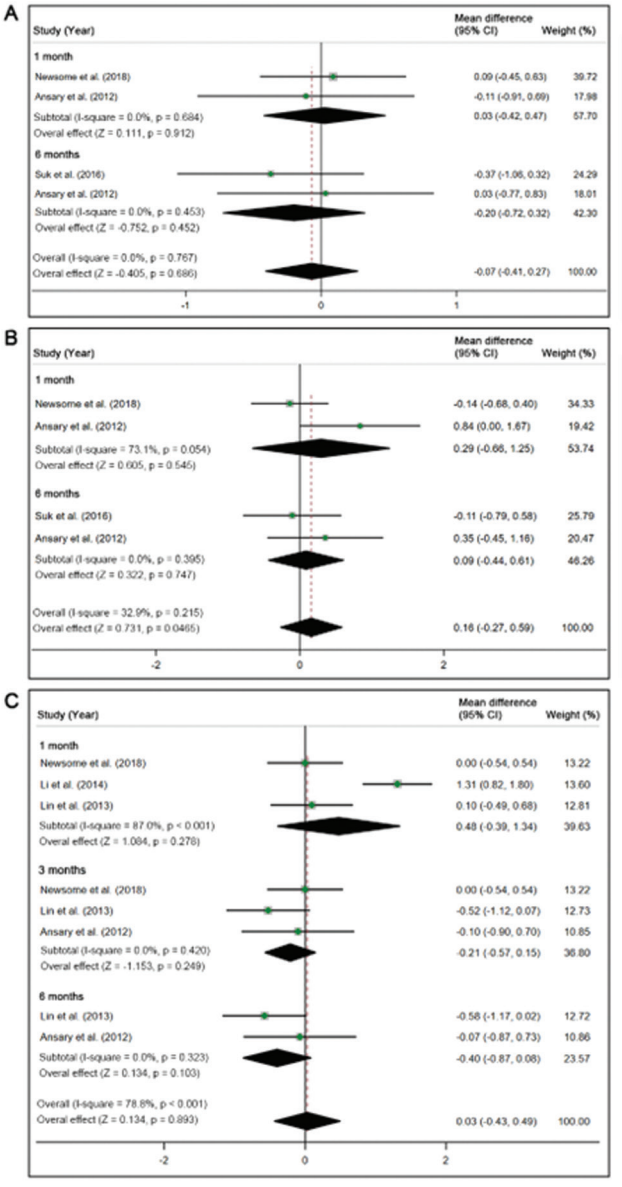


Figure 9. Forest plot of the effects comparison of SCT therapy on GTT, ALP, and AFP levels within 1 month, 3 months, and 6 months.



.069), and significant heterogeneity was found at 6 months (I^2 = 79.3%, P = .008). The sensitivity analysis was conducted for INR levels at 12 months, and the results suggested that the conclusions remained unchanged even after sequentially excluding individual studies. For the levels of PT, results from four studies indicated that there was no significant difference between SCT therapy and conventional therapy at any of the following time points: 1 month (SMD: 0.82, 95% CI: -0.53 to 2.17, P = .234), 3 months (SMD: -0.85, 95% CI: -2.75 to 1.06, P = .383), 6 months (SMD: -1.47, 95% CI: -3.67 to 0.73, P = 0.189), and 12 months (SMD: -1.71, 95% CI: -4.71 to 1.28, P = .262). The studies showed significant heterogeneity at all time points I^2 = 95.9% to 98.0%). See Figure 7.

Transaminase activity level (ALT and AST)

The results showed no significant difference in ALT and AST levels after 1 month (ALT: SMD: -0.42, 95% CI: -1.11 to .26, P = .223; AST: SMD: -0.31, 95% CI: -0.88 to 0.25, P = .281), 3 months (ALT: SMD: -0.13, 95% CI: -0.43 to 0.16, P = .377; AST: SMD: -0.02, 95% CI: -0.37 to 0.33, P = .908), and 6 months (ALT: SMD: -0.01, 95% CI: -0.47 to 0.45, P = .958; AST: SMD: 0.31, 95% CI: -0.16 to 0.77, P = .66) . There was significant heterogeneity found in ALT and AST levels at 1 month (I^2 = 83.3% for ALT and 76.1% for AST). See Figure 8.

Injury indicators (GGT, ALP, and AFP)

Patients receiving SCT treatment did not show significant differences in GTT, ALP, and AFP levels when compared to

the conventional therapy group over 1, 3, and 6 months. Heterogeneity was observed in the ALT and AST levels at 1 month, with $I^2 = 73.1\%$ for ALT ($P = .054$) and 87.0% for AST ($P < .001$). Sensitivity analysis was not performed on GTT and ALP levels due to the limited number of included studies. See Figure 9.

DISCUSSION

In recent years, with the development of stem cell transplantation technology, stem cells have gradually replaced liver transplantation as one of the treatment methods for liver cirrhosis because of their advantages of multi-directional differentiation, high proliferation, and convenient sampling.[16] Stem cell therapy for liver cirrhosis has demonstrated a discernible impact in clinical settings. A recent academic study was conducted concurrently in vitro and in vivo to assess its efficacy. The viability and cytokine profile of stem cells were examined through in vitro culture, while the primary objective of the in vivo test was to evaluate the safety of stem cell infusion combination. The findings of the study demonstrated that the co-administration of hepatic stellate cells and mesenchymal stem cells not only augmented the efficacy of stem cells and extended the duration of liver function enhancement, but also exhibited evident safety of cell infusion via the hepatic artery, devoid of any adverse reactions.[24] However, some studies have suggested that stem cell transplantation is not obvious in improving liver function and survival rate. A prior systematic review and meta-analysis of 31 studies assessed the clinical impact of stem cell transplantation from various human tissue sources in liver cirrhosis patients.[25] The review showed that stem cell therapy resulted in improved liver function without significant adverse events. However, the benefit was not statistically significant in terms of improving liver function and survival. Another meta-analysis of 5 studies evaluated the efficacy and safety of BMDSCs in uncompensated liver cirrhosis and found that SCT improved liver function with no severe side effects after a year.[26] However, this analysis combined single-arm and two-arm studies, and differences in the control group could have introduced biases. To provide a more comprehensive and up-to-date evaluation, we conducted this updated meta-analysis to systematically assess the efficacy and safety of SCT in liver cirrhosis patients.

Our study findings suggest that SCT treatment was initially associated with a decrease in MELD scores within a three-month timeframe. However, this effect appeared to diminish after six months. Nevertheless, the sensitivity analysis revealed that even after excluding two specific studies (conducted by Mohamadnejad et al. and Suk et al.), the impact of BMDSC on MELD scores remained statistically significant after six months. The limited sample size in the study conducted by Mohamadnejad et al. and the inclusion of less severe cases in the study conducted by Suk et al. may account for the inconsistent results observed. Consequently, it is plausible to consider that SCT may be more efficacious in patients with severe liver cirrhosis.

The summary results indicated that SCT treatment did not have a significant effect on ALT, albumin, PT, and Child-Pugh scores, regardless of the length of follow-up. The study found that BMDSC was associated with a reduction in TBIL levels within 3 months, but this effect was not seen after 6 months. However, sensitivity analysis suggested that BMDSC might increase albumin levels within 3 months or after 6 months. The aforementioned conclusion was revised subsequent to the exclusion of the study conducted by Mohamadnejad et al. This exclusion was warranted due to the predominance of patients with mild to moderate cirrhosis in their study, which could potentially result in fluctuating serum indexes owing to plasma volume expansion and concomitant administration of other medications. Furthermore, it has been demonstrated that macrophage infusion effectively diminishes Model for End-Stage Liver Disease (MELD) scores in the majority of liver cirrhosis patients, while concurrently avoiding the occurrence of severe complications.

Our results indicated SCT therapy could elevate the ALB levels and alleviate the MELD score and INR, short-term decreasing the Chile-Pugh score and increasing the platelets levels. However, to evaluate the long-term efficacy and safety of stem cell transplantation for cirrhosis, a larger prospective randomized controlled trial is needed.

There are several limitations in this study should be noted. (1) The study's limitations encompass the possibility of uncontrolled biases arising from the amalgamation of randomized controlled trials and observational studies, potentially resulting in inflated outcomes. (2) The restricted number of studies incorporated in the analysis hindered the capacity to perform more comprehensive stratified analyses. (3) Further prospective studies are required to validate the route of transfusion, predominantly through the hepatic artery in 8 out of 9 studies, as well as the findings pertaining to therapeutic effects stratified by the route of transfusion.(4) The limitations of this study include its reliance solely on published studies and the absence of access to unpublished data, potentially resulting in publication bias. (5) The study utilized pooled data and did not conduct a comprehensive analysis due to the unavailability of individual data.

In conclusion, a single infusion of SCT could improve serval clinical outcomes including MELD score and ALB levels, and could short-timely change the INR levels, blood platelets number, and Child-Pugh score. Furthermore, these studies must take into account various factors, including the administration method of transfusion, the specific cell type of stem cells utilized, the dosage and frequency of stem cell therapy, and the timing of initiating treatment, as these variables may impact the therapeutic outcomes. Additionally, it is crucial to conduct comparative analyses to assess the safety and effectiveness of stem cell therapy in comparison to other established treatments for liver cirrhosis. Moreover, future investigations should prioritize elucidating the underlying mechanism of action of bone marrow-derived stem cells (BMDSC) and their therapeutic effects, as this

knowledge will facilitate the optimization of stem cell therapy in the management of liver cirrhosis.

ETHICAL COMPLIANCE

Not applicable.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

XZ and QD designed the study and performed the experiments, DZ and LH collected the data, WL, WZ, and ZP analyzed the data, XZ and QD prepared the manuscript. All authors read and approved the final manuscript. Z

FUNDING

This study was supported in part by Fund: Medical Scientific Research Foundation of Zhejiang Province, China (Grant No.2021KY1018) and Ningbo Science and Technology Innovation Team Project (No.2011B82016) and Zhejiang Province and Ningbo City Co-constructed Project of Leading Medical & Health Discipline (2016-S04).

REFERENCE

1. Kitto LJ, Henderson NC. Hepatic Stellate Cell Regulation of Liver Regeneration and Repair. *Hepatol Commun*. 2020;5(3):358-370. doi:10.1002/hep4.1628
2. Gadd VL, Aleksieva N, Forbes SJ. Epithelial Plasticity during Liver Injury and Regeneration. *Cell Stem Cell*. 2020;27(4):557-573. doi:10.1016/j.stem.2020.08.016
3. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol*. 2013;58(3):593-608. doi:10.1016/j.jhep.2012.12.005
4. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet*. 2021;398(10308):1359-1376. doi:10.1016/S0140-6736(21)01374-X
5. Lee DS, Gil WH, Lee HH, et al. Factors affecting graft survival after living donor liver transplantation. *Transplant Proc*. 2004;36(8):2255-2256. doi:10.1016/j.transproceed.2004.08.073
6. Weijie T, Xinhua G, Jingqi H, XiLing Y, Zuoji F. The effect of synthesized cartilage tissue from human adipose-derived mesenchymal stem cells in orthopedic spine surgery in patients with osteoarthritis. *Cell Mol Biol (Noisy-le-grand)*. 2021;67(3):133-137. doi:10.14715/cmb/2021.67.3.19
7. Messina A, Luce E, Hussein M, Dubart-Kupperschmitt A. Pluripotent-Stem-Cell-Derived Hepatic Cells: Hepatocytes and Organoids for Liver Therapy and Regeneration. *Cells*. 2020;9(2):420. doi:10.3390/cells9020420
8. de Miguel MP, Prieto I, Moratilla A, Arias J, Aller MA. Mesenchymal Stem Cells for Liver Regeneration in Liver Failure: From Experimental Models to Clinical Trials. *Stem Cells Int*. 2019;2019:3945672. doi:10.1155/2019/3945672
9. Chen L, Zhang C, Chen L, et al. Human Menstrual Blood-Derived Stem Cells Ameliorate Liver Fibrosis in Mice by Targeting Hepatic Stellate Cells via Paracrine Mediators. *Stem Cells Transl Med*. 2017;6(1):272-284. doi:10.5966/sctm.2015-0265
10. Shi M, Li YY, Xu RN, et al. Mesenchymal stem cell therapy in decompensated liver cirrhosis: a long-term follow-up analysis of the randomized controlled clinical trial. *Hepatol Int*. 2021;15(6):1431-1441. doi:10.1007/s12072-021-10199-2
11. 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):40-49. doi:10.1111/jcmm.14788
12. Newsome PN, Fox R, King AL, et al. Granulocyte colony-stimulating factor and autologous CD133-positive stem-cell therapy in liver cirrhosis (REALISTIC): an open-label, randomised, controlled phase 2 trial. *Lancet Gastroenterol Hepatol*. 2018;3(1):25-36. doi:10.1016/S2468-1253(17)30326-6
13. Mohamadnejad M, Alimoghaddam K, Bagheri M, et al. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. *Liver Int*. 2013;33(10):1490-1496. doi:10.1111/liv.12228
14. Moore JK, Stutchfield BM, Forbes SJ. Systematic review: the effects of autologous stem cell therapy for patients with liver disease. *Aliment Pharmacol Ther*. 2014;39(7):673-685. doi:10.1111/apt.12645
15. Fausto N, Campbell JS. The role of hepatocytes and oval cells in liver regeneration and repopulation. *Mech Dev*. 2003;120(1):117-130. doi:10.1016/S0925-4773(02)00338-6
16. Suk KT, Yoon JH, Kim MY, et al. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. *Hepatology*. 2016;64(6):2185-2197. doi:10.1002/hep.28693
17. Ke M, Dong J, Wang Y, et al. MEL-pep, an analog of melittin, disrupts cell membranes and reverses 5-fluorouracil resistance in human hepatocellular carcinoma cells. *Int J Biochem Cell Biol*. 2018;101:39-48. doi:10.1016/j.biocel.2018.05.013
18. Sharma M, Rao PN, Sasikala M, et al. Autologous mobilized peripheral blood CD34(+) cell infusion in non-viral decompensated liver cirrhosis. *World J Gastroenterol*. 2015;21(23):7264-7271. doi:10.3748/wjg.v21.i23.7264
19. Zekri AR, Salama H, Medhat E, et al. The impact of repeated autologous infusion of haematopoietic stem cells in patients with liver insufficiency. *Stem Cell Res Ther*. 2015;6(1):118. doi:10.1186/s13287-015-0106-1
20. Cai T, Deng Q, Zhang S, Hu A, Gong Q, Zhang X. Peripheral blood stem cell transplantation improves liver functional reserve. *Med Sci Monit*. 2015;21:1381-1386. doi:10.12659/MSM.892990
21. Li DL, He XH, Zhang SA, Fang J, Chen FS, Fan JJ. Bone marrow-derived mesenchymal stem cells promote hepatic regeneration after partial hepatectomy in rats. *Pathobiology*. 2013;80(5):228-234. doi:10.1159/000346796
22. Lin H, Zhang Z, Shi M, et al. [Prospective controlled trial of safety of human umbilical cord derived-mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis]. *Zhonghua Gan Zang Bing Za Zhi*. 2012;20(7):487-491. doi:10.3760/cma.j.issn.1007-3418.2012.07.002
23. El-Ansary M, Abdel-Aziz I, Mogawer S, et al. Phase II trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in Egyptian patients with HCV induced liver cirrhosis. *Stem Cell Rev Rep*. 2012;8(3):972-981. doi:10.1007/s12015-011-9322-y
24. Sakai Y, Fukunishi S, Takamura M, et al. Regenerative Therapy for Liver Cirrhosis Based on Intrahepatic Arterial Infusion of Autologous Subcutaneous Adipose Tissue-Derived Regenerative (Stem) Cells: Protocol for a Confirmatory Multicenter Uncontrolled Clinical Trial. *JMIR Res Protoc*. 2020;9(3):e17904. doi:10.2196/17904
25. Qi X, Guo X, Su C. Clinical outcomes of the transplantation of stem cells from various human tissue sources in the management of liver cirrhosis: a systematic review and meta-analysis. *Curr Stem Cell Res Ther*. 2015;10(2):166-180. doi:10.2174/1574888X09666141112114011
26. Pan XN, Zheng LQ, Lai XH. Bone marrow-derived mesenchymal stem cell therapy for decompensated liver cirrhosis: a meta-analysis. *World J Gastroenterol*. 2014;20(38):14051-14057. doi:10.3748/wjg.v20.i38.14051