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Meta Analysis

Therapeutic efficacy and safety of mesenchymal stem cells transplantation for patients with liver failure: a systematic review and meta-analysis

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ABSTRACT

The aim was to pool the present clinical studies to assess the therapeutic efficacy and safety of mesenchymal stem cell transplantation (MSCT) compared with traditional supportive treatment (TST) for patients with liver failure. Publications were searched to identify relevant clinical trials in which LF patients accepted mesenchymal stem cell transplantation from the online databases of PUBMED, EMBASE, and Cochrane Library up to June 2020. Then, the short-term outcomes of 6 months, including models of end-stage liver disease (MELD) score, total bilirubin (TBIL), albumin (ALB), prothrombin activity (PTA), alanine aminotransferase (ALT), prothrombin time (PT) and cumulative survival rate were enrolled in a meta-analysis. In total, 446 patients, reported on 2 randomized controlled trials (RCTs) and 4 non-randomized trials, were included. Compared with TST, MSCT was associated with a faster decline of MELD score at 2-, 4-, 12- and 24-week, greater improvement of ALT levels at1-, 4-, 24-week, significant increase of ALB levels at 4-,12-week and remarkable raise of PTA levels at 12-, 24-week, while PT levels changed greatly at 4-week and TBIL levels observably decreased at 4-week. The cumulative survival rate of MSCT was shown significant difference at 12-week. There were no serious complications and HCC occurred after MSCT. This study suggests MSCT may be a more effective and safe strategy than TST to improve liver function parameters and alleviate liver damage in LF patients during the short-term duration of 6 months. However, more multi-center, large-scale RCTs are needed.

Keywords: Mesenchymal stem cells, MSCs, Liver failure

INTRODUCTION

Liver failure (LF) is a serious clinical syndrome with rapid progression, poor prognosis, and high mortality, leading to hepatocyte necrosis and severe liver dysfunction or decompensation of its synthesis, detoxification, excretion and biotransformation, which mainly occurs as coagulation disorder, jaundice, hepatic encephalopathy, ascites and other clinical symptoms.[1] In China, the most common etiology is hepatitis B or C virus infection, and the next is drug or hepatotoxic substances. The diagnosis of LF should be based on the medical history, clinical manifestations, histopathological features, and auxiliary inspection index, which is classified into four forms: acute liver failure (ALF), subacute liver failure (SALF), acute-on-chronic liver failure (ACLF) and chronic liver failure (CLF).[1-3] At present, ACLF and CLF are the most common types of LF, which usually accompany with a history of chronic liver disease or cirrhosis and a high mortality rate ranging up to 50%.[4]

Current therapeutic strategies of LF are mainly based on integrated therapy, including use of etiological therapy, general supportive therapy, artificial liver support therapy, and liver transplantation (LT).[5-8] However, internal therapy is a lack of specific medicine, and biological artificial liver exists with some problems due to difficulties of obtaining hepatocytes and rejection. LT is recognized as the final solution for LF. In China, the survival rate after LT for end-stage liver disease has approximated 80% at one year, but the low donors, high cost, immunological rejection, and complications restrict its application.[9,10] Therefore, a novel effective and safe therapeutic strategy as an alternative to orthotopic liver transplantation for LF is urgently required.

Recently, mesenchymal stem cell transplantation (MSCT) has been investigated in detail and holds great improvement for LF patients in preclinical and clinical trials. MSCs are a kind of stem cells with multipotentialities of differentiation and self-renewal, which mainly derive from bone marrow, umbilical cord, adipose tissue, spleen, and other tissues.[11,12] In the process of MSCT, firstly, mesenchymal stem cells start proliferation in vitro after laboratory collection, separation, and culture; and then, the stem cells were injected into the human body via different routes after several generations of self-renewal. On the one hand, MSCs integrate hepatic reparative effects through the following items: transdifferentiate into hepatocytes in vivo and in vitro, secrete cytokines/growth factors, angiogenesis, and inhibit activation of liver astrocytes to alleviate liver fibrosis; on the other hand, MSCs have abilities of anti-inflammation and immunomodulation by upregulation of anti-inflammatory cytokine IL-10, downregulation proinflammatory cytokines such as TNF-α and IL-6, adjusting the proliferation of T-lymphocytes, Dendritic cells, Natural killer cells, and improving the inflammatory microenvironment in tissue engineering.[13-16,17]

Although MSCT has extensive prospects in liver failure, which was mentioned in the clinical guideline because of greater potential regeneration and immunomodulatory for tissue repair in various diseases, including autoimmune diseases, diabetes, myocardial infarction, and graft-versus-host reaction, cirrhosis, it is not mature enough for its clinical application.[1,18-22] Therefore, this meta-analysis may be the first to systematically assess the therapeutic efficacy and safety between MSCT and TST for LF patients, with an objective to provide valuable reference for its clinical application and explore the optimum protocol of MSCT in the future.

METHODS

A meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines supplemental (Table 1).

Literature search and selection criteria

Online searching was performed through PubMed, EMBASE and Cochrane library - Cochrane Central Register of Controlled Trials (CENTRAL) until June 2018. The searching items were as follows: “Mesenchymal Stem Cell*”, “MSC*”, “liver failure” and “hepatic failure”, in which Boolean operators were used. The language or publication time was not restricted.

Clinical controlled clinical studies comparing MSCs group with the control group (traditional supportive treatment (TST)) for patients with liver failure were included. The trials were enrolled including of at least one interested quantitative outcome, such as MELD score, TBIL, ALT, ALB, PTA, PT, cumulative survival rate, and severe complications during follow-up. The diagnosis of LF was according to the guideline, such as ACLF (acute onset with a basis of chronic liver disease and accompanied with severe fatigue, obvious gastrointestinal symptoms, rapid progression of scarlet jaundice, serum total bilirubin as 10 times higher than normal value or daily increase to 17.1μmol/L, PTA≤40% or International Normalized Ratio (INR) ≥1.5 after other pathogenesis, with or without hepatic encephalopathy).[1] The studies were excluded if they were irrelevant topics, case reports, reviews, animal trials, and abstracts, or lack of outcomes.

Data extraction and quality assessment

Two authors independently extracted demographic and clinical characteristics of LF patients: first author, published year, country, study design, sample size, duration of follow-up interventions, injection route, dosage of MSCs, and liver function parameters (levels of TBIL, ALT and MELD score etc.). Discrepancies would be resolved by discussion.

RCTs were assessed by the Cochrane Handbook for Systematic Reviews of Interventions, which classified as three items: low risk of bias, unclear, and high risk of bias. The Newcastle-Ottawa Scale was adopted in non-randomized clinical trials, including of cohort or case-control studies, in which scores ranging from 0 to 9 were calculated by evaluating patient selection, comparability and outcome, and a score of 5 or more were on behalf of a high quality.

Statistical analysis

Data integration and analysis were performed with Review Manager 5.3 software. Dichotomous data were calculated with odds ratio (OR) and 95% confidence intervals (CI), while continuous variables were calculated with weighted mean difference (WMD) and 95% confidence interval (CI). There was a statistically significant difference when P value <0.05. The median and variance were calculated through formulas reported

by Hozo et al or extracted from the curve by a software (Engauge Digitizer 4.1) if not reported.[23]

Cochran's-Q test and I2 test were used to assess heterogeneity. The random-effect model was adopted if P value <0.10 or I2 >50%, which was on behalf of high heterogeneity; otherwise, fixed-effect model was used. Sensitivity analysis was conducted when heterogeneity was significant.

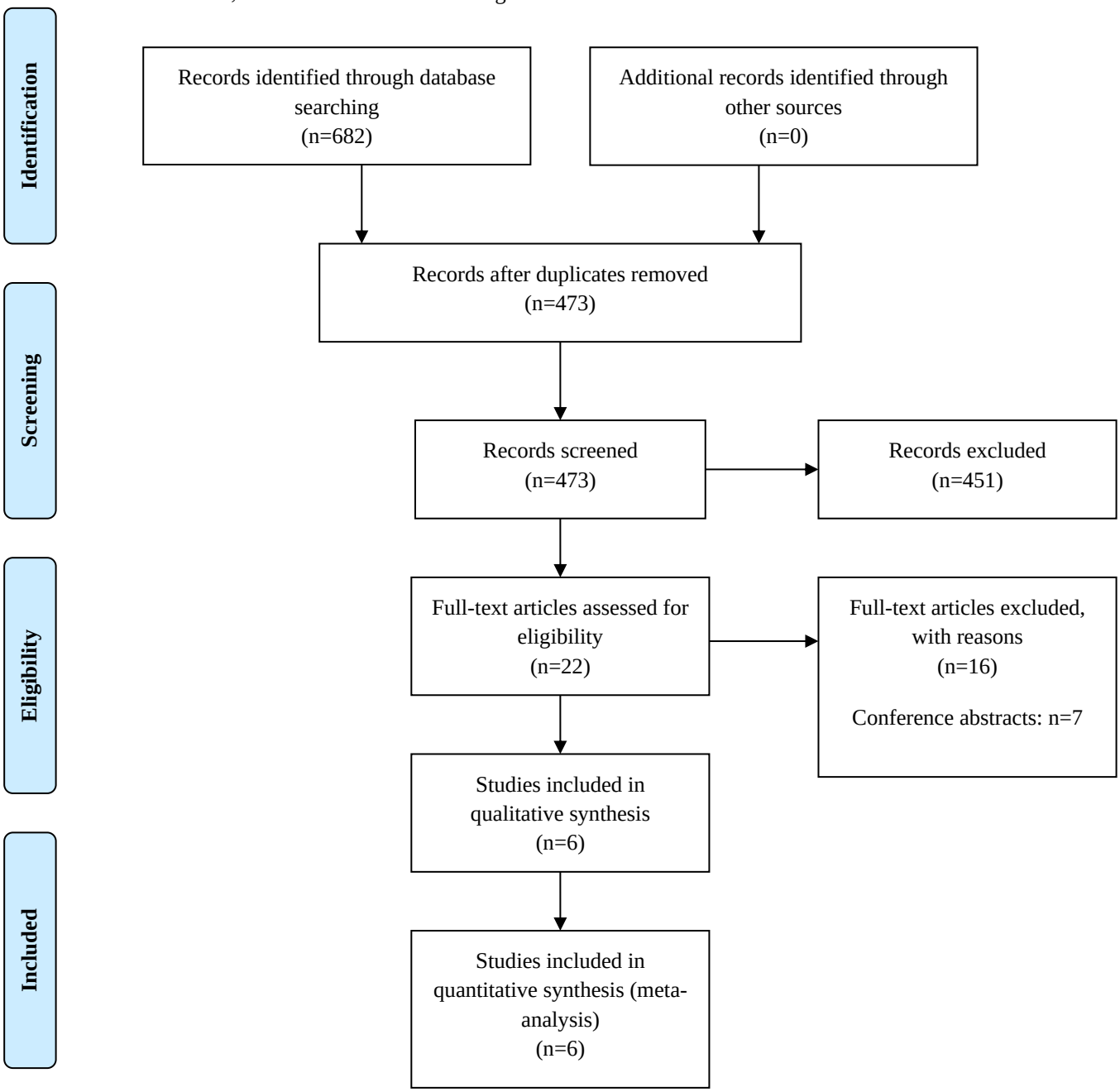

Figure 1: PRISMA flowchart for the selection of eligible studies.

RESULTS

Studies selection

As shown in Table 1, we identified a total of 682 eligible publications by initial searching from the database, of which 209 duplications were removed. Then after screening titles and abstracts, 451 articles were excluded as the following reasons: animal trials, case reports, reviews, or irrelevant studies. Therefore, the full-text versions of 22 studies were screened in detail. Of these 7 conference abstracts, 6 unfinished clinical trials, and 3 trials of liver cirrhosis were removed. At last, 6 eligible studies, comprising of 2 RCTs and 4 clinical controlled studies, were ultimately identified.

Characteristics and quality of selected studies

Demographic and clinical characteristics of LF patients from six studies were summarized in Table 2. Among them, five studies were conducted in China and 1 study in Egypt. In total, 446 patients were included, involving of 189 patients (MSCT group) and 257 patients (controlled group). The types of MSCs were BM-MSCs (n=3) and UC-MSCs (n=3). MSCs were administered via the peripheral vein (n=3), hepatic artery (n=3), splenic route (n=1), and derived from an autologous source (n=2), allogeneic source(n=4). The etiologies of liver failure were mainly hepatitis B (n=5) and hepatitis C (n=1). The varieties of liver failure were composed of ACLF (n=3) and CLF (n=3) with a history of cirrhosis. The duration of analysis was from baseline to 24 weeks.

Table 3 was presented the quality assessment of studies. All of the 6 trials, composed of 2RCTs and 4 non-randomized controlled trials, were open label. Thereinto, one RCT was unclear risk of bias and another was low risk of bias, while 4 non-randomized controlled trials were determined as relatively high quality with a score of 5 or more.

Therapeutic efficacy assessment through subgroups of time points after MSCT

To evaluate the therapeutic efficacy of MSCT, the liver parameters reported by six studies, such as the levels of TBIL, ALT, PTA, PT, ALB, and MELD score, were analysed from baseline to week 24 between the MSCT group and control group.

In LF patients, TBIL and ALT levels are the key factors to evaluate the severity of liver damage. The percentage of PTA and PT levels can reflect liver coagulation functions, where most of the coagulation factors and a variety of anti-thrombin synthesis were produced, while ALB levels are used to integrate liver synthesis functions. MELD score is an objective assessment of the prognosis of end-stage liver disease.[30] The Child-Turcotte-Pugh (CTP) score is a clinical classification standard for assessing the order of severity for liver diseases, whereas it was not included for the lack of enough data.[30]

MELD score

Five subgroup analysis reported the MELD scores in this section, and the results were shown in Fig 2. After MSCT, MELD scores significantly reduced at 2-, 4-, 12- and 24-week in a random-effects model (2-week: WMD:-1.25, 95%CI: -2.07 to -1.03, p<0.00001; 4-week: WMD:-2.44, 95%CI: -4.55 to -0.33, p=0.02; 12-week: WMD:-3.87, 95%CI: -7.04 to -0.70, p=0.02; 24-week: WMD:-2.92, 95%CI: -5.06 to -0.78, p=0.007).However, there existed significant heterogeneity at most time points(1-week:chi-square=19.60, df=1, p<0.00001,I2=95%; 4-week: chi-square=34.94, df=4, p<0.00001,I2=89%; 12-week: chi-square=41.66, df=4, p<0.00001,I2=90%; 24-week: chi-square=27.12, df=4, p<0.00001,I2=85%;).

Sensitivity analyses demonstrated that Lin et al affected the heterogeneity mostly.[27] The heterogeneity observably decreased without this study at 4-week (I2=74%); at 12-week (I2=44%); at 24-week (I2=58%). Publication bias was assessed. The reason the resulted high heterogeneity might be that ACLF was a life-threatening disease with rapid progression and high mortality, some patients died, and clinical outcomes dropped during the follow-up. And then, Lin et al used the delta value of liver function to partially solve this problem.[27]

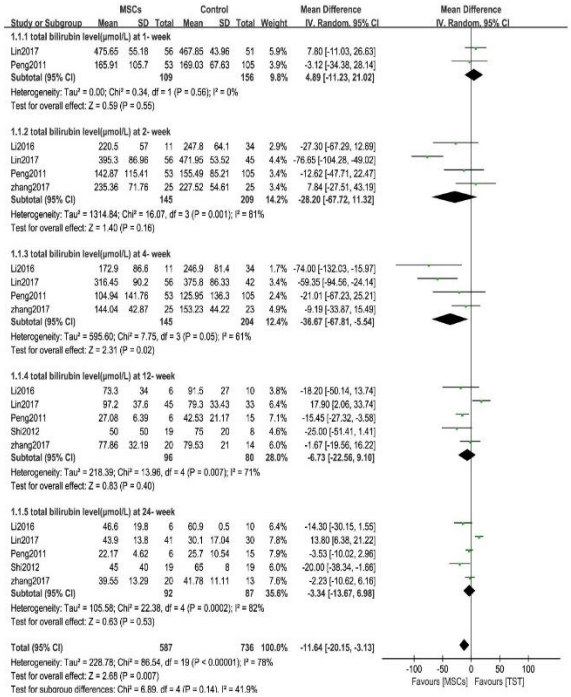

Figure 2: Forest plot of subgroup analysis between MSCT and TST on MELD score at different time points.

TBIL level

Figure 3 summarized that the TBIL levels showed a statistic difference at 4-week (WMD: -36.67, 95%CI: -67.81 to -5.54, p=0.02) in a random-effects model. High heterogeneity was in subgroups at 2-week (chi-square=16.07, df=3, p=0.001, I2 =81%); at 4-week (chi-square=7.75, df=3, p=0.05, I2=61%); at 12-week (chi-square=13.96, df=4, p=0.007, I2=71%) and at 24-week (chi-square=22.38, df=4, p=0.0002, I2=82%). Sensitivity analysis suggested that heterogeneity decreased at 2-week (I2=0%), 4-week (I2=51%), 12-week (I2=0%), and 24-week (I2=63%) after excluding Lin et al and heterogeneity decreased at 4-week (I2=18%) by excluding Zhang et al.[28,29] Respectively, the heterogeneity decreased at the above time points by excluding the studies.

Table 2: Characteristics of included studies.

First author, year	Country	Study design	No. of patients (MSCs/TST, n)	Diagnosis, Etiology	No. of male/female (n)	Cell type	Route of injection	Frequency of injection (n)	Dosage of MSCs(ml)	NO. of MSCs(n)	follow-up time (week)
Amer et al[19] 2011	Egypt	RCT	BM-MSCs:20	CLF, HCV	16/4	Autologous BM-MSCs	Intrasplenic and Intrahepatic	Once	5 ml	NR	24
			TST:20		17/3						
Peng et al[20] 2011	China	CCT	BM-MSCs:53	CLF, HBV	50/3	Autologous BM-MSCs	HA	Once	10 ml	1×10^7	192
			TST:105		99/6						
Shi et al[21] 2012	China	CCT	UC-MSCs:24	ACLF, HBV	20/4	Allogeneic UC-MSCs	PV	Thrice	NR	0.5 ×10^6 /kg	48
			TST:19		15/4						
Li et al[22] 2016	China	CCT	UC-MSCs:11	ACLF, HBV	8/3	Allogeneic UC-MSCs	HA	Once	60 ml	1 × 10^8	96
			TST:34		26/8						
Lin et al[23] 2017	China	RCT	BM-MSCs:56	ACLF, HBV	51/5	Allogeneic BM-MSCs	PV	Once	10 ml	1.0-10×10^5/kg	24
			TST:54		53/1						
Zhang et al[24] 2017	China	CCT	UC-MSCs:25	CLF, HBV	18/7	Allogeneic UC-MSCs	PV	Thrice	100 ml	1.4-2.3) ×10^6/kg	24
			TST:25		19/6						

MSCs: Mesenchymal stem cells; TST: traditional supportive treatment; HBV: hepatitis B virus; HCV: hepatitis C virus; BM-MSCs: Bone Marrow-Derived Mesenchymal Stem Cells; UC-MSCs: Umbilical Cord-Derived Mesenchymal Stem Cells; ACLF: acute-on-chronic liver failure; CLF: chronic liver failure; PV: peripheral vein; hepatic artery; RCT: randomized controlled trial; CCT: clinical controlled trial; NR: not reported.

Table 3: Quality assessment of included studies.

Cohort studies Newcastle-Ottawa scale						
First author, year	**Selection (Max 4★)**	**Comparability (Max 2★)**	**Outcome (Max 3★)**	**Total (Max 9★)**		
Peng et al[20] 2011	★★★	★★	★★★	★★★★★★★★		
Shi et al[21] 2012	★★★	★★	★★★	★★★★★★★★		
Li et al[22] 2016	★★★	★★	★★	★★★★★★★		
Zhang et al[24] 2017	★★	★★	★★★	★★★★★★★		
Randomized controlled studies Cochrane handbook for systematic reviews of interventions						
First author, year	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective outcome reporting**
Amer et al[19] 2011	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	High risk
Lin et al[23] 2017	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk

Only at 12-week, the difference changed significantly. However, the stabilities of other results were still reliable when each parameter was excluded or included in sequence.

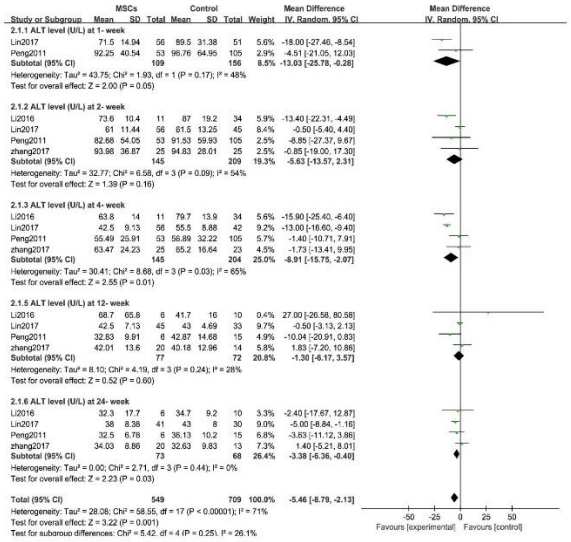

Figure 3: Forest plot of subgroup analysis between MSCT and TST on TBIL level at different time points.

ALT level

In the random effect model, the results indicated that ALT levels expressed a greater decline after MSCT at 1-week (WMD: -13.03, 95%CI: -25.78 to -0.28, p=0.05); at 4-week (WMD: -8.91, 95%CI: -15.75 to -2.07, p=0.01); at 24-week (WMD: -3.38, 95%CI: -6.36 to -0.40, p=0.03). High heterogeneity was observed in one subgroup at 4-week chi-square=8.68, df=3, p=0.03, I2 =65%)

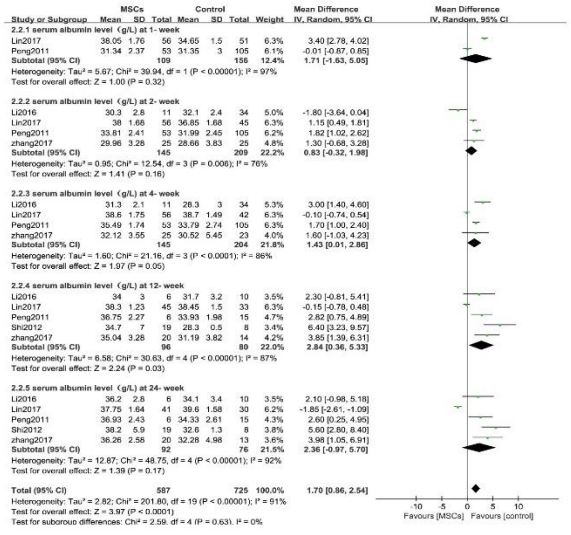

Figure 4: Forest plot of subgroup analysis between MSCT and TST with ALT level at different time points.

Sensitivity analyses are shown by Li et al and Lin et al studies affected the heterogeneity mostly at 2-week, and Peng et al affected mostly at 4-week.[27,28,25] When excluded over the studies, the I2 changed to 0% at 2-week and 48% at 4 weeks. The stability of the results was reliable when the above studies were excluded.

ALB level

In Figure 5, it was reported that serum albumin significantly increased at 4-week (WMD: 1.43, 95%CI: 0.01 to 2.86, p=0.05); at 12-week (WMD: 2.84, 95%CI: 0.36 to 5.33, p=0.03). Simultaneously, High heterogeneity existed as follows: at 1-week (chi-square= 39.94, df=1, p<0.00001, I2=97%), at 2-week (chi-square=12.54, df=3, p=0.006, I2=76%), at 4-week (chi-square=21.16, df=3, p<0.0001, I2=86%); at 12-week (chi-square=30.63, df=4, p<0.00001, I2=87%) and at 24-week (chi-square=48.75, df=4, p<0.00001, I2=92%).

Ultimately, Li et al affected the heterogeneity mostly at 2-week and Lin et al affected mostly at 4-, 12-, and 24 weeks sensitivity analyses.[27,28] The results were shown a decline at 2 weeks (I2=0%); at 4-, 12-, and 24-week (I2=8%; I2=30%; I2=17%) when studies were excluded. Especially, the difference changed significantly at 24-week (p<0.00001).

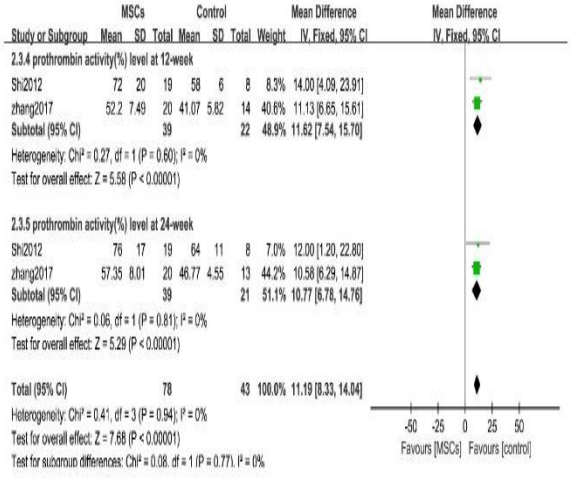

Figure 5: Forest plot of subgroup analysis between MSCT and TST on ALB level at different time points.

PTA level

Results with significant difference were shown in figure 6 with a fixed-effect model at 12-week (WMD: 11.62, 95% CI: 7.54 to 15.70, p<0.00001); at 24-week (WMD: 10.77, 95% CI: 6.78 to 14.76, p<0.00001). There was no high heterogeneity.

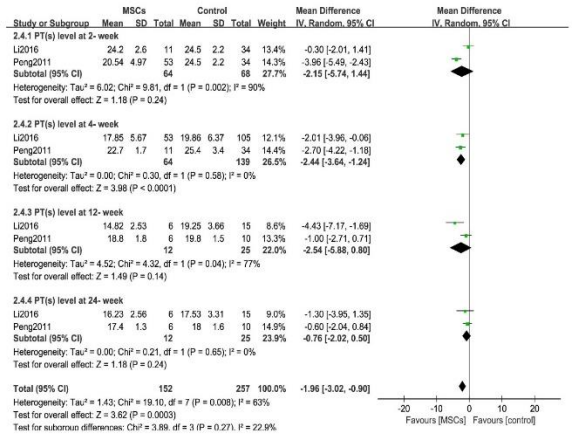

Figure 6: Forest plot of subgroup analysis between MSCT and TST on PTA level at different time points.

PT level

A random model was adopted in this section, which indicated a great increase of PT at 4-week (WMD: -2.44, 95%CI: -3.64 to -1.24, p<0.00001). There was high heterogeneity at 2-week (chi-square=9.81, df=1, p=0.002, I2=90%) and at 12-week (chi-square=4.32, df=1, p=0.04, I2=77%). Because of the inadequate number of studies, we didn't conduct the sensitivity analysis.

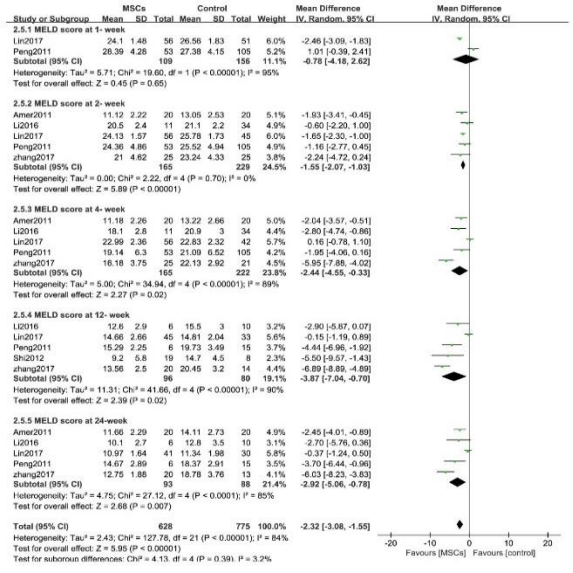

Figure 7: Forest plot of subgroup analysis between MSCT and TST on PT level at different time points.

Safety assessment of MSCT

Adverse events or side effects

The incidence of adverse events or side effects was assessed during the MSCs administration, we got that there were no serious complications and adverse events occurring after MSCs treatment, which was a 100% success rate of infection. Fever was the most common adverse effect, which usually subsided naturally within 24 hours.

Cumulative survival rate at 12-week

There were four studies involved in figure 8 to analyze the cumulative survival rate at 12-week with significant statistical difference (OR: 3.12, 95%CI: 1.77 to 5.52, p<0.0001) in a fixed-effect model. and no heterogeneity was identified.

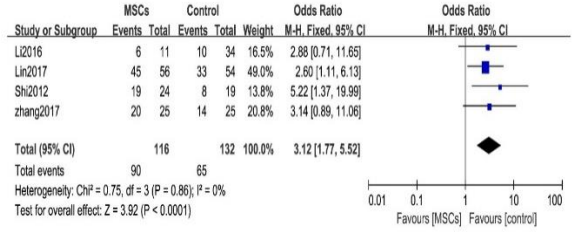

Figure 8: Forest plot of cumulative survival rate at 12-week between MSCT and TST.

DISCUSSION

Mesenchymal stem cell transplantation (MSCT) has been a promising alternative to orthotopic liver transplantation for the treatment of liver failure, with the following advantages for application: ease of isolation and cultivation, high expansion potential, a stable phenotype, low immunogenicity, mild side effects and great improvement of liver function after transplantation.[31]

In this study, the above analysis of forest plots proved the statistic differences between MSCs group and control group, associated with a rapid decline of MELD score, the level of TBIL, ALT, PT; a rise level of ALB, PTA at most time points; and an increase of cumulative survival rate at 12-week, which suggested MSCT was more effective to improve the coagulation and synthesis function of liver, and alleviate the liver damage of LF patients after transfusion. There were no serious complications and hepatocellular carcinoma (HCC) during the follow-up.

This study demonstrated that the TBIL levels significantly decreased at 4-week (p=0.02), while the ALT levels developed a better improvement at1-, 4-, and 24-week (p=0.05; p=0.01; p=0.03). However, the TBIL levels didn't show satisfactory advantage than TST group at 2-, 12-, and 24-week. We considered that the slow decline of TBIL levels might attribute to many factors (the long metabolic cycle, severity of disease, inflammatory response, etc.). Although there was no satisfactory advantage on the decreased levels of TBIL after MSCT, it also indicated that MSCT could alleviate liver damage in the short-term. The long-term outcomes still need further focus for the lack of enough RCTs.

The levels of ALB remarkably increased at 4-(p=0.05), 12-week (p=0.03), which showed a statistic difference after transplantation. We considered that extraneous transfusion of ALB might result in a brief rise.

The PTA levels raised greatly at 12-, 24-week and PT improved greatly at 4-week (p<0.00001). Among the forest plot analysis of PTA, no heterogeneity was revealed. However, there existed high heterogeneity in the subgroup analysis of PT at 2-week and 12-week. The reason might be that LF patients received plasma exchange (PE) before admission, which could improve hepatic function by providing an environment conducive to hepatic regeneration and eliminate accumulated intrahepatic toxins.

Our study suggested that MELD score significantly declined at 2-, 4-, 12- and 24-week, which indicated that the stem cell transplantation was effective to improve the prognosis of the LF patients, compared with the control group. Yet, heterogeneity was inevitable at a high level.

Furthermore, after infusion, we analyzed the cumulative survival rate at 12-week with significant difference (p<0.0001), and no high heterogeneity existed (I2=0%). In addition, there were no serious side effects during the duration. Fever was the highest incidence among adverse effects after MSCT, which was lasted less than 24 hours. Peng et al and Shi et al reported that MSCT improved serum α-fetoprotein (AFP) levels in participants after infusion, potentially as a kind of biomarker for predicting hepatocyte proliferation.[25,26] No supporting evidence of hepatocellular carcinoma (HCC) was found during the period. It was suggested that MSCT was a safe therapeutic strategy for LF patients.

As mentioned above, the heterogeneity was considerable at different time points between MSCT and TST groups. By conducting sensitivity analyses, the heterogeneity indeed decreased at some time points after excluding the studies of Li et al and Lin et al.[27,28] In two studies, we considered that the causes of high heterogeneity were as follows: firstly, there were diverse protocols which might affect the stability of outcomes, such as different etiology, type of MSCs, isolation of MSCs, delivery route and the number of stem cells; secondly, cirrhosis is a hostile microenvironment, which may inhibit the trans-differentiation of MSCs or the viability of hepatocytes; thirdly, LF patients had already received related supportive treatment, including antiviral therapy, symptomatic treatment and plasma exchange (PE), which could eliminate accumulated toxins in the bloodstream of patients and improved hepatic function by providing an environment conducive to hepatic regeneration; fourthly, marked variation in the study characteristics and the stage of progression of liver disease might also be sources of heterogeneity among the included studies; fifthly, due to the death of participants, the incomplete information resulted in a bias, even if used the delta value of liver functions could partially solve this problem; Besides, Publication bias states that studies reporting unfavorable or uninteresting results are less likely to be published.[32,33] These discrepancies might explain some heterogeneity in these studies. As a result, better experimental designs and large-scale RCTs are urgently needed.

It is not a coincidence that some previous studies have reported that MSCT was beneficial to improve the liver function parameters, alleviate liver damage, promote liver regeneration, and increase the survival rate for the treatment of liver diseases.[24-29,34-35] Liu et al transplanted autologous mesenchymal adipose cell precursors (ADSCs) following a repeat partial hepatectomy in rats, which significantly promoted an increase in liver-to-body weight ration and found that the liver essentially fully recovered from hepatocellular damage due to hepatectomy at 168h postoperatively.[37] It was suggested that MSCT might represent a new therapeutic option to treat acute liver failure after hepatectomy. However, regardless of the fact that hepatocyte-like cells derived from MSCs have many characteristics of mature liver cells and can engraft in vivo, the extent of functional liver repopulation has, to date, been limited.[38]

This meta-analysis exists with some limitations. Although pre-clinical and clinical investigations have demonstrated that MSCT was beneficial to alleviate liver damage and regenerate hepatocytes, there is still no uniform criteria on the application of MSCT (e.g., type of MSCs, the infusion route, and the number of MSCs). Significant heterogeneity was inevitable in this study. However, the data extracted from these studies were not enough to conduct more subgroup analysis. Additionally, there are no dynamic monitors on the histological changes and immunological status of patients in the liver after MSCT, such as the ratio of stem cells trans-differentiation, the function of hepatocyte-like cells derived from MSCSS, the expression of cytokines/growth factors, the change of intrahepatic microenvironment and the survival rate of liver cells. In addition, publication bias was inevitable among these studies. Finally, multicenter RCTs with long-term follow-up are required for further studies.

CONCLUSION

This meta-analysis suggested that MSCT might be an alternative therapeutic strategy for orthotopic liver transplantation in patients with liver failure, with a more safe and effective therapeutic effect than TST, which clearly improved the liver function parameters in the short-term and didn't discover serious complications, death or HCC related with MSCT. However, there are many problems to be solved, such as the unclear long-term outcomes of MSCT, no uniform criteria of stem cell transplantation, and the unclear histological changes in vivo. Further focus is necessary on more studies.

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REFERENCES

1. Failure L, Artificial Liver Group CSoID, Chinese Medical Association. [Diagnostic and treatment guidelines for liver failure (2012 version)]. Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology. 2013;21(3):177.
2. William M, Lee M, Larson AM, Stravitz RT. AASLD position paper: The management of acute liver failure: Update. Hepatology. 2011;55.
3. Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatology International. 2014;8(4):453-71.
4. Blachier M, Leleu H, Peckradosavljevic M, Valla DC, Roudotthoraval F. The burden of liver disease in Europe: a review of available epidemiological data. Journal of Hepatology. 2013;58(3):593-608.
5. Millis JM, Cronin DC, Johnson R, Conjeevaram H, Conlin C, Trevino S, et al. Initial experience with the modified extracorporeal liver-assist device for patients with fulminant hepatic failure: system modifications and clinical impact. Transplantation. 2002;74(12):1735.
6. AA D, Jr BR, RW B, J F, BM M, P R, et al. Prospective, Randomized, Multicenter, Controlled Trial of a Bioartificial Liver in Treating Acute Liver Failure. Annals of surgery. 2004;239(5):667-70.
7. Steadman RH, Van RA, Kramer DJ. Transplantation for acute liver failure: perioperative management. Current opinion in organ transplantation. 2010;15(3):368-73.
8. Mochida S. Indication criteria for liver transplantation for acute liver failure in Japan. Hepatology Research the Official Journal of the Japan Society of Hepatology. 2010;38(s1):S52-S5.
9. Wu J, Zheng SS. Liver transplantation in China: problems and their solutions. Hepatobiliary & Pancreatic Diseases International. 2004;3(2):170-4.
10. Takada Y, Kaido T, Asonuma K, Sakurai H, Kubo S, Kiuchi T, et al. Randomized, multicenter trial comparing tacrolimus plus mycophenolate mofetil to tacrolimus plus steroids in hepatitis C virus-positive recipients of living donor liver transplantation. Liver Transplantation. 2013;19(8):896-906.
11. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage Potential of Adult Human Mesenchymal Stem Cells. Science. 1994;284(5411):143-7.
12. L dSM, PC C, NB N. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. Journal of Cell Science. 2006;119(11):2204-13.
13. Eom YW, Kim G, Baik SK. Mesenchymal stem cell therapy for cirrhosis: Present and future perspectives. World J Gastroenterology. 2015;21(36):10253-61.
14. Mirotsou M, Jayawardena TM, Schmeckpeper J, Gnecchi M, Dzau VJ. Paracrine mechanisms of stem cell reparative and regenerative actions in the heart. J Molecular Cellular Cardiology. 2011;50(2):280-9.
15. Honczarenko M, Yi L, Swierkowski M, Ghiran I, Glodek AM, Leslie ESMD. Human Bone Marrow Stromal Cells Express a Distinct Set of Biologically Functional Chemokine Receptors. Stem cells (Dayton, Ohio). 2010;24(4):1030-41.
16. Parekkadan B, Poll DV, Megeed Z, Kobayashi N, Tilles AW, Berthiaume F, et al. Immunomodulation of activated hepatic stellate cells by mesenchymal stem cells. Biochemical Biophysical Res Communications. 2007;363(2):247-52.
17. Zhang Z, Wang FS. Stem cell therapies for liver failure and cirrhosis. J Hepatology. 2013;59(1):183-5.
18. Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurology. 2012;11(2):150-6.
19. Jiang R, Han Z, Zhuo G, Qu X, Li X, Wang X, et al. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. Frontiers of Medicine. 2011;5(1):94.
20. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet. 2012;379(9819):895-904.
21. Popp FC, Fillenberg B, Eggenhofer E, Renner P, Dillmann J, Benseler V, et al. Safety and feasibility of third-party multipotent adult progenitor cells for immunomodulation therapy after liver transplantation a phase I study (MISOT-I). Journal of Translational Medicine,9,1(2011-07-28). 2011;9(1):124.
22. Suk KT, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, et al. Transplantation with Autologous Bone Marrow-Derived Mesenchymal Stem Cells for Alcoholic Cirrhosis: Phase 2 Trial. Hepatology. 2016;64(6):2185.
23. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. Bmc Medical Research Methodology. 2005;5(1):13.
24. Amer MEM, El-Sayed SZ, El-Kheir WA, Gabr H, Gomaa AA, El-Noomani N, et al. Clinical and laboratory evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells. European J Gastroenterology and Hepatology. 2011;23(10):936-41.

25. Peng L, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, et al. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. Hepatology. 2011;54(3):820-8.
26. Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem cells translational medicine. 2012;1(10):725-31.
27. Li YH, Xu Y, Wu HM, Yang J, Yang LH, Yue-Meng W. Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation in Hepatitis B Virus Related Acute-on-Chronic Liver Failure Treated with Plasma Exchange and Entecavir: a 24-Month Prospective Study. Stem cell reviews. 2016;12(6):645-53.
28. Lin BL, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, et al. Allogeneic bone marrow–derived mesenchymal stromal cells for hepatitis B virus–related acute-on-chronic liver failure: A randomized controlled trial. Hepatology. 2017;66(1):209-19.
29. Zhang S, Liu LP, Ma WB, Jia B, Wang HF, Xie CJ. Therapeutic effect of human umbilical cord mesenchymal stem cells transplantation in the treatment of chronic liver failure. Chinese Journal of Tissue Engineering Research. 2017;21(13):2056-61.
30. Angermayr B, Cejna M, Karnel F, Gschwantler M, Koenig F, Pidlich J, et al. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut. 2003;52(6):879-85.
31. Xue R, Meng Q, Dong J, Li J, Yao Q, Zhu Y, et al. Clinical performance of stem cell therapy in patients with acute-on-chronic liver failure: a systematic review and meta-analysis. J Translational Medicine. 2018;16(1):126.
32. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatology. 2016;64(1):69-78.
33. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. Statistical Methods in Medical Research. 2000;9(5):421.
34. Zhu C, Wang K, Li Y, Zhang Y, Li W, Lin W, et al. Over-expression of c-Met in bone marrow mesenchymal stem cells improves their effectiveness in homing and repair of acute liver failure. Hepatology. 2017;66:18A-9A.
35. Shi M, Li Y, Xu R, Meng F, Wang F. Human mesenchymal stem cell therapy increased the survival of the patients with decompensated liver cirrhosis. Hepatology International. 2017;11(1):S895.
36. Mohamadnejad M, Alimoghaddam K, Bagheri M, Ashrafi M, Abdollahzadeh L, Akhlaghpoor S, et al. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. Liver International: official journal of the International Association for the Study of the Liver. 2013;33(10):1490-6.
37. Liu T, Hong MU, Shen Z, Song Z, Chen X, Wang Y. Autologous adipose tissue-derived mesenchymal stem cells are involved in rat liver regeneration following repeat partial hepatectomy. Molecular Med Reports. 2016;13(3):2053-9.
38. Van PD, Parekkadan B, Cho CH, Berthiaume F, Nahmias Y, Tilles AW, et al. Mesenchymal stem cell-derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. Hepatology. 2010;47(5):1634-43.

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