Bone Marrow-Derived Stem Cells for Patients with Liver Cirrhosis: A Systematic Review and Meta-analysis

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ABSTRACT

Background: *To date, studies have shown inconsistent results of treatment with bone marrow-derived stem cells (BMDSC) for patients with liver cirrhosis. This study aims to compare the efficacy and safety of BMDSC and standard therapy for liver cirrhosis.*

Methods: *Articles from PubMed, Embase, and the Cochrane library were searched from inception to April 2018. The index included Model for End-stage Liver Disease (MELD), alanine aminotransferase (ALT), albumin, total bilirubin (TBIL), prothrombin time (PT), Child–Pugh score, and all-cause mortality.*

Results: *A total of 9 studies with a total of 424 patients with liver cirrhosis were included in final meta-analysis. BMDSC therapy was associated with lower MELD within 3 months (P = .010), while it had no significant impact on MELD after 6 months (P = .074). There were no differences between BMDSC and standard therapy for ALT within 3 months (P = .336) and after 6 months (P = .379). BMDSC did not affect albumin level within 3 months (P = .196) and after 6 months (P = .840). BMDSC reduced the TBIL level within 3 months (P = .037) and was not associated with the TBIL level after 6 months (P = .914). There were no differences between BMDSC and standard therapy for PT within 3 months (P = .167) and after 6 months (P = .484). The Child–Pugh scores within 3 months (P = .342) and after 6 months (P = .133) were not associated with BMDSC treatment for liver cirrhosis patients. Finally, the BMDSC was not associated with the risk of all-cause mortality, as compared with standard therapy (P = .622).*

Conclusions: *BMDSC treatment for patients with liver cirrhosis could improve short-term MELD and TBIL, but not the risk of mortality, as compared with standard therapy.*

Keywords: *Bone marrow-derived stem cell, liver cirrhosis, systematic review*

INTRODUCTION

Liver cirrhosis is the late stage of progressive hepatic fibrosis, which causes excess risk of liver failure and portal hypertension. Moreover, liver cirrhosis can affect hepatic architecture and eventually form regenerative nodules. The clinical manifestations of liver cirrhosis include ascites, variceal hemorrhage, and encephalopathy.[1] No curative options are available for cirrhosis except for organ transplantation, which requires major surgery and life-long immunosuppression.[2] Alternative effective treatment strategies, including cell therapies, should be explored for all liver cirrhosis patients.

Bone marrow-derived stem cells (BMDSC) have been recommended as an effective therapy for patients with liver cirrhosis,[3,4] which can differentiate into the hepatocyte-like cells and[5-7] have the ability to secrete a series of signaling molecules and cytokines which can stimulate hepatocyte proliferation, regulate inflammatory reaction, and maintain hepatocyte function. BMDSC can be easily isolated and amplified from the bone marrow. Several previous studies have illustrated that BMDSC transplantation could accelerate the liver regeneration process, reduce hepatic fibrosis, and improve liver function and survival rate, in animal models of liver diseases.[8-10] Numerous studies have shown the efficacy and safety of BMDSC for patients with liver cirrhosis. While most of these studies were single-arm designs,[11-20] several two-arm studies have already evaluated the efficacy and safety of BMDSC for patients with liver cirrhosis, but the results have been

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inconsistent. There are scarce large-scale prospective trials that could convincingly evaluate the efficiency and safety of BMDSC as a candidate therapeutic strategy for liver cirrhosis. Thus, a systematic review and meta-analysis were conducted to appraise the efficiency and safety of BMDSC for liver cirrhosis.

METHODS

Data Sources, Search Strategy, and Selection Criteria

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement were followed to perform this systematic review and meta-analysis.[21] Studies evaluating the therapeutic effects of BMDSC for patients with liver cirrhosis and published in English were included in our study. Three electronic databases—PubMed, Embase, and the Cochrane library—were systematically searched from inception to April 2018, and the core search terms included "stem cell" AND ("liver cirrhosis" OR "hepatic cirrhosis") AND "human" AND "English." Studies included full-text articles, conference proceedings, and conference abstracts. The reference lists from studies fulfilling the inclusion criteria were manually reviewed in order to identify the additional eligible studies.

The literature search and study selection process were conducted by 2 authors following a standard approach, and any disagreement was resolved by an additional author. Studies were included if they met the following inclusion criteria: (1) Patients: all of the included patients were diagnosed with liver cirrhosis. (2) Intervention and control: the patients included received BMDSC or standard therapy. (3) Outcomes: the investigated outcomes included at least 1 of the following outcomes: Model for End-stage Liver Disease (MELD), alanine aminotransferase (ALT), albumin, total bilirubin (TBIL), prothrombin time (PT), Child–Pugh score, and all-cause mortality. (4) Study design: the studies conducted with a two-arm design, regardless of randomized controlled design or observational design.

The exclusion criteria are shown as follows: (1) patients diagnosed with other diseases; (2) the study had inappropriate controls; (3) the data variables were not available from identified studies; and (4) studies with a single-arm design.

Data Collection and Quality Assessment

The collected baseline variables, included the first author's surname, year of publication, country, sample size, mean age, percentage of males, the route of transfusion, intervention, and frequency of stem cell transfusions. Further, the outcome variables included MELD, ALT, albumin, TBIL, PT, Child–Pugh scores, and all-cause mortality. Studies with a randomized controlled design were evaluated by the Jadad scale,[22] and observational studies were assessed using the Newcastle–Ottawa Scale (NOS).[23] Items of the Jadad scale included randomization, blinding, allocation concealment, withdrawals and dropouts, and the use of intention-to-treat analysis, the NOS items including selection (4 items), comparability (1 item), and outcome (3 items). The data collection and quality assessment were performed by 2 authors with identical backgrounds, and any inconsistencies were examined and adjudicated by group discussion and by referring to the original studies.

Statistical Analysis

The weighted mean difference (WMD) and its 95% CI were calculated in each individual study for continuous data, while an odds ratio (OR) with corresponding 95% CI was used for dichotomous data. The pooled analyses for all outcomes were used in the random-effects model.[24,25] The studies that reported median values were translated into mean values according to the previously proposed method.[26] I-square and *P* values from Q statistic were used to investigate heterogeneity across the included studies, and $P < .10$ was regarded as indicating significant heterogeneity.[27,28] Sensitivity analyses for MELD, ALT, albumin, TBIL, and all-cause mortality were conducted by sequentially excluding individual studies.[29] Subgroup analyses were conducted for MELD, ALT, albumin, TBIL, PT, and Child–Pugh scores based on follow-up periods (within 3 months or after 6 months). The qualitative assessment of publication bias for MELD was done using funnel plots, and the quantitative assessment of publication bias for MELD using Egger[30] and Begg[31] tests. Two-sided *P* values were accepted with .05 as a significant level for all pooled results. Stata software was employed to evaluate all statistical analyses (Version 10.0; Stata Corporation, College Station, TX, USA).

RESULTS

Literature Search

A total of 397 articles were identified during the initial electronic searches in PubMed, Embase, and the Cochrane library. Of these, 370 studies were excluded after reading the titles and abstracts. A total of 27 potentially eligible studies were further evaluated, and 18 studies were excluded due to the following reasons: Other topics (*n* =

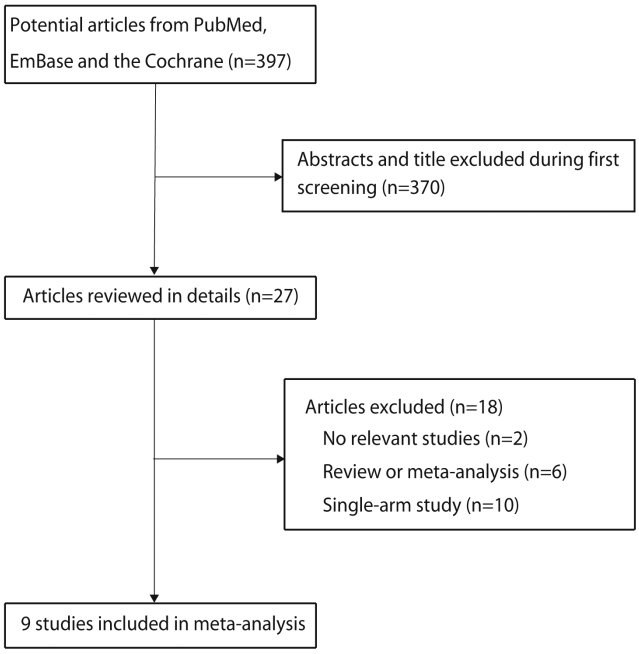

Figure 1. Flow diagram of the literature search and study selection process.

2), review or meta-analysis design (n = 6), and single-arm study (n = 10). Finally, 9 studies were selected for the final meta-analysis.[32-40] The results of manual searches from reference lists did not yield additional studies. The flow diagram of the study selection process is presented in Figure 1.

Study Characteristics

Of the 9 included studies (involving a total of 424 patients with liver cirrhosis), 5 were randomized controlled trials, and the remaining 4 studies with observational design. Table 1 summarizes the baseline characteristics of the included studies. Overall, the studies were published between 2008 and 2016, and 12-158 patients were included in each study. The mean age of included patients ranged from 39.4 to 55.0 years, and the percentage of males ranged from 52.0 to 94.3%. Three of the included studies were conducted in China, 2 in Egypt, 1 in Switzerland, 1 in Iran, 1 in Austria, and 1 in South Korea. Seven studies were on BMDSC transfusion into the hepatic artery, 1 study on intrasplenic or intrahepatic transfusion of BMDSC, and the remaining study on BMDSC transfusion into a cubital vein. Of a total of 5 of the included studies with randomized controlled design and the quality assessment using the Jadad scale, 2 trials scored 4, 2 trials scored 3, and the remaining trial scored 2. Furthermore, out of 4 of the included studies with observational design and the quality assessment using NOS, 1 study had a score of 7, 2 studies had a score of 6, and the remaining study had a score of 5.

Model for End-stage Liver Disease

Data for the MELD level within 3 months and after 6 months in patients who received BMDSC were available in 4 and 5 studies, respectively. We noted that patients who received BMDSC were associated with lower MELD level within 3 months (WMD: −2.11; 95% CI: −3.72 to −0.50; P = .010; Figure 2), while this significant difference was tapered to no significant difference after 6 months (WMD: −1.64; 95% CI: −3.44-0.16; P = .074; Figure 2). There was moderate heterogeneity in MELD within 3 months (I^2 = 42.0%; P = .160), and significant heterogeneity for MELD after 6 months (I^2 = 60.7%; P = .038). The results of sensitivity analyses suggested the pooled MELD within 3 months and after 6 months were variable, after sequentially excluding individual studies (Supplemental 1).

Alanine Amino Transferase

Data for the ALT level within 3 months and after 6 months in patients who received BMDSC were available in 3 and 3 studies respectively. There were no significant differences between BMDSC and standard therapy for the outcomes of ALT within 3 months (WMD: −6.37; 95% CI: −19.34-6.60; P = .336; Figure 3) and after 6 months (WMD: 6.67; 95% CI: −8.20-21.54; P = .379; Figure 3). Further, we noted significant heterogeneity among included studies for ALT within 3 months (I^2 = 58.2%; P = .091) and after 6 months (I^2 = 58.6%; P = .089). Sensitivity analyses for ALT within 3 months and after 6 months were conducted, while the conclusion was not altered by sequentially excluding individual studies (Supplemental 1).

Albumin

Data for the albumin level within 3 months and after 6 months in patients who received BMDSC were available in 5 and 4 studies respectively. We noted that BMDSC were not associated with albumin within 3 months (WMD: 1.25; 95% CI: −0.65 to 3.16; P = .196; Figure 4) and after 6 months (WMD: 0.34; 95% CI: −2.99 to 3.67; P = .840; Figure 4), as compared with standard therapy. Substantial heterogeneity across studies for albumin within 3 months (I^2 = 94.0%; P < .001) and after 6 months (I^2 = 79.9%; P = .002) were observed. Sensitivity analyses indicated that patients who received BMDSC were associated with increased albumin levels within 3 months (WMD: 2.31; 95% CI: 0.35-4.26; P = .021) and after 6 months (WMD:

Table 1. Baseline Characteristics of Studies Included in This Meta-Analysis

Study	Year of Publication	Country	Sample Size	Mean Age (years)	Male (%)	The Route of Transfusion	Intervention	Frequency of Stem Cell Transfusions	NOS* or Jadad Score
Peng[32]	2011	Guangzhou, China	158	42.2	94.3	Hepatic artery	MSCs from iliac crest	Once	7*
Amer[33]	2011	Cairo, Egypt	40	50.5	82.5	Intrasplenic or intrahepatic	Cultured bone marrow-derived MSCs stimulated to hepatic lineage using HGF-containing medium	Once	6*
El-Ansary[34]	2012	Cairo, Egypt	25	49.4	76.0	Hepatocytes	Undifferentiated or differentiated MSCs	Once	6*
Han[35]	2008	Xi'an, China	40	44.7	77.5	Hepatic artery	BM-derived peripheral blood monocytes from stem cells	Once	2
Spahr[36]	2013	Geneva, Switzerland	58	55.0	75.9	Hepatic artery	Autologous Transplantation of BM stem cells	Once	4
Mohamadnejad[37]	2013	Tehran, Iran	25	39.4	52.0	Cubital vein	Autologous transplantation of BM-MSC infusion	Once	3
Liao[38]	2013	Guangzhou, China	12	48.8	75.0	Hepatic artery	Autologous bone marrow-derived liver stem cell infusion	Once	5*
Lyra[39]	2010	Graz, Austria	30	53.4	NA	Hepatic artery	Autologous transplantation of BM stem cells	Once	4
Suk[40]	2016	South Korea	36	53.4	88.9	Hepatic artery	Autologous transplantation of BM-MSC infusion	Once	3

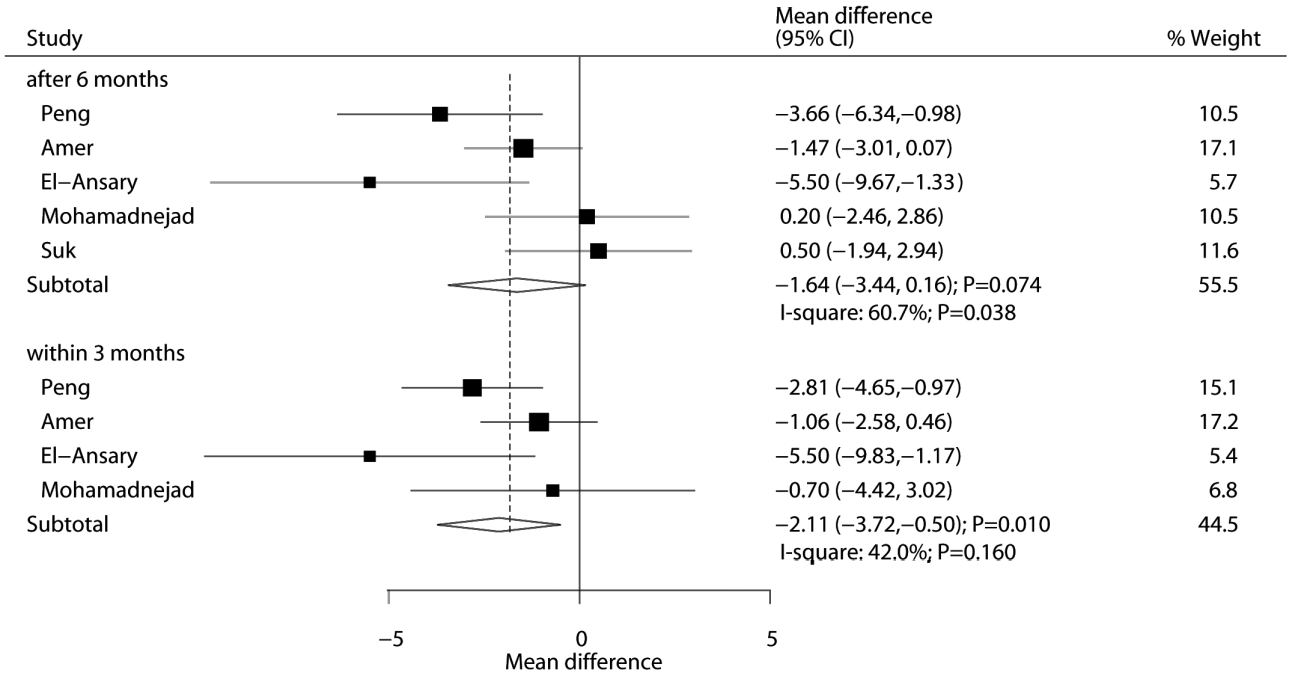

Figure 2. Effect of BMDSC on MELD within 3 months and after 6 months.

2.70; 95% CI: 1.57-3.83; $P < .001$), when excluding the study conducted by Mohamadnejad et al.,[37] as this study specifically focused on BMDSC transfusion into the cubital vein (Supplemental 1).

Total Bilirubin

Data for the TBIL within 3 months and after 6 months in patients who received BMDSC were available in 3 and 3 studies respectively. The summary results indicated that

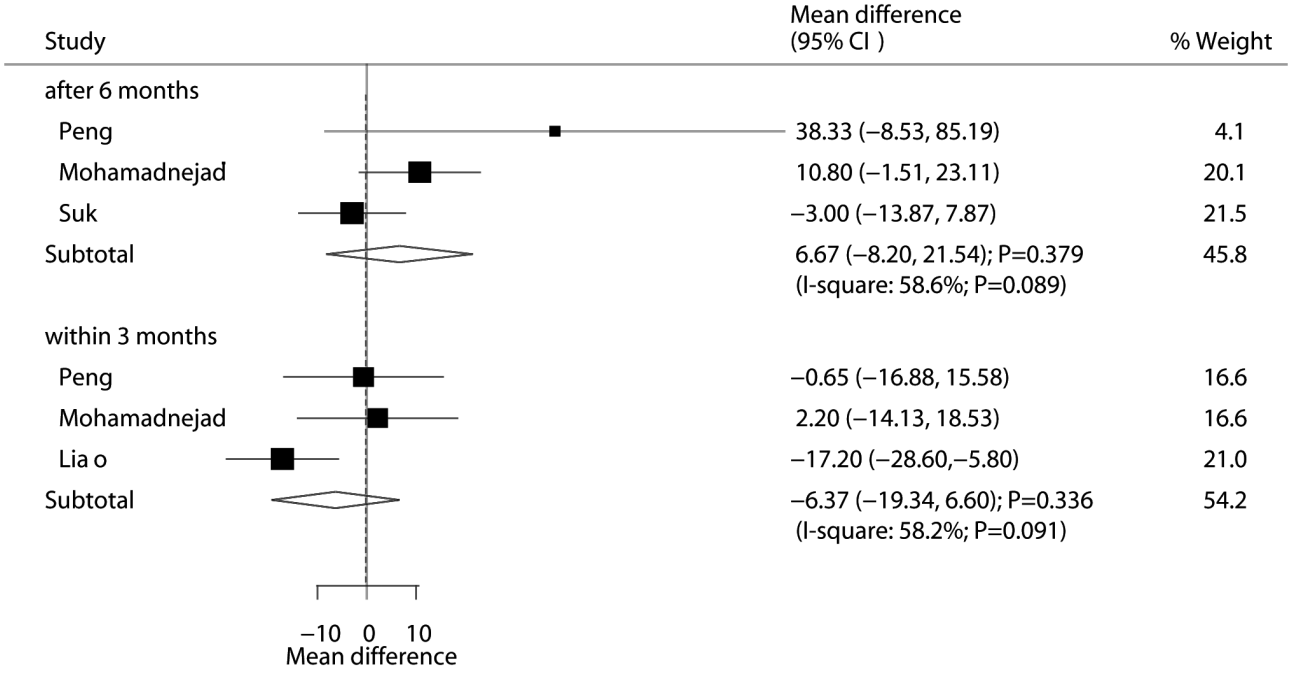

Figure 3. Effect of BMDSC on ALT within 3 months and after 6 months.

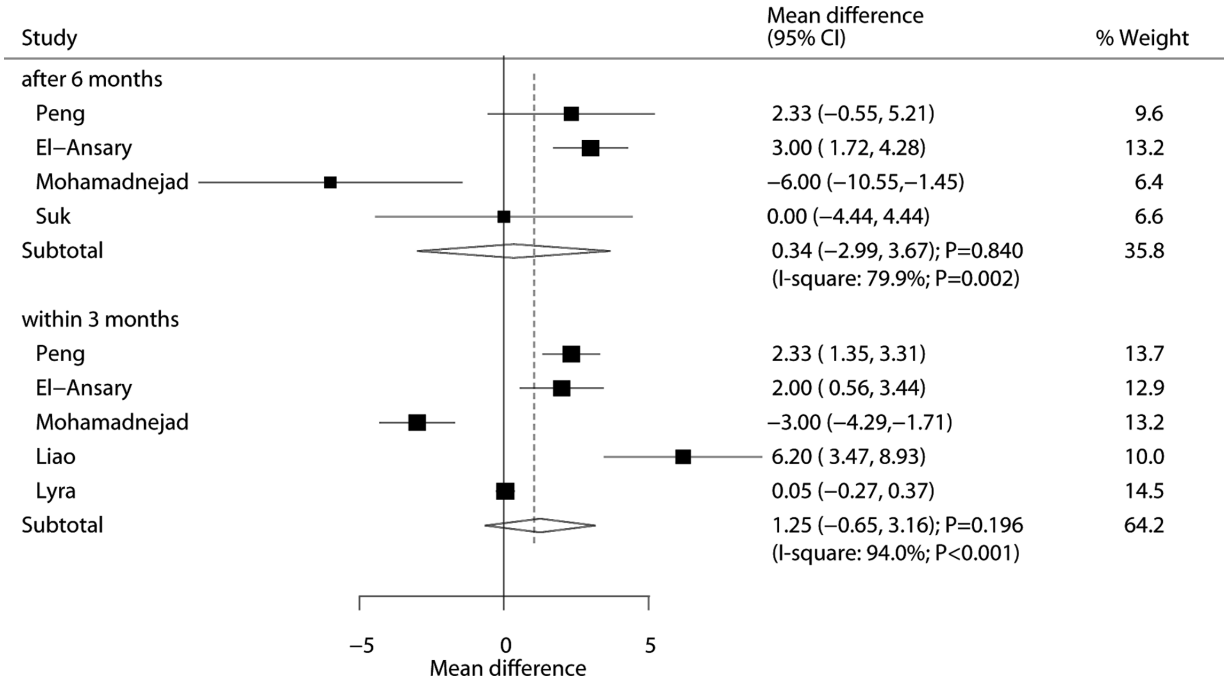

Figure 4. Effect of BMDSC on albumin within 3 months and after 6 months.

BMDSC was associated with lower TBIL within 3 months (WMD: −26.23; 95% CI: −50.84 to −1.61; *P* = .037; Figure 5), while it has no significant effect on TBIL after 6 months (WMD: −1.43; 95% CI: −27.22 to 26.36; *P* = .914; Figure 5). The results of sensitivity analyses indicated that TBIL within 3 months was variable, while TBIL after 6 months was persistent as no significant difference was seen between BMDSC and standard therapy (Supplemental 1).

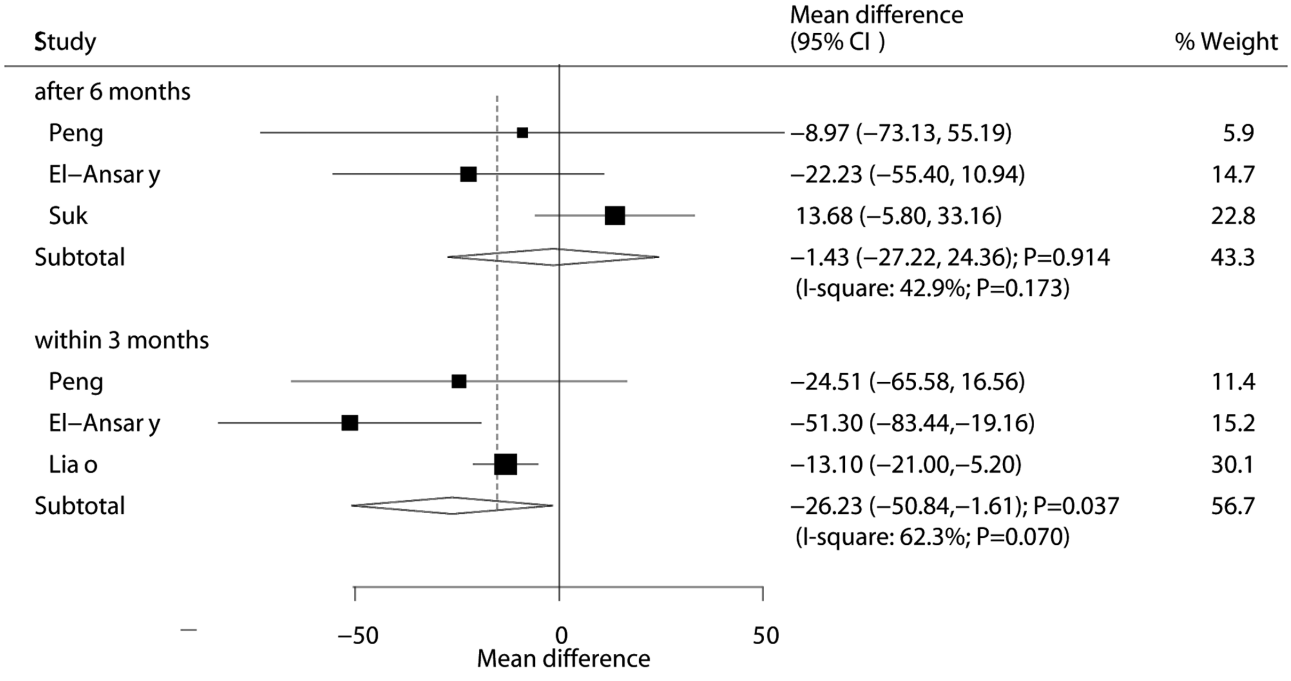

Figure 5. Effect of BMDSC on TBIL within 3 months and after 6 months.

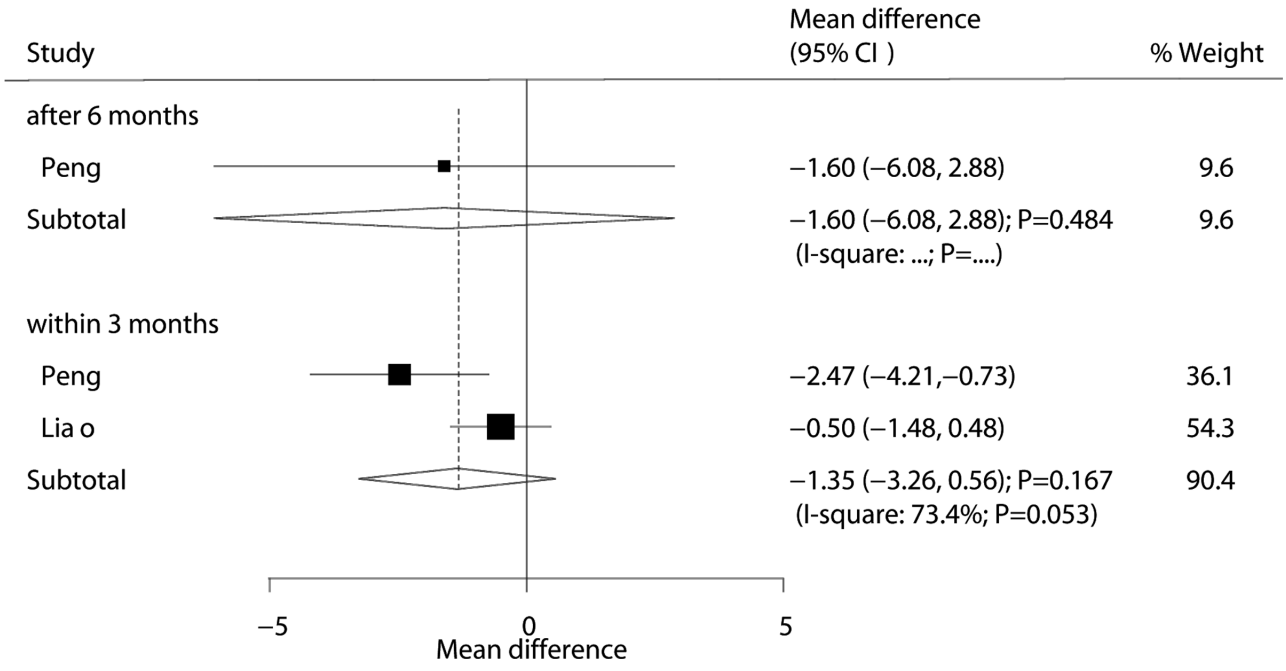

Figure 6. Effect of BMDSC on PT within 3 months and after 6 months.

Prothrombin Time

Data for the PT within 3 months and after 6 months in patients received BMDSC were available in 2 and 1 study respectively. There were no significant differences between BMDSC and standard therapy for the outcomes of PT within 3 months (WMD: −1.35; 95% CI: −3.26 to 0.56; *P* = .167; Figure 6) and after 6 months (WMD: −1.60; 95% CI: −6.08 to 2.88; *P* = .484; Figure 6). Although significant heterogeneity was observed for PT within 3 months, the sensitivity analysis was not conducted because only 2 studies reported this result.

Child–Pugh Score

Data for the Child–Pugh score within 3 months and after 6 months in patients who received BMDSC were available in 2 and 3 studies respectively. The summary results indicated no significant differences between BMDSC and standard therapy for Child–Pugh scores within 3 months (WMD: −0.88; 95% CI: −2.69 to 0.93; *P* = .342; Figure 7) and after 6 months (WMD: −0.45; 95% CI: −1.04 to 0.14; *P* = .133; Figure 7). Significant heterogeneity across the included studies was observed for Child–Pugh scores within 3 months, and mild heterogeneity for Child–Pugh scores after 6 months. As for PT, the results of sensitivity analyses for Child–Pugh scores were not conducted.

All-cause Mortality

A total of 5 studies reported an association between BMDSC and all-cause mortality. The summary of results did not indicate that BMDSC was associated with the risk of all-cause mortality when compared with standard therapy (OR: 0.86; 95% CI: 0.47-1.57; *P* = .622; with no evidence of heterogeneity; Figure 8). The conclusion was not changed by the sequential exclusion of individual studies (Supplemental 1).

Publication Bias

The funnel plots for MELD within 3 months and after 6 months are shown in Figure 9. Further, the Egger and Begg test results suggested no significant publication biases for MELD within 3 months (*P* value for Egger: .526; *P* value for Begg: .308) and after 6 months (*P* value for Egger: .542; *P* value for Begg: .221).

DISCUSSION

This meta-analysis was based on published two-arm studies and evaluated the efficacy and safety of BMDSC for patients with liver cirrhosis. This comprehensive, quantitative meta-analysis included 424 liver cirrhosis patients from 5 randomized controlled trials and 4 observational studies. Our results indicated that BMDSC could significantly affect MELD and TBIL levels within 3 months. Furthermore, the sensitivity analysis suggested that BMDSC might play an important role on the outcomes of MELD after 6 months, and on albumin levels within 3 months or after 6 months. While the result indicated BMDSC was not associated with the risk of all-cause

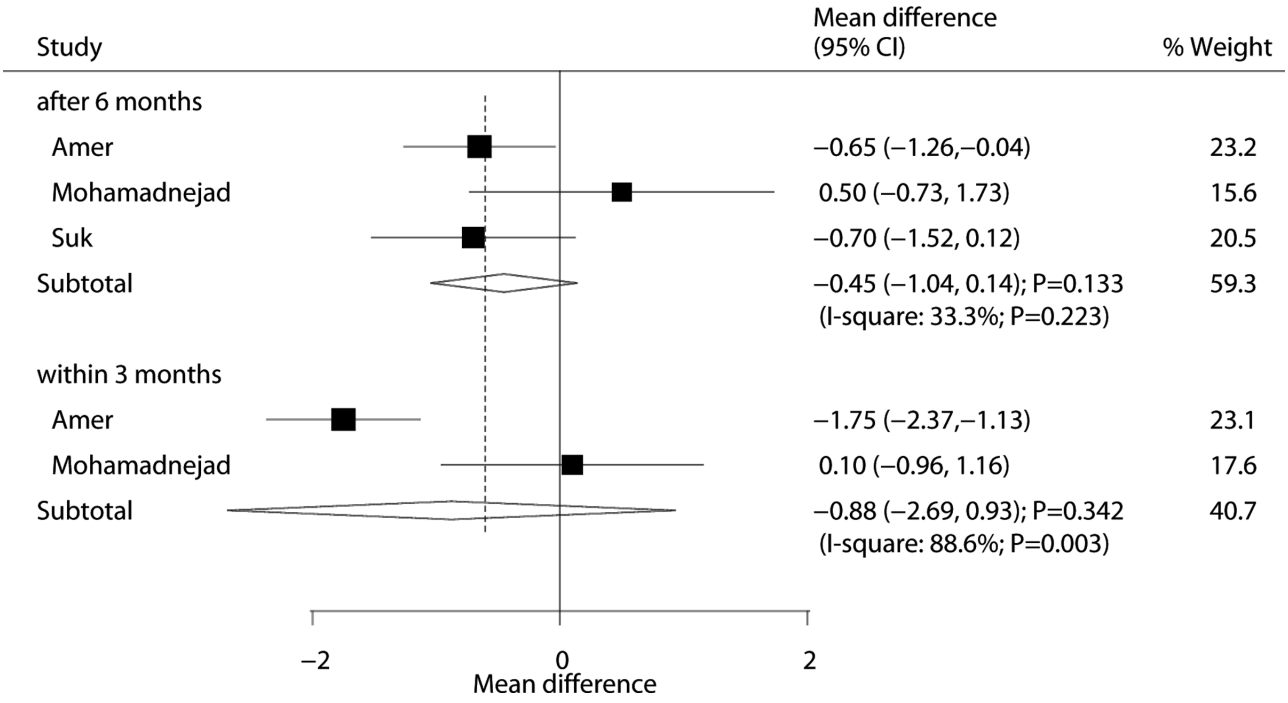

Figure 7. Effect of BMDSC on the Child–Pugh score within 3 months and after 6 months.

mortality when compared with standard therapy. The sequential exclusion of individual studies also supported this conclusion about BMDSC on all-cause mortality.

A previous systematic review and meta-analysis of 31 studies was conducted to evaluate the clinical outcome of transplantation of stem cells from various human tissue sources in patients with liver cirrhosis.[41] It indicated that stem cell therapy was associated with the improvement of liver function, without severe complications. However, the benefit of stem cell therapy was not significant in improving the liver function and survival. Another important quantitative meta-analysis based on 5 studies was performed to explore the efficacy and safety of BMDSC for patients with uncompensated liver cirrhosis, and found that BMDSC could improve liver function, and no serious complications were seen after 1 year.[42] However, this study combined single-arm and two-arm studies and

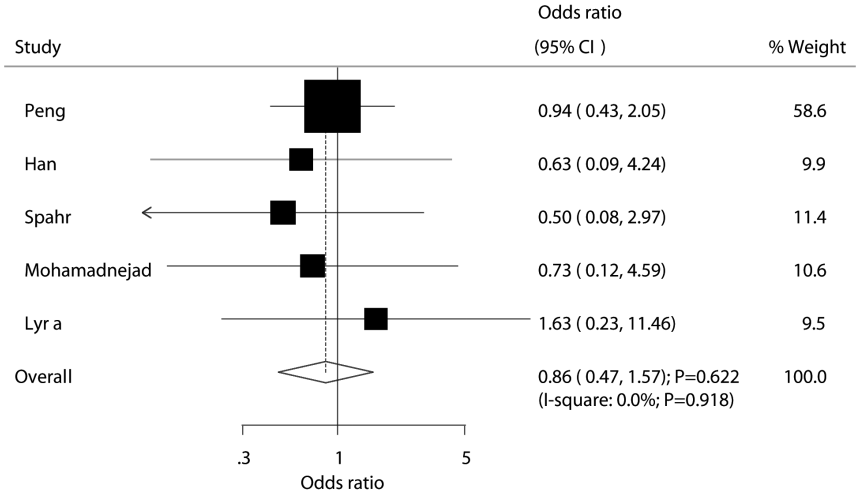

Figure 8. Effect of BMDSC on the risk of all-cause mortality.

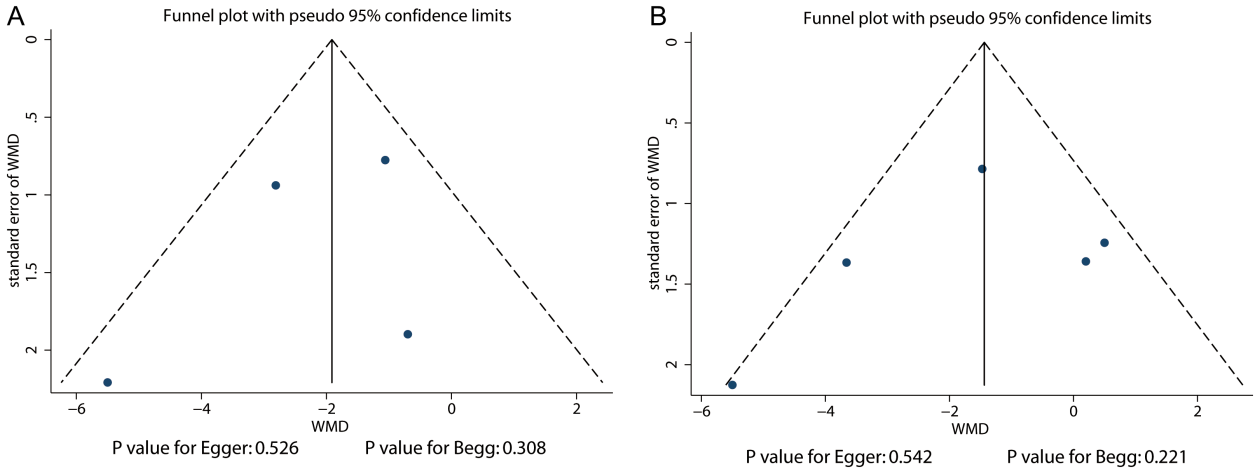

Figure 9. Funnel plots for MELD within 3 months and after 6 months.

different characteristics in the control group which might lead to uncontrolled biases. Furthermore, several other important studies were not included in this quantitative meta-analysis. Therefore, we performed this updated meta-analysis to systematically illustrate the efficacy and safety of BMDSC for patients with liver cirrhosis.

The current study suggested that BMDSC was associated with lower MELD within 3 months after BMDSC therapy, while this influence was less at 6 months after BMDSC therapy. However, the result of MELD after 6 months was associated with statistically significant results when excluding the study conducted by Mohamadnejad et al.[37] or Suk et al.[40] The study conducted by Mohamadnejad et al., on patients who received MSC or placebo infusions into the cubital vein and the ability of liver tissue regeneration, might be smaller than expected.[37] Further, Suk et al. found that autologous BMDSC transplantation could improve histologic fibrosis and liver function, while after 6 months, patients who received BMDSC did not show any treatment effect on MELD.[40] The reason for this could be that this study included patients with relatively low MELD, while several other studies included patients with more severe conditions.[4,33,43] Therefore, BMDSC might be more effective in patients with severe liver cirrhosis.

The summary results indicated that BMDSC could not affect ALT, albumin, PT, and Child–Pugh scores, regardless of follow-up duration. Further, we found that BMDSC was associated with a lower TBIL level within 3 months, while it could not affect the TBIL level after 6 months. However, sensitivity analyses indicated that patients who received BMDSC might show an increase in albumin levels within 3 months or after 6 months. These results were altered after excluding the study conducted by Mohamadnejad et al.[34] They point out this study mostly included patients with mild to moderate uncompensated cirrhosis, and serum indexes might widely fluctuate over time, which could have been affected by plasma volume expansion and in who patients received other drugs.[44] To date, other than stem cells, macrophage infusion also showed a reduction in MELD score in most of the liver cirrhosis patients without severe complications.[45]

Our results indicated although there was a modest effect in all-cause mortality, this did not reach statistical significance. The reason for this could be that the follow-up duration was shorter than what was needed to show a clinical benefit, and the event rates were lower than we expected in most trials. This situation always caused broad CIs, that is, no statistically significant difference. Therefore, further large-scale prospective randomized controlled trials should be conducted to evaluate the long-term treatment effects of BMDSC for liver cirrhosis.

Several limitations of this meta-analysis should be acknowledged: (1) Our study combined randomized controlled trials and observational studies, which might induce uncontrolled biases and acquired overestimate results. (2) A smaller number of studies were included for the reported outcomes, due to which more detailed stratified analyses were not conducted. (3) The route of transfusion was the hepatic artery, reported in 8/9 studies, and the results of therapeutic effects stratified by the route of transfusion are consistent with sensitivity analyses. These results need further prospective study to be verified. (4) This study was based on published studies, and unpublished data were not available, which might

cause publication bias. (5) The current study was based on pooled data, and more a detailed analysis was not performed because individual data were not available.

In conclusion, patients who received BMDSC could show improved short-term MELD and TBIL as compared with standard therapy. Further, it might play an important role on MELD after 6 months, and on albumin, regardless of follow-up duration. And, we also found there was a modest effect in all-cause mortality, while this did not reach statistical significance. Future large-scale prospective studies should be conducted to verify the long-term effects of BMDSC for patients with cirrhosis. Furthermore, we can pay attention to the other kinds of cell therapies for liver cirrhosis, like macrophage therapy.

Ethics Committee Approval: The study was approved by the Ethical Committee in The Fifth Affiliated Hospital of Guangzhou Medical University(IRB:2018-001).

Informed Consent: Informed written consent was obtained from all enrolled patients prior to their participation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.O., L.O., L.B.; Design – S.O., L.O., Y.L.; Supervision – S.O., L.O.; Resources – S.O., Y.Y.; Materials – S.O., L.B.; Date Collection and/or Processing – S.O., Y.L.;Analysis and/or Interpretation – S.O., L.O.; Literature Search – S.O., Y.Y.; Manuscript Writing – S.O., L.B.; Critical Review – S.O., L.B.

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Conflict of Interest: The authors have no conflict interest to declare.

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