

## Bone marrow-derived mesenchymal stem cell therapy for decompensated liver cirrhosis: A meta-analysis

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### Abstract

**AIM:** To assess the efficacy and safety of bone marrow-derived mesenchymal stem cell (BM-MSC) in the treatment of decompensated liver cirrhosis.

**METHODS:** The search terms "bone marrow stem cell" "chronic liver disease" "transfusion" and "injection" were used in the Cochrane Library, Med-Line (Pub-Med) and Embase without any limitations with respect to publication date or language. Journals were also hand-searched and experts in the field were contacted. The studies which used BM-MSC in the treatment of any chronic liver disease were included. Comprehensive Review Manager and Meta-Analyst software were used for statistical analysis. Publication bias was evaluated using Begg's test.

**RESULTS:** Out of 78 studies identified, five studies were included in the final analysis. The studies were conducted in China, Iran, Egypt and Brazil. Analysis of pooled data of two controlled studies by Review Manager showed that the mean decline in scores for the model for end-stage liver disease (MELD) was -1.23 [95%CI: -2.45(-0.01)], -1.87 [95%CI: -3.16(-0.58)],

-2.01 [95%CI: -3.35(-0.68)] at 2, 4 and 24 wk, respectively after transfusion. Meta-analysis of the 5 studies showed that the mean improvement in albumin levels was -0.28, 2.60, 5.28, 4.39 g/L at the end of 8, 16, 24, and 48 wk, respectively, after transfusion. MELD scores, alanine aminotransferase, total bilirubin levels and prothrombin times improved to some extent. BM-MSC injections resulted in no serious adverse events or complications.

**CONCLUSION:** BM-MSC infusion in the treatment of decompensated liver cirrhosis improved liver function. At the end of year 1, there were no serious side effects or complications.

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**Key words:** Decompensated liver cirrhosis; Bone marrow stem cell; Transfusion; Meta-analysis

**Core tip:** Out of 78 studies identified, five studies were included in the final analysis, which showed that the mean decline in scores for the model for end-stage liver disease was -1.23 [95%CI: -2.45(-0.01)], -1.87 [95%CI: -3.16(-0.58)], -2.01 [95%CI: -3.35(-0.68)] at 2, 4 and 24 wk, respectively. The mean improvement in albumin levels was -0.28, 2.60, 5.28, 4.39 g/L at the end of 8, 16, 24, and 48 wk, respectively. Alanine aminotransferase, total bilirubin levels and prothrombin times improved to some extent. Bone marrow-derived mesenchymal stem cell injections resulted in no serious adverse events or complications.

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## INTRODUCTION

Liver fibrosis is the main cause of morbidity in patients with chronic liver disease (CLD). The most common causes of CLD are hepatitis B virus (HBV), alcohol, hepatitis C virus (HCV), autoimmune liver disease and primary biliary cirrhosis (PBC). CLD frequently progresses to liver cirrhosis (LC)<sup>[1]</sup>. LC usually progresses irreversibly to a decompensated stage which is characterized by liver functional impairment and portal hypertension. Many patients die from one or more clinical complications of decompensated liver cirrhosis (DLC)<sup>[2]</sup>. Although DLC can be treated conventionally, liver transplantation is the only option that can improve the survival rate of these patients. However, because of the shortage of donor livers, high costs, and potential serious complications, the availability of liver transplantation is limited worldwide<sup>[3-5]</sup>. Therefore, alternative strategies are under intense investigation.

Mesenchymal stem cells (MSC) originate from the many mesenchymal and connective tissues and have the potential to differentiate into various lineages<sup>[6,7]</sup>. Petersen *et al*<sup>[8]</sup> suggested that bone marrow can differentiate into mature hepatocytes. Furthermore, bone-marrow stem cells are thought to contribute to liver regeneration<sup>[9-11]</sup>, and this aspect has been studied in the treatment of some liver diseases<sup>[12,13]</sup>. However, the effectiveness of bone marrow-MSC (BM-MSC) in the treatment of DLC has been inconclusive. Some studies on animal models have shown that BM-MSC infusions ameliorated liver fibrosis, and reversed fulminant hepatic failure<sup>[14-17]</sup>. Clinical trials have shown that BM-MSC transfusion can quickly improve liver function without significant side effects<sup>[18-22]</sup>. Use of BM-MSCs decreased ascites and fatigue as well as improving survival rates<sup>[18]</sup>. Some studies have suggested that BM-MSCs improved cases of liver fibrosis and hepatocellular carcinoma<sup>[23]</sup>. In contrast, other studies have reported that treatment using BM-MSC did not improve liver function or survival, and even aggravated liver fibrosis<sup>[24]</sup>. The aim of the current study was to determine the efficacy and safety of BM-MSC in the treatment of DLC by meta-analysis.

## MATERIALS AND METHODS

### Literature search

We searched the Cochrane Library, Pub-Med and EMBASE for BM-MSC infusions in the treatment of CLD using key words, “bone marrow stem cell”, “chronic liver disease”, “liver cirrhosis”, “transfusion”, and “injection”. No language limitation was imposed. Major journals were hand-searched and experts in this field were contacted to identify potentially eligible clinical studies, published, and unpublished.

### Inclusion and exclusion criteria

Adults between the ages of 18 and 74 years were enrolled with advanced CLD of various etiologies. These included

chronic hepatic failure, evidence of ultrasonographic cirrhosis and portal hypertension with abnormal serum albumin (ALB) and/or total bilirubin (TBIL) levels and/or prothrombin times (PT), model for end-stage liver disease (MELD) scores less than 25, and platelet counts  $\geq 30000/\text{mm}^3$ . Exclusion criteria were the presence of liver tumors, human immunodeficiency virus infection, kidney or heart failure, portal vein thrombosis, and pregnancy or lactation.

### Data collection

In order to avoid systematic error in this meta-analysis, two reviewers, Zheng LQ and Pan XN, independently assessed all the studies to ensure conformity in the application of the inclusion and exclusion criteria. Disagreements were resolved by discussion with a third author until a consensus was reached.

### Statistical analysis

The data were analyzed using Meta-Analyst (version 3.13 Beta), and Review Manager (version 5.1) software was used to extract and pool data for summary estimates. Results for continuous outcomes were expressed as weighted mean differences and variances by using Review Manager. The data of mean differences before and after treatment were calculated by Forest plot by using meta-analysis in one arm. Statistical heterogeneity of the results was evaluated using Cochrane  $Q$ -test and the  $I^2$  statistic with significance set at  $P < 0.10$ . We used a fixed-effect model for non-heterogeneous data using 95% CIs. For data with significant heterogeneity, a random-effects statistical model was used. Publication bias was assessed using the Begg-test.

## RESULTS

We identified 78 potentially eligible studies and excluded 73 studies for the following reasons: they were either animal studies, review articles, meeting reports, or there was a lack of proper data. Finally, 5 appropriate studies, including a total of 80 patients were selected for analysis (Figure 1). The characteristics of the 5 studies are shown in Table 1. These studies were published between 2007 and 2011, and used injections of between  $10^6$  to  $10^8$  cells in the treatment groups. The studies were from four countries (China, Iran, Egypt, and Brazil). In a study by Peng *et al*<sup>[19]</sup>, reduced glutathione, glycyrrhizin, ademetonine, polyene phosphatidylcholine, alprostadil, and human serum albumin were administered to both the BM-MSC and the control group<sup>[18]</sup>. None of the other trials used this extra treatment.

### Efficacy of BM-MSC in the treatment of chronic liver disease

Long-term follow-up studies were performed by Peng *et al*<sup>[19]</sup> in which 6 cases of end-stage liver disease were reported. After injection of BM-MSC, the liver function improved significantly. The minimum MELD score oc-

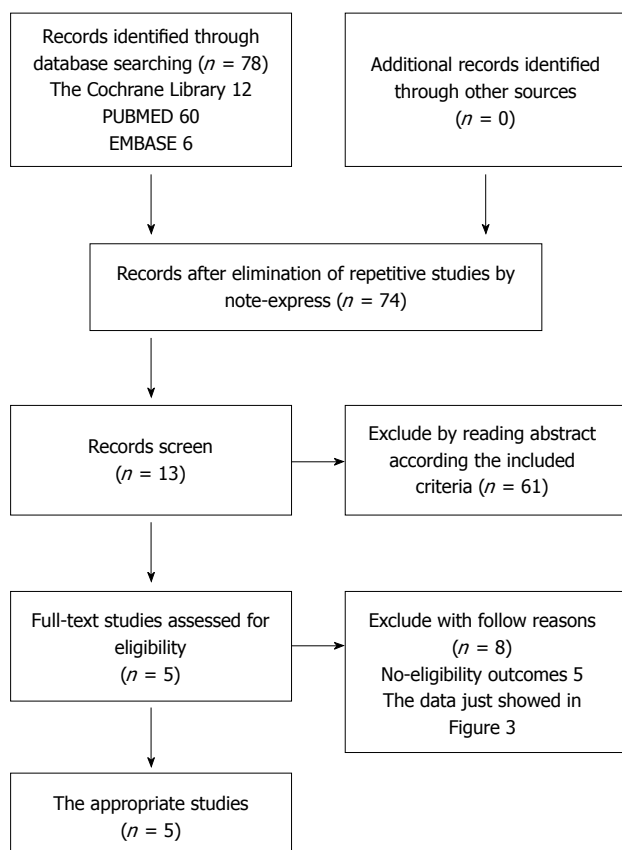


Figure 1 Flow chart indicating the selection process for this meta analysis.

occurred at 6 mo, and minimum PT occurred at 3-mo after infusion. Values increased slowly thereafter. The maximum decline in TBIL levels occurred at 3 mo while the peak ALB level occurred at 1 mo post-infusion. However, the TBIL levels were maintained at low levels during the follow-up period. The ALB levels remained at about 7 g/L higher than baseline after 1 year of follow-up (Figures 1 and 2). After 36 wk, there were no significant differences compared with the control group ( $P = 0.132$ )<sup>[19]</sup>.

We found 2 control trials<sup>[18,19]</sup> (61 participants) which reported declines of MELD scores. There was no heterogeneity at the 2 and 24 wk time points among the studies included, using the fixed-effects model [total of mean difference was 1.68, 95%CI: -2.42-(-0.94),  $P < 0.001$ ]. The outcomes of the subgroup at 2, 4 and 24 wk were -1.23 [95%CI: -2.45-(-0.01),  $P = 0.05$ ], -1.87 [95%CI: -3.16-(-0.58),  $P = 0.005$ ], -2.01 [95%CI: -3.35-(-0.68),  $P = 0.003$ ], respectively. As time progressed, the magnitude of the mean differences became more obvious as shown in Figure 3.

Five studies<sup>[18-22]</sup> reported changes in levels of alanine aminotransferase (ALT), TBIL, ALB, PT-value and MELD scores. We extracted and pooled differences in the means before and after BM-MSC infusions in treatment group using Meta Analyst software (one arm). According to the heterogeneity evaluation, there was significant heterogeneity between these studies (Table 2). Therefore, a random effects model was used. The trend

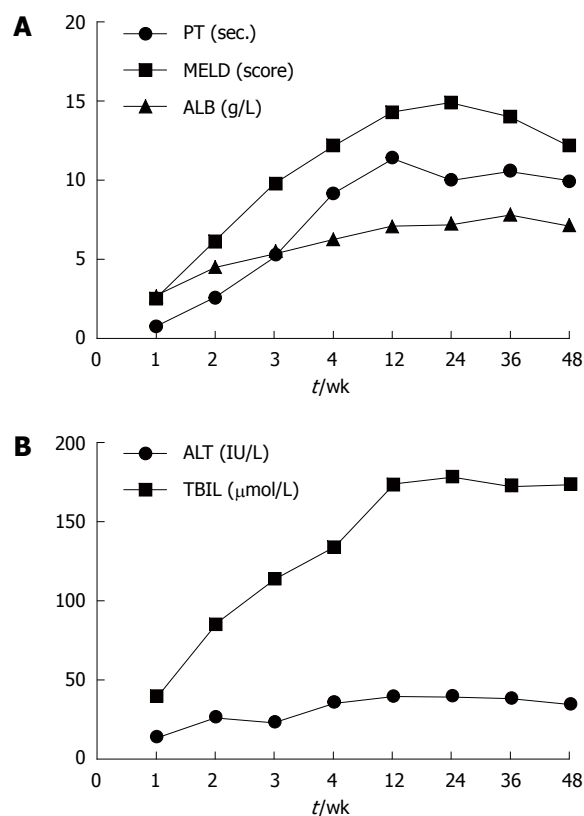


Figure 2 Mean relative changes from baseline of liver function and model for end-stage liver disease scores during 48 wk follow-up. A: The change-trend of model for end-stage liver disease (MELD) scores, and prothrombin times (PT) and abnormal serum albumin (ALB) levels; B: The change-trend of alanine aminotransferase (ALT) and total bilirubin (TBIL) levels (Data were from Peng *et al*<sup>[19]</sup>).

in ALB levels gradually increased after 8 wk, which was significantly better than before transfusion. After BM-MSC treatment, levels of ALT and TBIL increased while PT and MELD scores decreased during 1 year follow-up. The results are shown in Table 2. None of the studies described the changes in liver histology before and after the transfusion.

#### Other evidence of the efficacy of the BM-MSC infusions

A control trial reported by Amer *et al*<sup>[18]</sup> in which 40 HCV patients were treated with BM-MSC or control revealed that fatigue scores were significantly lower, and the performance status significantly better in the BM-MSC group than the control group (Figure 4). The amount of ascites in the treatment group was less than that in the control group at 2 wk ( $\chi^2 = 0.01$ ,  $P = 0.00-0.04$ ), but this was not maintained beyond 6 mo ( $\chi^2 = 1.03$ ,  $P = 0.311$ ). Other studies<sup>[20,25]</sup> demonstrated that after injecting BM-MSC, the liver volume increased compared to that before treatment.

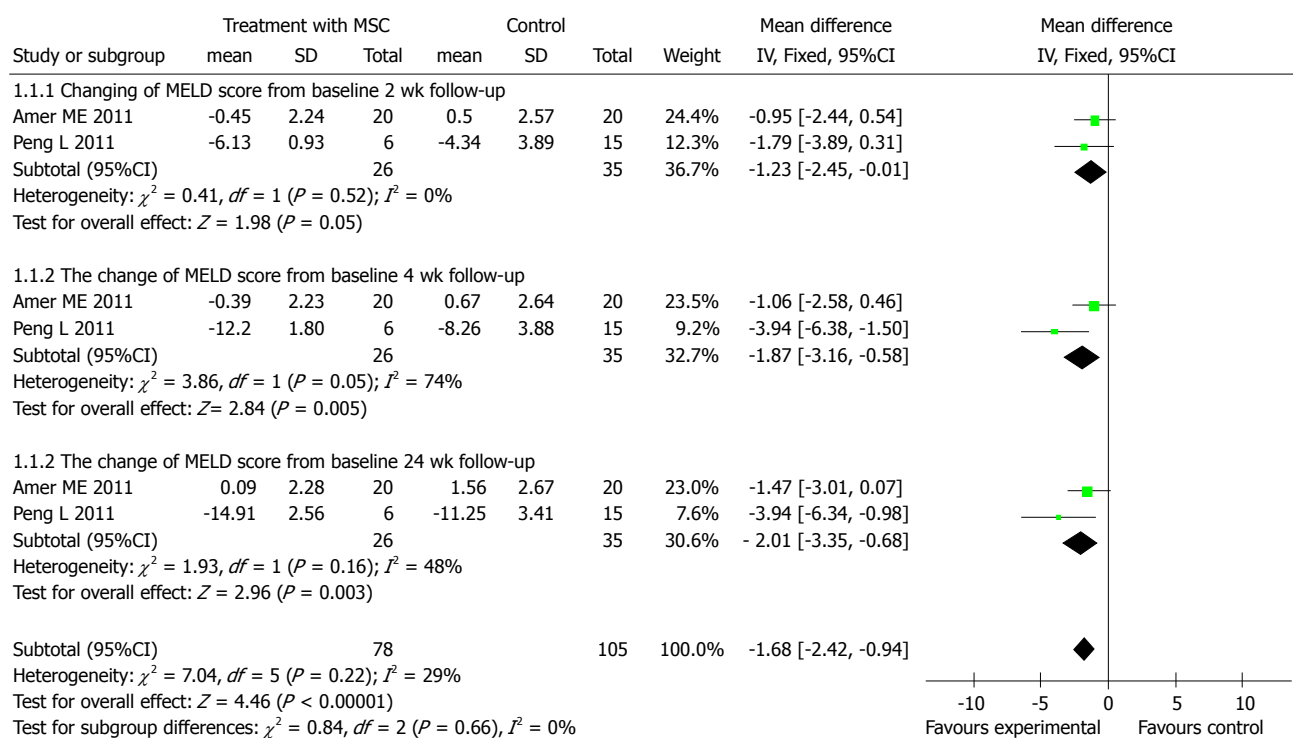
#### Side effects

There were no significance adverse effects after the infusions. Peng *et al*<sup>[19]</sup> reported that in 53 cases there were no serious side effects or complications observed in

**Table 1 Characteristics of the included studies**

Ref.	Year	Country	Assessment of purity	Type of infused cells and volume	Infused cells (n)	Patients and disease etiology (n)	Frequency of stem cell transfusions	The route of transfusion
Peng <i>et al</i> <sup>[19]</sup>	2011	China	Flow cytometry	BMNCs (MSCs) from iliac crest (120 mL)	NA	6 HBV + 15ctrl. after 48 wk follow-up	Once	Hepatic artery
Mohamadnejad <i>et al</i> <sup>[20]</sup>	2007	Iran	Fluorescence-assisted cell sorting flowcytometry	Cultured bone marrow-derived MSCs (80-100 mL)	31.7 × 10 <sup>6</sup> (mean)	3 Cryptogenic, 1 AIH	Once	Cubital vein of the arm over 30 min
Mohamadnejad <i>et al</i> <sup>[21]</sup>	2007	Iran	FACS Calibur flow cytometer	Bone marrow-derived CD34+ Cells from iliac crest (200 mL)	5.25 × 10 <sup>6</sup> (mean)	1 HBV, 1 PBC, 1 AIH <sup>1</sup> , 1 cryptogenic	Once	Hepatic artery
Amer <i>et al</i> <sup>[18]</sup>	2010	Egypt	Immunophenotyping	Cultured bone-marrow derived MSCs stimulated to hepatic lineage using HGF-containing medium (95 ± 25 mL)	2 × 10 <sup>8</sup>	20 HCV + 20 ctrl	Once	Intrasplenic or intrahepatic
Lyra <i>et al</i> <sup>[22]</sup>	2007	Brazil	NA	BMNCs (MSCs) from iliac crest (maximum 50 mL)	1 × 10 <sup>8</sup>	10 NA	Once	Hepatic artery

<sup>1</sup>This patient developed progressive renal failure, and went on to develop type 1 hepatorenal syndrome and died of liver failure. MSCs: Mesenchymal stem cells; FACS: Florescence-assisted cell sorting; NA: Not available; HBV: Hepatitis B virus; AIH: Autoimmune liver disease; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus.



**Figure 3 Forest plot of overall model for end-stage liver disease scores during follow up.**

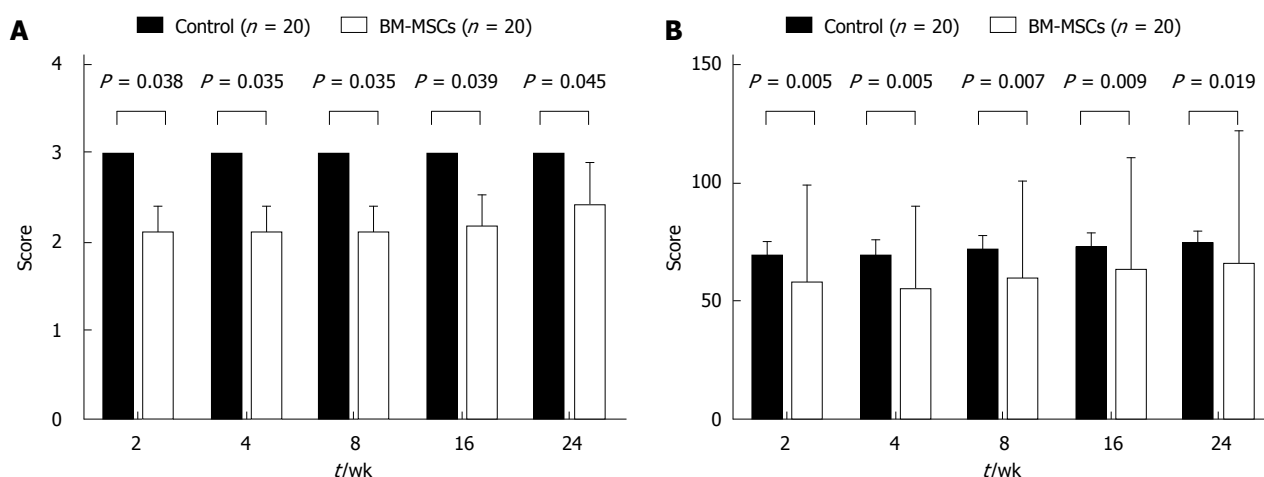
short- and long-term follow up. However, in the study by Mohamadnejad *et al*<sup>[20]</sup> which included 4 patients, one of them appeared to develop some degree of renal failure after 5 mo follow-up. Another patient developed progressive renal failure and died of liver failure. The authors speculate that radio-contrast nephropathy may have contributed to the acute renal failure in that case. Clinical studies by Lyra *et al*<sup>[22]</sup> in Brazil, which included 10 pa-

tients, reported that two patients experienced mild pain at the sites of bone marrow puncture, but no other complications or specific side effects related to the infusion. In a report by Amer *et al*<sup>[18]</sup> which included 40 patients, fever was observed within 24 h. This responded to antipyretic therapy. In summary, there were no significant side effects in the treatment of chronic liver disease using BM-MSCs.

**Table 2** Albumin, total bilirubin, prothrombin times, and model for end-stage liver disease values during follow-up

Time point	Studies (n)	Cases (n)	Type of model	I <sup>2</sup>	P value	Estimate	95%CI
Change from baseline of albumin levels (g/L)							
8 wk	2	9	RE	0.000	0.969	-0.28	-3.31-2.85
16 wk	2	13	RE	0.000	0.995	2.60	-0.35-5.56
24 wk	3	13	RE	0.413	0.185	5.28	1.81-8.75
48 wk	2	14	RE	0.831	0.015	4.39	-1.62-10.40
Change from baseline of ALT levels (IU/L)							
4 wk	2	16	RE	0.667	0.083	-16.33	-50.71-18.06
24 wk	3	13	RE	0.647	0.059	-7.04	-33.99-19.91
48 wk	2	10	RE	0.333	0.221	-18.18	-44.03-7.06
Change from baseline of TBIL levels							
4 wk	2	16	RE	0.948	0.000	-69.34	-191.12-53.45
24 wk	3	13	RE	0.945	0.000	-47.21	-130.18-35.76
48 wk	2	10	RE	0.966	0.000	-86.17	-254.53-82.19
Change from baseline of PT values (s)							
24 wk	3	13	RE	0.843	0.002	-4.77	-9.22-0.33
48 wk	2	10	RE	0.931	0.000	-5.88	-13.42-1.65
Change from baseline MELD scores							
2 wk	2	26	RE	0.977	0.000	-3.27	-8.84-2.30
4 wk	2	26	RE	0.994	0.000	-6.28	-17.86-5.29
8 wk	2	23	RE	0.606	0.111	-1.43	-4.92-2.06
16 wk	2	23	RE	0.000	0.644	0.31	-0.67-1.30
24 wk	4	33	RE	0.982	0.000	-4.28	-13.39-4.83
48 wk	2	10	RE	0.948	0.000	-7.62	-16.86-1.63

PT: Prothrombin times; MELD: Model for end-stage liver disease; TBIL: Total bilirubin; ALT: Alanine aminotransferase; RE: Random effects.



**Figure 4** Comparison of changes in performance scale and fatigue scale at various times after transfusion of bone marrow-derived mesenchymal stem cells. A: Changes in performance scale; B: Changes in fatigue scale (Data were from Amer *et al*<sup>[18]</sup>). BM-MSCs: Bone marrow-derived mesenchymal stem cells.

## DISCUSSION

Peng *et al*<sup>[19]</sup> showed that improvements of liver function and MELD score were not maintained after 36 wk, and there were no significant differences in the incidence of HCC or survival rates between the two groups during 192 wk of follow-up. The animal studies of Zheng *et al*<sup>[15]</sup> showed that the number of human BM-MSCs which were injected into the liver by the intraportal route decreased significantly by week 15. However, 13 of 15 pigs achieved long-term survival in the intraportal transplantation group while all of the animals that received peripheral vein transplantations and the animals in the control group died within 96 h. Some recent studies considered

that these preliminary outcomes suggested that transient benefit was most likely to occur in persons with acute liver diseases.

A pilot randomized controlled study by Lyra *et al*<sup>[25]</sup> showed that MELD scores stabilized in the cell therapy group, but increased in the control group. Peng *et al*<sup>[19]</sup> showed that liver function and MELD scores gradually declined from 4 to 24 wk (Figure 2). Similarly, in the current studies, MELD scores declined from -1.23 to -2.01 during the first 24 wk, and were significantly different from those of the control group ( $P < 0.05$ ) (Figure 3). In one arm analysis, the MELD scores were also decreased at 4, 8, 24, and 48 wk, but were stable at 16 wk. This phenomenon may be due to renal failure at 16 wk in some



studies. Some trials reported that the improvement of liver function began at 1 wk, but was not maintained after 36 wk. In studies by Kharaziha *et al*<sup>[26]</sup> which included 8 patients, ALB and TBIL levels were improved and remained up to 24 wk. In the current studies, ALB increased after 8 wk, and remained stable during the 1 year follow-up. Since the half-life of ALB is about 21 d, the improvement observed in the first few weeks may have been due to an injection of blood product in some studies. As seen in previous studies, the levels of ALT and TBIL increased, while PT and MELD scores decreased after transplantation. These levels were maintained at low levels during the 1 year follow-up (Table 2). There were no serious side effects or complications.

There are some limitations to this meta-analysis. The population, purity, method of assessment, type of infused cells and volume of cells in the included studies were not consistent. For example, in the studies of Peng *et al*<sup>[19]</sup>, the BM-MSCs were isolated from the iliac crest, and grown to a density of  $1.0 \times 10^6$  cells/mL. Cells were detected by flow cytometry (FACScan; BD Biosciences) using mouse isotype immunoglobulin G1 as a control. Mohamadnejad *et al*<sup>[20]</sup> extracted about 80-100 mL bone marrow from the iliac crest, harvested and cultured MSCs at density at  $1.0 \times 10^6$  cells/cm<sup>2</sup>. Typical surface marker proteins were analyzed using fluorescence-assisted cell sorting (FACS) flow cytometry. In another study by Mohamadnejad *et al*<sup>[21]</sup>, a total of 200 mL of bone marrow was aspirated from four different sites of the iliac crest. The cells were counted and assessed for viability using trypan blue dye exclusion. Purity was determined using a FACS Calibur flow cytometer (Becton Dickinson, San Jose, CA, United States). In a study by Amer *et al*<sup>[18]</sup>, 120 ml of bone marrow was aspirated from three different sites in the iliac crest, and immunophenotyping was done on the mononuclear cell population using CD34, CD133, CD90, CD105, CD73, and CD44 markers. In a study by Lyra *et al*<sup>[22]</sup>, approximately 50 mL of bone marrow was aspirated from the iliac crest, centrifuged, and about  $10^8$  mononuclear- enriched BMC was suspended in 20 mL of saline. Assessing these methodologies, it appears possible that the LC preparations were not the same throughout the trials, and it is therefore likely that some variations in the infusions may have affected the results.

The methodology of the studies was generally poor. Due to ethical and other issues, we did not include many studies, and these studies included only two controlled trials, neither of which were randomized or blinded. This might have generated high performance bias and measurement bias. In the studies by Peng *et al*<sup>[19]</sup>, HBV load, genotype, and E antigen status for subjects and controls were not matched. In order to reduce the effect from baseline, we calculated the mean relative changes from baseline. Although this method can reduce some selection bias, it may also have affected the stability of the outcome. We did not perform the Begg's test for publication bias because there were less than 5 studies in each subgroup. Some included studies which did not men-

tion the application and effects of the antiviral and antifibrosis treatment that could have influenced the stability of the results.

The findings of this meta-analysis indicate that BM-MSCs may be beneficial in improving liver function in the treatment of LC. There were few symptoms and no serious side effects or complications after 1 year follow-up. BM-MSC therapy may potentially improve fibrosis and reduce ascites. However, this improvement was not maintained in long term follow-up analyses. Further studies using multicenter, randomized, prospective trials to control for the primary disease, number of transfusions, and routes of injection are needed to substantiate the findings of this meta-analysis.

## COMMENTS

### Background

Many patients die from one or more clinical complications of decompensated liver cirrhosis (DLC), and conventional treatment is limited worldwide. Mesenchymal stem cells (MSC) originate from the many mesenchymal and connective tissues that can differentiate into mature hepatocytes. However, the effectiveness of bone marrow (BM)-MSC in the treatment of DLC has been inconclusive.

### Research frontiers

After the research by Petersen suggested that bone marrow can differentiate into mature hepatocytes, many studies have been performed to demonstrate the safety and effectiveness of BM-MSC in the treatment of DLC. Moreover, several systematic reviews were also recently performed to investigate these results. However, these reviews were methodologically insufficient and thus could not achieve a comprehensive conclusion.

### Innovations and breakthroughs

Based on this meta-analysis, the mean decline in scores for the model for end-stage liver disease (MELD) was -1.23, -1.87 and -2.01 at 2, 4 and 24 wk, respectively, and the mean improvement in albumin levels was -0.28, 2.60, 5.28, 4.39 g/L at the end of 8, 16, 24, and 48 wk, respectively. BM-MSC injections resulted in no serious adverse events or complications. These findings were not presented clearly in previous systematic reviews.

### Applications

BM-MSCs can improve the liver function of DLC, and there were no serious side effects or complications. Base on these, BM-MSCs may become a new method of therapy for DLC.

### Terminology

Alanine aminotransferase is the indicator that reacted to liver inflammation. Flow cytometry is conducted for cell analysis and sorting automatically. It can quickly measure, store, display cells that are suspended in a liquid dispersion in a series of important characteristic parameters, and separate the cells from the liquid. Trypan blue dye exclusion is a way to detect survival rates of the cells.

### Peer review

The authors describe the role of transfusion of autologous bone marrow-derived mesenchymal stem cells in the treatment of decompensated cirrhosis based on meta-analysis. The issue presented is noteworthy and the result showed that BM-MSCs can improve the liver function and MELD scores during the first 1 year, with no serious side effect and complications. This paper is well-written and has interesting and important findings.

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