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Therapeutic Effects of Mesenchymal Stem Cells for Patients with Chronic Liver Diseases: Systematic Review and Meta-analysis

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Based on their ability to differentiate into multiple cell types including hepatocytes, the transplantation of mesenchymal stem cells (MSCs) has been suggested as an effective therapy for chronic liver diseases. The aim of this study was to evaluate the safety, efficacy and therapeutic effects of MSCs in patients with chronic liver disease through a literature-based examination. We performed a systematic review (SR) and meta-analysis (MA) of the literature using the Ovid-MEDLINE, EMBASE and Cochrane Library databases (up to November 2014) to identify clinical studies in which patients with liver diseases were treated with MSC therapy. Of the 568 studies identified by the initial literature search, we analyzed 14 studies and 448 patients based on our selection criteria. None of the studies reported the occurrence of statistically significant adverse events, side effects or complications. The majority of the analyzed studies showed improvements in liver function, ascites and encephalopathy. In particular, an MA showed that MSC therapy improved the total bilirubin level, the serum albumin level and the Model for End-stage Liver Disease (MELD) score after MSC treatment. Based on these results, MSC transplantation is considered to be safe for the treatment of chronic liver disease. However, although MSCs are potential therapeutic agents that may improve liver function, in order to obtain meaningful insights into their clinical efficacy, further robust clinical studies must be conducted to evaluate the clinical outcomes, such as histological improvement, increased survival and reduced liver-related complications, in patients with chronic liver disease.

Keywords: Mesenchymal Stem Cells; Chronic Liver Diseases; Systematic Review; Meta-analysis

INTRODUCTION

Cirrhosis is the end stage of chronic liver disease and can be induced by viral hepatitis, alcohol, drugs, metabolic diseases and autoimmune processes. Although liver transplantation is currently recognized as the most effective treatment for chronic liver diseases (1), cell therapy has been widely studied in an effort to develop alternative strategies due to the problems associated with transplantation, such as donor shortage, surgical complications, immunological rejection and high medical costs. Cell therapies can be divided into bio-artificial liver devices and the direct infusion of cells. Bio-artificial liver devices that carry mainly porcine hepatocytes are primarily intended for the short-term support of patients with acute liver failure (2). For direct infusion, cells such as primary hepatocytes, unsorted bone marrow cells (BMCs), hematopoietic stem cells (HSCs), and mesenchymal stem cells (MSCs) have all been used. Of these cell types, MSCs have been isolated by plastic adherence from adipose tissue, umbilical cord blood, peripheral blood, brain, lung, liver, dermis and skeletal muscle (3-5). MSCs have the potential for self-renewal and differentiation into multiple cell lineages, including hepatocytes. Moreover, MSCs can migrate toward areas of injury in response to signals of cellular damage, which are known as homing signals. Based on this migratory property of MSCs, intravenous, intraperitoneal, intrahepatic, intrasplenic or portal-venous injections have been shown to deliver MSCs to the liver, although the reported effectiveness has differed slightly based on the injection route and the research group. Although the therapeutic mechanisms of BMC, HSC and MSC treatments are still not fully characterized, the available evidence has more clearly demonstrated the therapeutic mechanisms of MSCs compared to BMCs or HSCs with respect to liver regeneration. MSCs have been increasingly used in clinical practice, and thus, individual studies have increased. However, studies have presented conflicting results regarding the effect of MSCs. Therefore, we systematically examined the efficacy and safety of MSCs using a literature-based approach in an attempt to confirm the usefulness of MSC therapy for chronic liver disease. Indeed, systematic review (SR) and meta-analysis (MA) have been shown to enable objective analyses of the existing evidence (6). In this study, we aimed to evaluate the safety, efficacy and therapeutic effects of human MSCs for patients with chronic liver

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disease through a literature-based examination.

MATERIALS AND METHODS

We conducted an SR and MA of the literature using the Ovid-MEDLINE (1966 to November 2014), EMBASE (1988 to November 2014) and Cochrane Library databases (up to November 2014) to identify clinical studies where patients with liver diseases were treated with MSC therapy. Databases were searched with a combination of MeSH terms and textwords for the population and the interventions; Boolean operators were also used. The search terms included ([liver OR hepatic] AND [cirrhosis OR fibrosis OR disease OR failure OR cirrhotic] AND ([(mesenchymal stem cell*) OR MSC*] AND [therapy OR treatment* OR transplantation]).

Studies were included if they met the following criteria: 1) they used MSC therapy for chronic liver disease (liver cirrhosis, liver fibrosis and liver failure, among others) and 2) they involved humans. Studies were excluded for the following reasons: 1) they did not use MSC therapy; 2) they did not include any primary outcome (e.g., safety and feasibility of the intervention recorded as prognostic liver scores, change in liver function tests); 3) they were review articles; 4) they were not published in English; or 5) they were unpublished.

Using the search strategy described above, approximately 568 articles were considered. After the review, 14 articles met the selection criteria and were included in the analyses.

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (7) and the statement by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (8).

Data extraction and methodological quality assessment

Data were extracted by two reviewers according to the following specific items: authors, the year the study was conducted, country, study design, sample size, patient characteristics, duration of follow-up, type of cells used, injection route, injection dose, frequency of the administration of cells and liver function tests to measure the therapeutic efficacy including adverse events or side effects. Any disagreements or misunderstandings between reviewers were resolved by discussion until a consensus was reached.

The critical appraisals of the selected studies were assessed with SIGN's checklists (9) according to the study designs. The possible risk of bias was assigned to the following domains: sequence generation, allocation concealment, blinding of investigators and outcome assessors and handling of the outcome data. The quality of the included studies was assessed with criteria that were adapted from the SIGN checklist and a grade of "++", "+", or "-" was applied. Potential publication bias was assessed using asymmetrical funnel plots.

Data synthesis and analysis

The outcome measures included safety and efficacy along with changes in liver function tests and the associated prognostic markers of liver disease, such as the MELD score or Child-Pugh score.

Data analyses were performed with the RevMan 5.3 program from the Cochrane collaboration to analyze the efficacy of the MSC interventions (10). Random effects models were used, as this method provides a more conservative estimate in the presence of potential heterogeneity. The standardized mean differences (SMDs) were calculated by means and SDs or by the changed scores for each intervention. Heterogeneity was assessed with the I^2 statistic. Potential publication bias was assessed by the inspection of funnel plots. If significant heterogeneity was present, the summary MA was abandoned and the possible sources were explored with stratified analyses.

RESULTS

General characteristics of the selected studies

Our initial literature search yielded 568 citations, of which 131 were duplicate studies. Following the screening process, a total of 423 studies were excluded based on the selection criteria, of which 14 were ultimately identified as relevant to our review. Therefore, we analyzed 14 studies (11-24) and 448 patients (Table 1). A detailed flow chart of the literature search and the study selection is presented in Fig. 1.

In this review, controlled trials (14, 16, 18, 20-24) and before-after studies (11-13, 15, 17, 19) were included. The sample sizes of most before-after studies were small ranging from 4 to 20, compared to controlled studies ranging from 12 to 158. From three randomized controlled trials (14, 16, 24), while two study demonstrated permuted block as a randomization method (14, 24), the other did not elucidate the method of randomization used (16). Marked heterogeneity was observed across the studies regarding the outcome measures, the etiology of the liver disease, the type of cells that were given as well as the dose and injection route. The mean duration of follow-up was 9 months.

The majority of the studies used MSCs, 8 of which used the peripheral route, while the other studies used the intrasplenic (3 studies), hepatic artery (2 studies) and portal vein (1 study) routes. One compared intrasplenic administration with peripheral administration, while another compared the intrasplenic route with the intrahepatic route.

The included studies were published between 2007 and 2014. Five of the studies were conducted in China (17-19, 21, 22) and Egypt (11, 16, 20, 23, 24), while the others were conducted in Iran (14, 15), Korea (12) and Sweden (13) (Table 1).

Largely, the studies that have been published to date were designed to investigate safety and feasibility as the primary outcome measures.

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Table 1. Summary of the included studies

First author, publish year	Conducted country	Study design, F/U (month)	Patients, sample size	Mean age range (mean ± SD), (yr)	Injection route	Cell source	Cell dosage	Overall study quality
Amin MA, 2013 (11)	Egypt	Before-after study 6	Post-HCV LC (patient with end-stage LC), Child C n = 20 (M:F = 14:6)	42-60 (51.3 ± 6.2)	IS	BM	10×10^6 in 10 mL PBS	-
Jang YO, 2014 (12)	Korea	Before-after study 6	Alcoholic cirrhosis n = 11 (M:F = 10:1)	37-60 (50 ± 8)	HA	BM	Each 5×10^7 in 10 mL NS, twice	-
Kharaziha P, 2009 (13)	Sweden	Before-after study 6	LC, end stage liver disease (HBV 4, HCV 1, alcoholic 1, cryptogenic 2), MELD score ≥ 10 n = 8 (M:F = 4:4)	38-67 (55.63 ± 10.45)	Portal vein (n = 6) or PV (n = 2)	BM	3×10^7-5×10^7 in 10 mL NS	-
Mohamadnejad M, 2013 (14)	Iran	Controlled trials 12	Decompensated LC (cirrhosis cryptogenic 11, PBC 2, HBV 2, HCV 1, AIH 9) n = 25 (M:F = 13:12), 1) MSC (n = 14), 2) Control (placebo) (n = 11)	1) MSC 43.1 ± 17.6 2) Control 34.6 ± 13.8	PV	BM	Median of 195 million (120-295 million) in 100 mL NS	+
Mohamadnejad M, 2007 (15)	Iran	Case series 12	Decompensated LC (cryptogenic 3, AIH1) n = 4 (M:F = 1:3)	34-56 (47.3)	PV	BM	31.7×10^6 (10.2-60×10^6) in 20 mL NS	-
Salama H, 2014 (16)	Egypt	Controlled trials 6	Post-HCV end-stage liver disease n = 40 (M:F = 33:7) 1) MSC (n = 20), 2) Control (n = 20)	1) MSC 50.27 ± 6.05 2) Control 50.9 ± 7.23	PV	BM	1×10^6/kg	++
Wang L, 2013 (17)	China	Before-after study 12	UDCA-resistant PBC n = 7 (M:F = 1:6)	33-58 (49)	PV	UC	Each 0.5×10^6/kg in NS, thrice	-
Zhang Z, 2012 (18)	China	Controlled trials 12	HBV with decompensated LC n = 45 (M:F = 40:5) 1) MSC (n = 30), 2) Control (saline) (n = 15)	1) MSC 48 (25-64) 2) Control 47 (29-64)	PV	UC	Each 0.5×10^6/kg in NS, thrice	+
Wang L, 2014 (19)	China	Before-after study 12	UDCA-resistant PBC n = 10 (M:F = 1:9)	31-61 (49.1)	PV	BM	$3\text{-}5 \times 10^5$/kg	-
El-Ansary M, 2010 (20)	Egypt	Controlled trials 6	CHF due to HCV or HBV, MELD > 12, Child C , LC n = 12 (M:F = 8:4), 1) IS (n = 6), 2) PV (n = 6)	1) IS 48.50 ± 11.09 (32-69) 2) PV 50.83 ± 6.88 (43-59)	1) IS 2) PV	BM	1×10^7 in 5 mL NS	+
Shi M, 2012 (21)	China	Controlled trials 18	ACLF associated HBV n = 43 (M:F = 35:8), 1) MSC (n = 24), 2) Control (saline) (n = 19)	1) MSC m 40 (24-59) 2) Control m 45 (26-62)	PV	UC	Each 0.5×10^6/kg, thrice	+
Peng L, 2011 (22)	China	Controlled trials 45 (192 weeks)	LF caused by HBV n = 158 (M:F = 149:9), 1) MSC (n = 53), 2) Control (n = 105)	1) MSC 42.19 ± 10.80 2) Control 42.22 ± 11.47	HA	BM	NR	+
El-Ansary M, 2012 (23)	Egypt	Controlled trials 6	CHF due to HCV, MELD > 12, Child C, LC n = 25 (M:F = 19:6), 1) MSC (n = 15), 2) Control (n = 10)	1) MSC 48.0 ± 7.4 (32.0-60.0) 2) Control 51.6 ± 7.2 (39.0-60.0)	PV	BM	1×10^6/kg in NS	+
Amer ME, 2011 (24)	Egypt	Controlled trials 6	Chronic HCV-associated LF, MELD > 25, Child C, LC n = 40 (M:F = 33:7) 1) MSC (n = 20), 2) Control (n = 20)	1) MSC 50.5 + 4.1 2) Control 45-55 + 3.6	(1) IS (n = 10) (2) IH (n = 10)	BM	2×10^7	++

AIH, auto immune hepatitis; BM, bone marrow; CHF, chronic hepatic failure; Child C, end-stage liver cirrhosis; HA, hepatic artery; HBV, hepatitis B virus; HCV, hepatitis C virus; IH, intrahepatic; IS, intrasplenic; LC, liver cirrhosis; LF, liver failure; MELD, model for end-stage liver disease; MSC, mesenchymal stem cell; NS, normal saline; PBC, primary biliary cirrhosis; PBS, phosphate-buffered saline; PV, peripheral vein; RCT, randomized controlled trials; UC, umbilical cord; UDCA, ursodeoxycholic acid; ACLF, acute-on-chronic liver failure; NR, not report.

Methodological quality and risk of bias in the included studies

The quality assessment of each study is found in Table 1 and Fig. 2. Overall, 8 controlled trials (14, 16, 18, 20-24) were determined to have a grade of "++" or "+" (Table 1). While all non-randomized controlled tirals were graded as "+" (18, 20-23), three randomized clinical trials were determinded to have a grade of "++" or "+" (14, 16, 24) according to blindness and randomization method. The assessment items used for evaluation were as follows: selection bias (random sequence generation, allocation concealment), performance bias, attrition bias, detection bias and reporting bias. Before-after studies were not evaluated

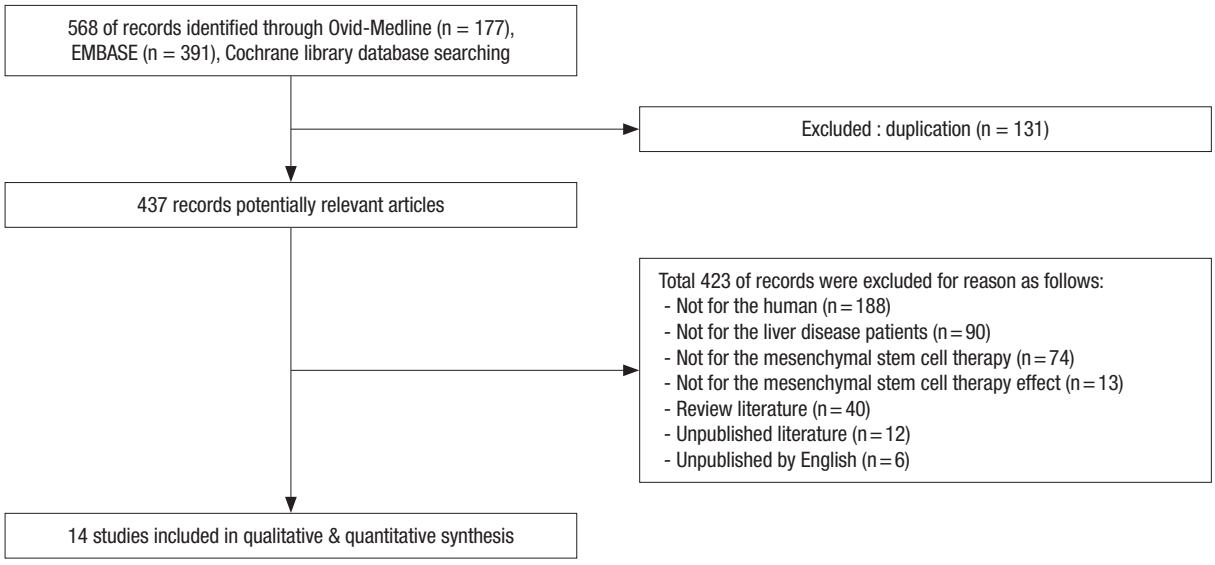

Fig. 1. Flow chart of the study selection.

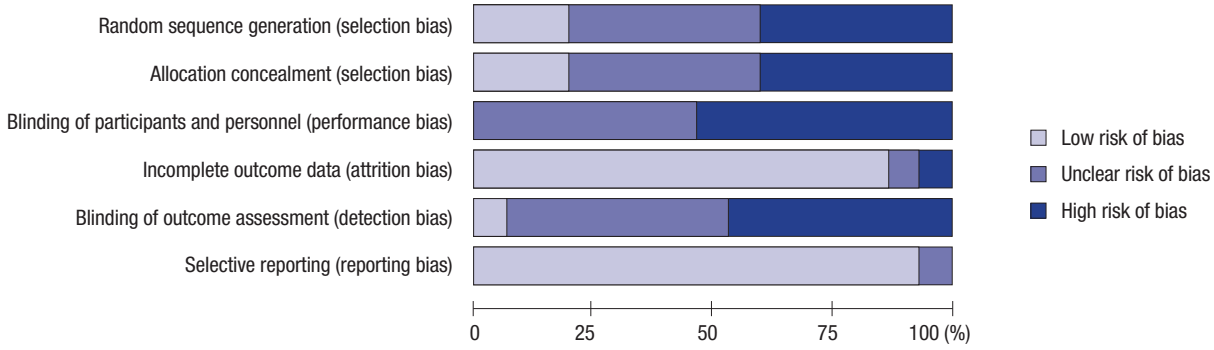

Fig. 2. Risk of bias. Summary of risk of bias for 14 selected studies.

with a checklist according to SIGN's recommendation and marked as a grade of "-" (Table 1). All grades of biases presented as a RevMan's risk of bias graph (Fig. 2).

Efficacy of MSCs: liver function parameters/prognostic MELD and Child-Pugh scores

These studies were analyzed with a random effects model, which covers both sampling error and random error, in light of the high value of I^2 that was obtained in the test for homogeneity. As a result of the analyses, the overall effect size was 0.538 (95% confidence interval [CI], 0.240-0.835; standard error [SE], 0.129; $P < 0.001$), which was higher than the median found by Cohen (1988). Bias was investigated using a visual tool (funnel plot) to determine the validity of the outcomes. With the exception of a few extreme values, a relatively stable distribution was displayed. The outcomes were investigated according to the indices described below.

In relation to liver function, the values of total bilirubin showed a significant decrease after intervention compared with pre-intervention in seven studies among the 14 pooled studies. In a MA of studies that compared the effects of experimental groups and control groups, the experimental groups showed statistically significant reductions in the SMD values, which were -0.75 (95% CI, -0.99– -0.51; I^2, 0%; $P < 0.001$), -0.52 (95% CI, -0.75– -0.28; I^2, 0%; $P < 0.001$), and -0.28 (95% CI, -0.54– -0.01; I^2, 54%; $P = 0.04$) in the 3, 6, and 9 months after treatment, respectively. On the contrary, no statistical significance was observed in the 12 months after treatment (SMD -0.14 [95% CI, -0.70-0.42; I^2, 74%; $P = 0.62$]) (Tables 2 and 3, and Fig. 3). No significant difference was observed between the intrasplenic and peripheral groups (20) and between the hepatic and splenic groups (24). It was reported that serum albumin was significantly increased in the post-intervention group compared with the pre-intervention group in five out of 13 studies. In an MA of studies that compared the effects of experimental groups to those of control groups, the effects on the experimental groups were increased compared with controls according to the SMD, which was 0.74 (95% CI, 0.07-1.42; $P = 0.03$), 0.67 (95% CI, -0.05-1.39; $P = 0.07$), 0.59 (95% CI, 0.33-0.85; $P < 0.001$), and 0.55 (95% CI, -0.64-1.74; $P = 0.37$) in the 3, 6, 9, and 12 months after treatment, respectively. I^2, which

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Table 2. Experimental group vs. control group change value

		Group	No. of patients	Baseline	3 months	6 months	9 months	12 months	Unit
INR	Mohamadnejad M, 2013 (14)	Experimental	14	1.5 ± 0.5	1.8 ± 0.5	1.5 ± 0.4	NR	1.5 ± 0.3	
		Control	11	1.6 ± 0.2	1.6 ± 0.4	1.4 ± 0.3	NR	1.3 ± 0.4	
	Salama H, 2014 (16)	Experimental	20	1.53 ± 0.19	1.47 ± 0.23	1.52 ± 0.36	E	E	
		Control	20	1.66 ± 0.33	0.73 ± 0.4	1.84 ± 0.39	E	E	
	Zhang Z, 2012 (18)	Experimental	30	1.4 ± 0.3	1.3 ± 0.15	1.3 ± 0.1	1.28 ± 0.1	1.25 ± 0.12	
		Control	15	1.3 ± 0.15	1.2 ± 0.1	1.2 ± 0.12	1.25 ± 0.15	1.2 ± 0.12	
PT	Salama H, 2014 (16)	Experimental	20	55.3 ± 9.06	59.45 ± 15.23	57.59 ± 14.68	E	E	Prothrombin concentration %
		Control	20	52.85 ± 10.16	50.45 ± 11.42	45.03 ± 10.92	E	E	
	Zhang Z, 2012 (18)	Experimental	30	58 ± 14	66 ± 12	72 ± 20	70 ± 12	72 ± 14	Prothrombin activity %
		Control	15	64 ± 12	75 ± 15	74 ± 14	70 ± 14	72 ± 10	
	Shi M, 2012 (21)	Experimental	24	35 ± 4	72 ± 20	76 ± 17	82 ± 16	85 ± 14	Prothrombin activity %
		Control	19	32 ± 9	58 ± 6	64 ± 11	66 ± 14	67 ± 8	
	Peng L, 2011 (22)	Experimental	53	26.25 ± 5.34	14.82 ± 2.53	16.23 ± 2.56	15.64 ± 3.17	16.32 ± 2.97	Prothrombin time (sec)
		Control	105	25.95 ± 5.72	19.25 ± 3.66	17.53 ± 3.31	17.19 ± 3.07	17.75 ± 3.14	
	El-Ansary, 2012 (23)	Experimental	15	44.3 ± 14.7	51.6 ± 13.6	50 ± 15	E	E	Prothrombin concentration %
		Control	10	41.7 ± 14.2	39.5 ± 15.5	36.8 ± 16	E	E	
S.Alb	Mohamadnejad M, 2013 (14)	Experimental	14	3.3 ± 0.6	3.3 ± 0.7	3.3 ± 0.5	NR	3.1 ± 0.8	g/dL
		Control	11	3.5 ± 0.6	3.8 ± 0.5	3.9 ± 0.7	NR	3.9 ± 0.3	
	Salama H, 2014 (16)	Experimental	20	2.59 ± 0.28	2.99 ± 0.26	3.06 ± 0.36	E	E	g/dL
		Control	20	2.62 ± 0.37	2.63 ± 0.3	2.43 ± 0.36	E	E	
	Zhang Z, 2012 (18)	Experimental	30	28 ± 7	32.5 ± 5.5	33 ± 4	33 ± 7	35 ± 5	g/L
		Control	15	28 ± 18	30 ± 5	32 ± 7	30 ± 5	30 ± 3	
	Shi M, 2012 (21)	Experimental	24	3.14 ± 0.27	3.47 ± 0.7	3.82 ± 0.59	NR	4.18 ± 0.53	g/dL
		Control	19	2.82 ± 0.39	2.83 ± 0.05	3.26 ± 0.13	NR	3.08 ± 0.4	
	Peng L, 2011 (22)	Experimental	53	29.67 ± 3.14	36.75 ± 2.27	36.93 ± 2.43	37.50 ± 2.31	36.83 ± 2.18	g/L
		Control	105	29.40 ± 3.92	33.93 ± 1.98	34.33 ± 2.61	36.17 ± 1.97	36.73 ± 2.71	
T.Bil	Mohamadnejad M, 2013 (14)	Experimental	14	2.6 ± 1.4	4.1 ± 2.4	2.2 ± 1	NR	2.2 ± 1.4	mg/dL
		Control	11	3.5 ± 2.2	5.3 ± 1.9	3 ± 1.6	NR	2.7 ± 1.4	
	Salama H, 2014 (16)	Experimental	20	1.88 ± 1.05	1.82 ± 1.3	2.06 ± 1.26	E	E	mg/dL
		Control	20	2.51 ± 0.94	4.02 ± 3.29	4.24 ± 2.48	E	E	
	Zhang Z, 2012 (18)	Experimental	30	42.0 ± 22.0	30.0 ± 17.0	29.0 ± 16.0	28.0 ± 18.0	26.0 ± 18.0	μM
		Control	15	48.0 ± 7.0	38.0 ± 12.0	36.0 ± 14.0	30.0 ± 9.0	29.0 ± 6.0	
	Shi M, 2012 (21)	Experimental	24	325.0 ± 124.0	50.0 ± 50.0	45.0 ± 40.0	28.0 ± 10.0	25.0 ± 10.0	μM
		Control	19	330.0 ± 130.0	75.0 ± 20.0	65.0 ± 40.0	50.0 ± 35.0	52.0 ± 60.0	
	Peng L, 2011 (22)	Experimental	53	201.170 ± 75.450	27.080 ± 6.390	72 ± 20	70 ± 12	72 ± 14	μM
		Control	105	295.730 ± 56.020	42.530 ± 21.170	22.170 ± 4.620	27.600 ± 10.290	26.830 ± 5.780	
MELD	Mohamadnejad M, 2013 (14)	Experimental	14	15.4 ± 5.4	15.3 ± 8.2	NR	NR	14 ± 3.6	
		Control	11	14.4 ± 3.7	14.7 ± 5.1	NR	NR	12.5 ± 4.3	
	Shi M, 2012 (21)	Experimental	24	24.05 ± 4.0	9.2 ± 5.8	NR	NR	NR	
		Control	19	26.5 ± 4.6	14.7 ± 4.5	NR	NR	NR	
	Peng L, 2011 (22)	Experimental	53	29.58 ± 0.93	15.29 ± 2.25	14.67 ± 2.89	15.55 ± 1.73	17.39 ± 2.68	
		Control	105	29.62 ± 3.75	19.73 ± 7.49	18.37 ± 2.91	18.79 ± 2.73	18.0 ± 2.52	
	Amer ME, 2011 (24)	Experimental	20	11.57 ± 2.26	NR	11.66 ± 2.29	E	E	
		Control	20	12.55 ± 2.61	NR	14.11 ± 2.73	E	E	
Child	Mohamadnejad M, 2013 (14)	Experimental	14	7.7 ± 2.5	7 ± 2.9	NR	NR	7.2 ± 1.7	
		Control	11	8.3 ± 1.8	6.8 ± 2.1	NR	NR	6.6 ± 1.5	
	Amer ME, 2011 (24)	Experimental	20	11.45 ± 1.09	NR	11.45 ± 0.95	E	E	
		Control	20	11.7 ± 1.08	NR	12.35 ± 0.67	E	E	

Data represent mean ± SD. INR, international normalized ratio; PT, prothrombin time; S.Alb, serum albumin; T.Bil, total bilirubin; MELD, model for end-stage liver disease; Child, child-pugh score; NR, not reported; E, end of study.

is one measure of heterogeneity, was 84%, 87%, 0%, and 93% in the 3, 6, 9, and 12 months after treatment, respectively (Tables 2 and 3, and Fig. 3).

In four studies (11, 15, 18, 21) out of 10 (11, 14-18, 20-23) that included measurements of prothrombin time, a significant decrease was observed in the post-intervention data compared with the pre-intervention data. In an MA of studies that compared the experimental groups and controls, the experimental groups showed SMDs of 0.03 (95% CI, -1.04-1.11; I^2, 94%; P = 0.95), 0.37 (95% CI, -0.29-1.02; I^2, 85%; P = 0.27), 0.15 (95% CI, -0.75-1.04; I^2, 89%; P = 0.75), and 0.31 (95% CI, -0.79-1.42; I^2, 93%; P = 0.58) in the 3, 6, and 9 months after treatment, respectively, indicating high heterogeneity; however, these differences were not statistically significant (Tables 2 and 3, and Fig. 3). In terms of the international normalized ratio (INR), while five studies (11-13, 15, 16) out of nine (11-18, 24) showed significant effects, only one study (16) among 3 total studies (14, 16, 18) showed a significant difference in an MA of trials that compared controls

Table 3. Pre-post change value

	Study	Baseline			3 months		6 months		9 months		12 months			Significant improved
		M pre	SD pre	No.	M post	SD post	M post	SD post	M post	SD post	M post	SD post		
INR	Amin MA, 2013 (11)	2.5	0.5	20	1.7	0.2	1.2	0.1	E	E	E	E		Y
	Jang YO, 2014 (12)	1.2	0.1	11	NR	NR	1.1	0.1	E	E	E	E		Y
	Kharaziha P, 2009 (13)	1.9	0.4	8	1.4	0.5	NR	NR	E	E	E	E		Y
	Mohamadnejad M, 2013 (14)	1.5	0.5	14	1.8	0.5	NR	NR	NR	NR	1.5	0.3		N
	Mohamadnejad M, 2007 (15)	1.88	0.34	4	NR	NR	1.4	0.41	NR	NR	1.53	0.15		Y
	Salama H, 2014 (16)	1.53	0.19	20	1.47	0.23	1.52	0.36	E	E	E	E		N
	Wang L, 2013 (17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		N
	Zhang Z, 2012 (18)	1.4	0.3	30	1.3	0.15	1.3	0.1	1.28	0.1	1.25	0.12		Y
	Amer ME, 2011 (24)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		N
PT	Amin MA, 2013 (11)	22.5	2.5	20	19	1.5	17	1	E	E	E	E		Y
	Mohamadnejad M, 2013 (14)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		N
	Mohamadnejad M, 2007 (15)	18.35	1.89	4	NR	NR	15.18	2.57	NR	NR	16.05	1.31		Y
	Salama H, 2014 (16)	55.3	9.06	20	59.45	15.23	57.59	14.68	E	E	E	E		N
	Wang L, 2013 (17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		N
	Zhang Z, 2012 (18)	58	14	30	66	12	72	20	70	12	72	14		Y
	El-Ansary M, 2010 (20) Intrasplenic	35.81	4.89	6	NR	NR	48.93	13.06	E	E	E	E		N
	El-Ansary M, 2010 (20) Peripheral	41.83	16.52	6	NR	NR	57	11.3	E	E	E	E		N
	Shi M, 2012 (21)	35	4	24	72	20	76	17	82	16	85	14		Y
	Peng L, 2011 (22)	26.25	5.34	53	14.82	2.53	16.23	2.56	15.64	3.17	16.32	2.97		N
	El-Ansary, 2012 (23)	44.3	14.7	15	51.6	13.6	50	15	E	E	E	E		N
S.Alb	Amin MA, 2013 (11)	2.8	0.2	20	2.9	0.15	3.15	0.05	E	E	E	E	mg/dL	Y
	Jang YO, 2014 (12)	3.5	0.6	11	NR	NR	3.9	0.5	E	E	E	E	mg/dL	Y
	Kharaziha P, 2009 (13)	30	5	8	NR	NR	33	5	E	E	E	E	g/L	N
	Mohamadnejad M, 2013 (14)	3.3	0.6	14	3.3	0.7	3.3	0.5	NR	NR	3.1	0.8	mg/dL	N
	Mohamadnejad M, 2007 (15)	3.3	0.59	4	NR	NR	3.55	0.62	NR	NR	3.4	0.39	mg/dL	Y
	Salama H, 2014 (16)	2.59	0.28	20	2.99	0.26	3.06	0.36	E	E	E	E	mg/dL	N
	Wang L, 2013 (17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	N
	Zhang Z, 2012 (18)	2.8	0.7	30	3.25	0.55	3.3	0.4	3.3	0.7	3.5	0.5	mg/dL	Y
	El-Ansary M, 2010 (20) Intrasplenic	2.2	0.12	6	NR	NR	2.43	0.39	E	E	E	E	mg/dL	N
	El-Ansary M, 2010 (20) Peripheral	2.48	0.28	6	NR	NR	2.76	0.28	E	E	E	E	mg/dL	N
	Shi M, 2012 (21)	31.4	2.7	24	34.7	7.0	38.2	5.9	NR	NR	41.8	5.3	g/L	Y
	Peng L, 2011 (22)	29.67	3.14	53	36.75	2.27	36.93	2.43	37.5	2.31	36.83	2.18	g/L	N
	El-Ansary, 2012 (23)	2.3	2.0-2.8	15	2.5	2.0-3.0	2.6	2.0-2.9	E	E	E	E	mg/dL	N
	Amer ME, 2011 (24)	2.1	NR	20	2.0	NR	NR	NR	NR	NR	NR	NR		N

(Continued to the next page)

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Table 3. Continued

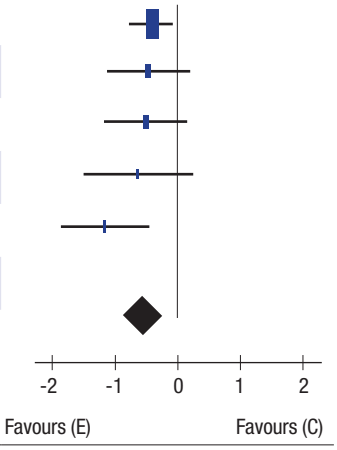
	Study	Baseline			3 months		6 months		9 months		12 months			Significant improved
		M pre	SD pre	No.	M post	SD post	M post	SD post	M post	SD post	M post	SD post		
T.Bil	Amin MA, 2013 (11)	2.4	0.5	20	2.1	0.7	1.6	0.3	E	E	E	E	mg/dL	Y
	Jang YO, 2014 (12)	1.3	0.9	11	NR	NR	1.1	0.7	E	E	E	E	mg/dL	N
	Kharaziha P, 2009 (13)	2.7	1.7	8	NR	NR	2.41	1.82	E	E	E	E	mg/dL	N
	Mohamadnejad M, 2013 (14)	2.6	1.4	14	4.1	2.4	2.2	1	NR	NR	2.2	1.5	mg/dL	N
	Mohamadnejad M, 2007 (15)	2.65	1.32	4	NR	NR	3.12	1.59	NR	NR	2.51	1.12	mg/dL	Y
	Salama H, 2014 (16)	1.88	1.05	20	1.82	1.3	2.06	1.26	E	E	E	E	mg/dL	N
	Wang L, 2013 (17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	N
	Zhang Z, 2012 (18)	42	22	30	30	17	29	16	28	18	26	18	μM	Y
	Wang L, 2014 (19)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	N
	El-Ansary M, 2010 (20) Intrasplenic	4.3	1.73	6	NR	NR	2.79	1.21	E	E	E	E	mg/dL	Y
	El-Ansary M, 2010 (20) Peripheral	2.86	0.86	6	NR	NR	1.53	0.39	E	E	E	E	mg/dL	Y
	Shi M, 2012 (21)	325	124	24	50	50	45	40	28	40	25	10	μM	Y
	Peng L, 2011 (22)	201.17	75.45	53	27.08	6.39	22.17	4.62	27.6	10.29	26.83	5.78	μM	Y
	El-Ansary, 2012 (23)	5.4	1.0-44.4	15	2.4	1.0-10.7	0.9	0.2-6.9	E	E	E	E	mg/dL	Y
	Amer ME, 2011 (24)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	N
MELD	Jang YO, 2014 (12)	9.2	2.8	20	NR	NR	8.3	2.4	E	E	E	E		Y
	Kharaziha P, 2009 (13)	17.9	5.6	8	NR	NR	10.7	6.3	E	E	E	E		Y
	Mohamadnejad M, 2013 (14)	15.4	5.1	14	15.3	8.2	NR	NR	NR	NR	14	3.6		Y
	Mohamadnejad M, 2007 (15)	17	1.41	4	13.75	4.5	13.75	4.5	NR	NR	15.25	3.4		Y
	Wang L, 2013 (17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	N
	El-Ansary M, 2010 (20) Intrasplenic	23.33	5.95	6	NR	NR	18.16	4.49	E	E	E	E		Y
	El-Ansary M, 2010 (20) Peripheral	17	3.41	6	NR	NR	11.33	2.16	E	E	E	E		Y
	Shi M, 2012 (21)	24.05	4	24	9.2	5.8	NR	NR	NR	NR	NR	NR		Y
	Peng L, 2011 (22)	29.58	1.93	53	15.29	2.25	14.67	2.89	15.55	1.73	17.39	2.68		Y
	El-Ansary, 2012 (23)	21.0	12.0-38.0	15	17.0	9.0-31.0	17.0	9.0-26.0	E	E	E	E		Y
	Amer ME, 2011 (24)	11.57	2.26	20	NR	NR	11.66	2.29	E	E	E	E		N
Child	Jang YO, 2014 (12)	7.1	0.9	20	NR	NR	5.4	0.7	E	E	E	E		Y
	Mohamadnejad M, 2013 (14)	7.7	2.5	14	7	2.9	NR	NR	NR	NR	7.2	1.7		Y
	Salama H, 2014 (16)	Child A0, B0, C10			Child A1, B16, C3		Child A0, B14, C6		E	E	E	E		Y
	Amer ME, 2011 (24)	11.45	1.09	20	NR	NR	11.45	0.95	E	E	E	E		N

INR, international normalized ratio; PT, prothrombin time; S.Alb, serum albumin; T.Bil, total bilirubin; MELD, model for end-stage liver disease; Child, child-pugh score; M, mean; SD, standard deviation; pre, pretest; post, posttest; No., number of patients; NR, not reported; E, end of study; Y, yes; N, no.

Total bilirubin

	Experimental			Control			Weight (%)	Std. Mean difference IV, fixed, 95% CI	Year
	Mean	SD	No.	Mean	SD	No.			
Peng L (22)	22.17	4.62	53	25.7	10.54	105	50.1	-0.39 (-0.72– -0.06)	2011
Zhang Z (18)	29	16	30	36	14	15	14.1	-0.45 (-1.04–0.18)	2012
Shi M (21)	45	40	24	65	40	19	14.9	-0.49 (-1.10–0.12)	2012
Mohamadnejad M (14)	2.2	1	14	3	1.6	11	8.5	-0.60 (-1.46–0.21)	2013
Salama H (16)	2.06	1.26	20	4.24	2.48	20	12.4	-1.09 (-1.75– -0.42)	2014
Total (95% CI)			141			170	100.0	-0.52 (-0.75– -0.28)	

Heterogeneity: $Chi^2 = 3.44$, df = 4 ($P = 0.49$); $I^2 = 0\%$
Test for overall effect: Z = 4.30 ($P < 0.0001$)

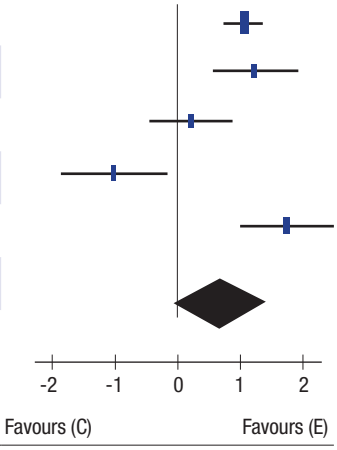


A

Serum albumin

	Experimental			Control			Weight (%)	Std. Mean difference IV, fixed, 95% CI	Year
	Mean	SD	No.	Mean	SD	No.			
Peng L (22)	36.93	2.43	95	34.33	2.61	105	22.9	1.03 (0.73–1.32)	2011
Shi M (21)	38.2	5.9	24	32.6	1.3	19	19.8	1.22 (0.56–1.88)	2012
Zhang Z (18)	33	4	30	32	7	15	20.2	0.19 (-0.43–0.81)	2012
Mohamadnejad M (14)	3.3	0.5	14	3.9	0.7	11	18.0	-0.97 (-1.82– -0.13)	2013
Salama H (16)	3.06	0.36	20	2.43	0.36	20	19.1	1.72 (0.98–2.45)	2014
Total (95% CI)			183			170	100.0	0.67 (-0.05–1.39)	

Heterogeneity: $Tau^2 = 0.57$; $Chi^2 = 30.22$, df = 4 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: Z = 1.82 ($P = 0.07$)



B

Fig. 3. Forest plots. The effects of MSC treatment on total bilirubin (**A**) and serum albumin (**B**) were estimated after 6 months of treatment. SD, standard deviation; N, number of patients; CI, confidence interval; E, experimental; C, control; IV, inverse variance.

and experimental groups (Tables 2 and 3).

In regard to aspartate aminotransferase levels, among the six pooled trials, a significant reduction in this level was observed only in three trials. In particular, a significant decrease in the peripheral group was observed in one study (20). In three trials that compared experimental groups and control groups (14, 16, 23), no significant differences were observed. In terms of alanine aminotransferase levels, five trials (11, 14, 15, 19, 21) out of 11 pooled trials showed a statistically significant decrease. In two trials (16, 21) out of five (14, 16, 21-23), a significant difference was observed in studies that compared experimental groups to controls. In regard to renal function, the creatinine level was significant in three out of six trials; however, significant differences compared with the control groups were observed in only one (18) out of two pooled research studies (18, 23).

When the ten trials (12-15, 17, 20-24) were pooled in relation to the MELD score, eight trials (12-15, 20-23) demonstrated a significant decrease after intervention compared with before the intervention. In the 3, 6, 9, and 12 months after treatment, the experimental groups showed a decrease compared with the control groups (SMD -0.69 [95% CI, -0.98– -0.41; I^2, 30%; $P < 0.001$], -1.02 [95% CI, -1.33– -0.71; I^2, 59%; $P < 0.001$], -1.11 [95% CI, -1.46– -0.75; I^2, 0%; $P < 0.001$], -0.14 [95% CI, -0.45-0.16; I^2, 0%; $P = 0.36$]), and these decreases were statistically significant for the 3, 6, and 9 months (Tables 2 and 3, and Fig. 3).

With regards to the Child-Pugh score, among four pooled tri-

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als (12, 14, 16, 24), three trials showed a significant post-intervention reduction compared with the pre-intervention scores. While a pooled estimate of two trials (14, 24) included in the MA showed a decrease (SMD -0.06 [95% CI, -1.26-1.14; I^2, 82%; P = 0.92]), it was not statistically significant (Tables 2 and 3, and Fig. 3).

Although the use of the portal vein and the peripheral vein demonstrated the highest efficacy, followed by intrasplenic injection, no significant differences were noted with respect to the injection method. Furthermore, in terms of cell source, no significant difference was observed between cells from the umbilical cord and cells from the bone marrow. Funnel plots for MELD score showed symmetrical distributions, indicating no publication bias.

Efficacy of MSCs: histological changes and hepatic encephalopathy

Two research papers (12, 19) reported histological improvement without histological liver deterioration after MSC injection. Out of 11 research papers (11, 13-20, 23, 24) that included information on the ascites status, ten studies reported improvement in this measure. All eight research papers (11, 13, 16, 17, 19, 20, 23, 24) that included data on encephalopathy reported an improvement in this outcome.

Safety of MSCs: adverse effects and complications

All 14 research papers (11-24) included in this analysis reported no statistically significant adverse events, side effects or complications. Therefore, according to this MA, it was concluded that no safety issues are associated with MSC treatment.

DISCUSSION

This SR and MA demonstrated that MSC therapy is feasible and safe in patients with chronic liver disease due to the lack of reports of significant adverse effects in the included studies, although a marked heterogeneity was observed among studies with regards to injection dose, cell source, delivery route and study design. Moreover, chronic liver diseases such as auto immune hepatitis (AIH), acute-on-chronic liver failure (ACLF), chronic hepatic failure (CHF), liver cirrhosis (LC), liver failure (LF) and primary biliary cirrhosis (PBC) can be induced by viral hepatitis, alcohol, drugs, metabolic diseases and autoimmune processes (Table 1). Therefore, this diversity of chronic liver disease might cause different results in MSC therapy and then result in selection bias.

Of the 568 studies identified, 14 were eligible for inclusion (11-24). The majority of the analyzed studies evaluated the clinical efficacy of MSCs via the assessment of whether liver function was improved after MSC treatment. Most results showed positive therapeutic effects, even though the dosage of the injected MSCs varied from 1×10^7 to 2.95×10^8 cells per patient (11, 14, 17, 18, 21). A low cell dosage for transplantation is very important to reduce the transplant costs and decrease the delay for optimal therapeutic timing in the clinical application of MSCs; this goal can be accomplished through time and cost reductions related to the ex vivo expansion of MSCs. Therefore, these findings suggest that the therapeutic value of MSCs for chronic liver disease will be high, even if a low cell dosage (i.e., 1×10^7) can be demonstrated to improve liver function.

Most of the studies evaluated used bone marrow-derived MSCs (BM-MSCs; 10 autologous and 1 allogeneic), whereas 3 used allogeneic umbilical cord-derived MSCs (UC-MSCs). Particularly, 4 allogeneic MSCs (1 BM-MSCs and 3 UC-MSCs) were transplanted into patients with ursodeoxycholic acid (UDCA)-resistant primary biliary cirrhosis (PBC), decompensated liver cirrhosis (LC) and acute-on-chronic liver failure (ACLF) (17-19, 21). Interestingly, allogeneic MSC infusion is clinically safe and is not associated with transplantation-related side effects and could improve liver function. These results suggest that MSCs can be readily applied in clinical studies as an "off-the-shelf" drug.

However, based on the analyzed studies, few studies evaluated histological changes and liver-related death or complications following MSC treatment. In addition, well-designed randomized clinical trials were rare, and the study quality was moderate or poor.

MSCs have the potential to differentiate into hepatocytes, and therapeutic value exists in their immune-modulatory properties and secretion of trophic factors, such as growth factors and cytokines. In addition, MSCs can suppress inflammatory responses, reduce hepatocyte apoptosis, increase hepatocyte regeneration, regress liver fibrosis and enhance liver functionality. In spite of the wide usage of MSCs in clinical and pre-clinical studies of chronic liver disease (25-28), several issues must be carefully considered, including the low stemness and fibrogenic potential of MSCs, the best route of administration, the optimal therapeutic timing, the most effective number of cells and the optimal period or number of injections. The stemness of MSCs, which can be defined by their potential to proliferate and differentiate, gradually decreases during serial passages that are needed to obtain a sufficient cell number for clinical trials. Therefore, the regulation of stemness in MSCs is one of the important issues in the achievement of a maximum effect of stem cell therapy. Moreover, depending on the MSC injection route and liver disease status, MSCs can differentiate into myofibroblasts rather than hepatocytes (29, 30). MSCs are rarely observed in normal and acutely injured livers compared with chronically injured livers, and a significant number of human MSCs exhibit a myofibroblast-like morphology in cases of acute liver injury (29). Baertschiger et al. (30) observed that stable engraftment of MSCs in the liver was not achieved following intra-

splenic injection; however, after intrahepatic injection, MSCs permanently remained in the liver but primarily differentiated into myofibroblasts. Therefore, the MSC injection route and the optimal therapeutic timing according to liver disease status must be considered to reduce the fibrogenic potential of MSCs. Furthermore, the most effective number of cells and the optimal period or number of injections must be determined to improve the therapeutic effects of MSCs in clinical and pre-clinical studies of chronic liver disease. Finally, biomarkers that do not cause cell damage and that are specific to the injected MSCs must be developed to validate the duration of survival and the fate of the engrafted MSCs, even if the development of such tools requires a long period of time.

Taken together, MSCs treatments are considered to be safe and may serve as a potential therapeutic supplementary tool to improve liver function in patients with chronic liver disease. However, to obtain meaningful insights into the clinical efficacy of these cells, further robust clinical studies are needed to evaluate the effects of MSCs on clinical outcomes and histological improvement. In addition, pre-clinical and clinical studies are necessary to determine the best route of MSC delivery that would result in maximal treatment efficacy and the development of useful biomarkers.

DISCLOSURE

The authors do not have any disclosure to report.

AUTHOR CONTRIBUTION

Conceived and designed the experiments: Kim G, Baik SK. Analyzed the data: Kim G, Shin Y, Lim YL, Kim MY, Kwon SO, Chang SJ. Contributed reagents/materials/analysis tools: Kim G, Baik SK, Shin Y, Chang SJ. Wrote the first draft of the manuscript: Kim G, Eom YW. Wrote the paper: Kim G, Eom YW, Baik SK. ICMJE criteria for authorship read and met: Kim G, Eom YW, Baik SK. Agree with manuscript results and conclusions: Kim G, Eom YW, Baik SK, Kim MY, Kwon SO, Chang SJ.

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