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ORIGINAL ARTICLE

Therapeutic efficacy and safety of umbilical cord mesenchymal stem cell transplantation for liver cirrhosis in Chinese population: A meta-analysis

Weiwei Sang[a], **Benji Lv**[b], **Ke Li**[c], **Yan Lu**[a,*]

[a] *Department of Gastroenterology, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, Dongchang West Road, No.67, 252000 Liaocheng, Shandong Province, China*
[b] *Department of Blood Transfusion, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, 252000 Liaocheng, Shandong Province, China*
[c] *Department of Central Laboratory, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, Dongchang West Road, No.67, 252000 Liaocheng, Shandong Province, China*

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KEYWORDS
Umbilical cord mesenchymal stem cells;
Traditional supportive therapy;
Liver cirrhosis;
Meta-analysis

Summary
Background and objective: Mesenchymal stem cells transfusion has been considered as a promising option for liver cirrhosis (LC). The aim of this study was to systematically evaluate the efficacy and safety of umbilical cord mesenchymal stem cells (UMSC) combined with traditional supportive therapy (TST) for the treatment of patients with LC.
Methods: Data was extracted from clinical trials published on Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database. The evaluated outcome measurements included liver function, coagulation function, liver fibrosis indexes, clinical symptoms, quality of life (QOL) and adverse events.
Results: A total of 14 trials including 717 LC patients met our selection criteria were involved. The liver function of LC patients was significantly improved after combined therapy (UMSC plus TST), indicated by decreased total bilirubin, alanine aminotransferase and prothrombin time, and increased serum albumin, cholinesterase and prothrombin activity. The QOL of patients was also improved after UMSC therapy. Compared with TST alone, the combined therapy showed better treatment effect based on measurements of hyaluronic acid (OR = −143.20, CI = −181.58 to −104.82, $P < 0.00001$), laminin (OR = −50.65, CI = −53.70 to −47.61, $P < 0.00001$), type III procollagen (OR = −8.68, CI = −9.00 to −8.36, $P < 0.00001$), type IV collagen (OR = −105.79, CI = −132.44 to −79.14, $P < 0.00001$) and plasma prolidase (OR = −876.54, CI = −911.89 to −840.56, $P < 0.00001$). Moreover, the patients' clinical symptoms including fatigue (4th, $P = 0.003$; 8th, $P = 0.01$), appetite (4th, $P < 0.0001$; 8th,

* Corresponding author.
E-mail address: luyanxiaohua@163.com (Y. Lu).

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$P = 0.06$), ascites (4th, $P = 0.03$; 8th, $P = 0.17$), and abdominal distension (4th, $P = 0.0008$; 8th, $P = 0.64$) were also improved in patients treated by combined therapy without adverse events observed.
Conclusion: UMSC and TST combined therapy for LC patients improved their liver function, clinical symptoms and QOL without severe adverse events, therefore is safe and effective in LC therapy.

Introduction

Liver cirrhosis (LC) is a common complication of progressive liver disease with irreversible diffuse liver damage, which usually caused by alcohol or viral hepatitis [1,2]. Reduced liver regeneration and dysfunction in LC may cause portal hypertension, end-stage liver disease and other complications, such as hepatic encephalopathy and secondary infection [3,4]. LC morbidity and mortality has been increased remarkably in the past years, while most LC patients were not able to be diagnosed at early stage and had shown irreversible liver damage [1,5]. The currently available curative treatment for compensated LC is liver transplantation. [6] However, its implementation usually confronts with obstruction of donor shortage, and maybe accompanied with complications, immunological rejection, high medical costs and ethical restraints [3,6].

In order to develop new strategies to stimulate liver regeneration in LC, researchers have conducted considerable studies. Mesenchymal stem cells (MSC) are derived from mesoderm with self-renewal and multi-differentiation capacity [7—11]. They are able to differentiate into hepatocyte-like cells under appropriate in vivo and in vitro conditions, and were found with capability in promoting hepatocytes regeneration. MSC transplantation showed beneficial effects in LC preclinical studies, therefore MSC was considered with great potentiality in LC treatment [6—9]. Bone marrow mesenchymal stem cells (BMSC) are mainly used in current clinical application [9,11,12], which is usually thwarted by the invasiveness of bone marrow aspiration and age-dependent quantity and quality variation of BMSC [11,13].

Human umbilical cord is another source of MSC, which shows advantages over BMSC with wider range of collection sources, easier collection approach and fewer ethical constraints [14,15]. It has been reported in several clinical trials that UMSC transfusion was able to alleviate liver fibrosis with enhanced liver functions, while not causing severe side effects [14,16,17]. Compare to traditional supportive therapy (TST), the combination of UMSC transfusion and TST has been reported more effective in LC treatment in multiple researches with various respective focuses. To systematically assessing the therapeutic efficacy of this combined therapy for LC, we conducted a systematical review and meta-analysis of the published clinical trials, with the objective to provide valuable reference for its clinical application in the future.

Materials and methods

Data sources and selection criteria

This meta-analysis was conducted in accordance with the PRISMA guidelines. The main source of the searched literatures included Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database. The search was performed in February 2017 and updated in April 2017, with key terms ''umbilical cord mesenchymal stem cells'' AND (''liver cirrhosis'' OR ''hepatocirrhosis'').

The manually searched literatures are reviewed, and those met the following inclusion criteria were involved in this study:

- case controlled clinical trials;
- more than 30 LC patients were included;
- patients had no hepatocellular carcinoma (HCC) or other malignant tumor, and without pregnancy or lactation;
- patients received either UMSC and TST combined therapy, or treated by TST alone.

Data extraction and quality assessment

According to the recommendations of Cochrane Collaboration and PRISMA statement, two authors (Weiwei Sang and Benji Lv) performed the literature research and data extraction independently. The following information of selected articles were summarized when available: first author's name, time of publication and enrollment, study location, LC stages, number of enrolled patients, age, cause of LC, therapeutic regimen, administration route, dosage of UMSC and parameter types. Discrepancies were resolved upon authors' discussion. The included studies' methodological quality was assessed according to Cochrane Handbook [18].

Outcome definition

The main interested outcomes in this research include treatment efficacy, clinical symptoms, quality of life (QOL) and adverse events. Treatment efficacy was assessed in terms of the levels of total bilirubin (TBIL), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (CHE), prothrombin time (PT), prothrombin activity (PTA), and liver fibrosis indexes

of hyaluronic acid (HA), laminin (LN), type III procollagen (PC III), type IV collagen (CIV) and plasma prolidase (PLD).

Patients' clinical symptoms were evaluated based on the following indicators: fatigue, appetite, ascetics and abdominal distension. Patients' QOL was assessed by short form 36 questionnaire (SF-36) which includes physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE) and mental health (MH).

Adverse events occurred during therapy were also taken into assessment.

Statistical analysis

We performed a comparative analysis between patients treated by TST alone and UMSC transfusion/TST combined therapy with Review Manager 5.2 (Cochrane Collaboration). $P < 0.05$ indicates the differences reached statistical significance. In order to assess the heterogeneity cross the involved studies, Cochran's Q test was conducted, and $I2 < 50\%$ or $P > 0.1$ indicated homogenous studies [19]. Primary outcome variables were odds ratio (OR) of therapeutic effects with respective 95% confidence interval (CI).

Results

Search results

Initial retrieve produced 284 articles. In total, 206 articles without clinical trials, 14 unrelated studies, 21 duplicated articles, 5 reviews or meta-analyses, 13 articles without control group and 11 with insufficient data were excluded, yielding 14 studies [16,20–32] including 717 LC patients met the inclusion criteria for our meta-analysis (Fig. 1).

Patient characteristics

All included trials met the inclusion criteria were conducted in China, including a total of 397 LC patients treated by UMSC and TST combined therapy and 380 treated by TST. Tables 1 and 2 presented detailed information about the involved studies and participates. Patients received UMSCs

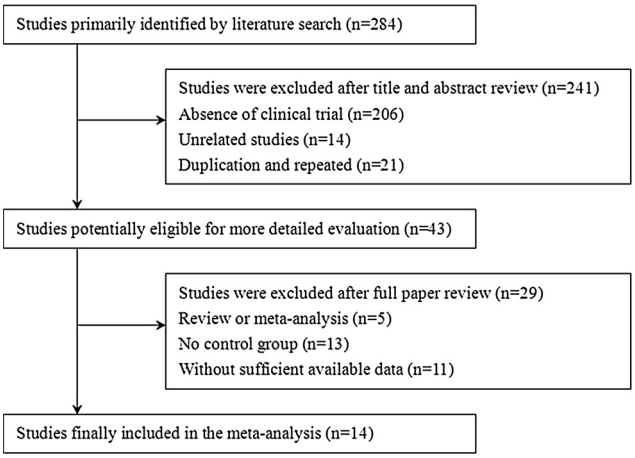

Figure 1 Flow diagram of the selection process.

transfusion through hepatic artery ($n = 4$), peripheral vein ($n = 8$) or other methods ($n = 2$).

Quality assessment outcome

Fig. 2 presented the outcome of quality assessment. Among the 14 involved studies, 6 were determined as low risk of bias, 3 were not randomized controlled trials, and the remaining 5 did not provide clearly descript the randomization process. All included trials were considered as unclear risk of bias for selection, performance and detection because they did not provide clear description. Two studies absent of follow-up were regarded as high risk of attrition bias, and two studies were considered as unclear risk of reporting bias for selective reporting.

Therapeutic efficacy assessments

The effectiveness of UMSC on TBIL, ALB, ALT, AST, CHE, coagulation function, multiple markers associated with patients' status were taken into assessment in our research. After UMSC and TST combined therapy, TBIL level was reduced especially at the 2nd, 4th and 12th week (Table 3, 2nd: OR = −6.14, CI = −11.73 to −0.54, $P = 0.03$; 4th: OR = −18.53, CI = −33.40 to −3.66, $P = 0.01$; 12th: OR = −53.96, CI = −88.04 to −19.88, $P = 0.002$), while reduction at the 1st, 8th and 24th week was not significant (1st: OR = 1.85, CI = −7.68 to 11.38, $P = 0.70$; 8th: OR = −26.22, CI = −58.25 to 5.81, $P = 0.11$; 24th: OR = −5.75, CI = −13.30 to 1.80, $P = 0.14$).

At all measured time points after first week, ALB level was greatly increased after combined therapy (Table 3, 1st: OR = 1.08, CI = −1.71 to 3.87, $P = 0.45$; 2nd: OR = 2.99, CI = 1.06 to 4.92, $P = 0.002$; 4th: OR = 4.12, CI = 2.43 to 5.81, $P < 0.00001$; 8th: OR = 4.43, CI = 2.83 to 6.03, $P < 0.00001$; 12th: OR = 3.83, CI = 1.96 to 5.69, $P < 0.0001$; 24th: OR = 4.27, CI = 1.35 to 7.19, $P = 0.004$), which was also much higher than that in patients treated by TST alone.

ALT level was reduced at the 12th week after combined therapy (Table 3, 1st: OR = −1.68, CI = −9.02 to 5.66, $P = 0.65$; 2nd: OR = −4.60, CI = −13.39 to 4.20, $P = 0.31$; 4th: OR = −14.72, CI = −32.21 to 2.78, $P = 0.10$; 8th: OR = −9.41, CI = −31.80 to 12.98, $P = 0.41$; 12th: OR = −11.86, CI = −22.72 to −1.00, $P = 0.03$; 24th: OR = −3.88, CI = −9.45 to 1.68, $P = 0.17$).

AST level was increased at the 8th week after combined therapy (Table 3, 1st: OR = 1.92, CI = −4.11 to 7.95, $P = 0.53$; 2nd: OR = 2.42, CI = −3.23 to 8.08, $P = 0.40$; 4th: OR = −15.67, CI = −46.48 to 15.14, $P = 0.32$; 8th: OR = 6.91, CI = 0.54 to 13.28, $P = 0.03$; 12th: OR = −15.34, CI = −40.35 to 9.66, $P = 0.23$; 24th: OR = −0.09, CI = −19.95 to 19.76, $P = 0.99$). Most studies reported decreased AST level in combined treated patients. Notably, Lin et al. reported an increased AST level at the 8th week after UMSC therapy, which may require further discussion.

CHE level was significantly reduced at the 2nd, 4th and 12th week after combined therapy (Table 3, 1st: OR = 79.00, CI = −320.39 to 478.39, $P = 0.70$; 2nd: OR = 263.40, CI = 13.89 to 512.91, $P = 0.04$; 4th: OR = 557.56, CI = 294.93 to 820.19, $P < 0.0001$; 8th: OR = 1020.50, CI = 229.16 to 1811.85, $P = 0.01$; 12th: OR = 679.20, CI = 276.77 to 1081.63,

Table 1 Clinical information from the eligible trials in the meta-analysis.

Included studies	Nation	Stage of LC	Patients con/exp	Age (year)		Cause of liver cirrhosis
				Con	Exp	
Du et al., 2011 [20]	China	Child-Pugh B-C	25/25	ND	ND	HBV (45), HCV (5)
Gong et al., 2014 [21]	China	Child-Pugh B-C	22/24	46 (mean)	48 (mean)	ND
He et al., 2010 [22]	China	Child-Pugh B-C	26/26	48.6 (mean)	46.0 (mean)	HBV (51), HCV (1)
Ji et al., 2017 [23]	China	ND	46/46	57.2 ± 3.5 (mean)	58.1 ± 4.2 (mean)	HBV
Lin et al., 2012 [16]	China	ND	16/38	48 (mean)	47 (mean)	HBV (39), HCV (1), Alcohol (2), PBC (1), mixed (10), OC (1)
Luo and Lei, 2016 [24]	China	ND	40/40	49 ± 7 (mean)	48 ± 8 (mean)	HBV
Luo et al., 2015 [25]	China	Child-Pugh C	46/50	43 ± 10 (mean)	44 ± 12 (mean)	HBV
Sun and Pi, 2012 [26]	China	ND	22/22	47.0 ± 9.0 (mean)	48.6 ± 9.8 (mean)	HBV
Sun et al., 2016 [27]	China	ND	30/29	ND	ND	ND
Tong et al., 2015 [28]	China	Child-Pugh A-C	20/20	56.0 ± 10.3 (mean)	56.4 ± 10.4 (mean)	HBV
Zhang et al., 2017 [29]	China	Child-Pugh A-C	30/30	55.5 ± 9.3 (mean)	56.0 ± 9.1 (mean)	HBV
Zhang et al., 2012 [30]	China	Child-Pugh A-C	18/12	49.9 ± 10.3 (mean)	48.6 ± 11.0 (mean)	PC (21), Alcohol (9)
Zheng et al., 2015 [31]	China	Child-Pugh B-C	19/13	ND	ND	HBV (25), Alcohol (7)
Zhu et al., 2013 [32]	China	Child-Pugh B-C	20/22	49.2 ± 11.9 (mean)	48.5 ± 10.6 (mean)	Viral (37), Alcohol (5)

Con: control group (TST alone group); Exp: experimental group (TST plus USC therapy); LC: liver cirrhosis; UMSC: umbilical cord mesenchymal stem cells; TST: traditional supportive therapy; ND: non-determined; HBV: hepatitis B virus; HCV: hepatitis C virus; PBC: primary biliary cirrhosis; OC: occult cirrhotic; PC: posthepatitic cirrhosis.

Table 2 Information of UMSC therapy.

Included studies	Therapeutic regimen		Administration route	Cell dose	Parameter types
	Exp group	Con group			
Du et al., 2011 [20]	Con Reg + UMSC	TST	Hepatic artery	$1–7 \times 10^8$	CHE
Gong et al., 2014 [21]	Con Reg + UMSC	TST	Hepatic artery	ND	TBIL, ALB, QOL
He et al., 2010 [22]	Con Reg + UMSC	TST	Hepatic artery	$8–10 \times 107^{-8}$	HA, LN, PC III, CIV
Ji et al., 2017 [23]	Con Reg + UMSC	TST + CM	IV	0.5–1 × 106/kg	HA, LN, PC III, CIV, PLD
Lin et al., 2012 [16]	Con Reg + UMSC	TST	IV	0.5–1 × 106/kg	TBIL, ALT, CHE
Luo and Lei, 2016 [24]	Con Reg + UMSC	TST	IV	$6–15 \times 10^8$	HA, LN, PC III, CIV, PLD
Luo et al., 2015 [25]	Con Reg + UMSC	TST	IV	ND	TBIL, ALB, ALT, AST, PT, CSS
Sun and Pi, 2012 [26]	Con Reg + UMSC	TST	ND	0.5 × 106/kg	QOL
Sun et al., 2016 [27]	Con Reg + UMSC	TST + CM	IV	$\geq 1.5 \times 10^7$	TBIL, ALB, ALT, AST, PT
Tong et al., 2015 [28]	Con Reg + UMSC	TST	IV	$2–4 \times 10^7$	CSS
Zhang et al., 2017 [29]	Con Reg + UMSC	TST	IV	$2–4 \times 10^7$	TBIL, ALB, ALT, AST, CHE, PTA, CSS
Zhang et al., 2012 [30]	Con Reg + UMSC	TST	Hepatic artery	$\geq 2 \times 10^7$	TBIL, ALB, PT, CSS
Zheng et al., 2015 [31]	Con Reg + UMSC + BMSC	TST	Hepatic artery + IV	$6–7 \times 10^7$/kg	TBIL, ALB, ALT, PT
Zhu et al., 2013 [32]	Con Reg + UMSC	TST	IV	1×10^8	TBIL, ALB, ALT, PT, PTA, CSS

Con: control group (TST alone group); Exp: experimental group (TST plus USC therapy); Con Reg: Control group regimen; UMSC: umbilical cord mesenchymal stem cells; TST: traditional supportive therapy; CM: Chinese medicine; BMSC: bone marrow stem cells; ND: non determined; IV: intravenous infusion; CHE: cholinesterase; TBIL: total bilirubin; ALB: albumin; QOL: quality of life; HA: hyaluronic acid; LN: laminin; PC III: type III procollagen; CIV: type IV collagen; PLD: plasma prolidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; CSS: clinical signs and symptoms; PTA: prothrombin activity.

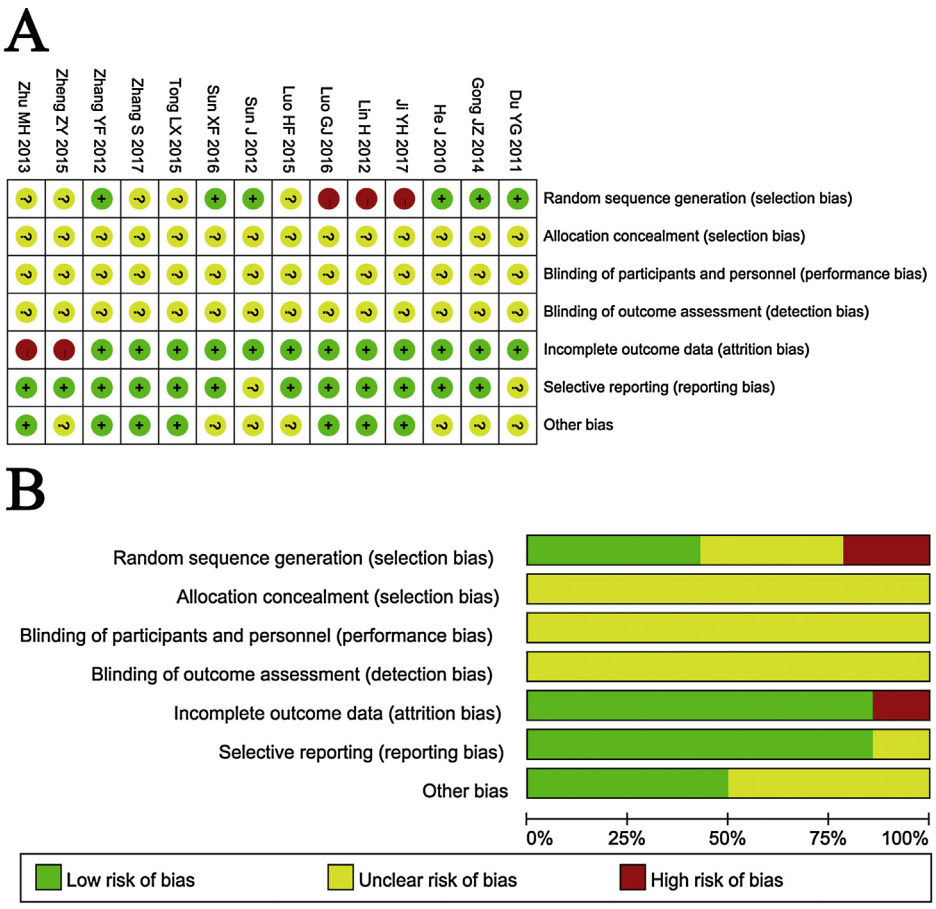

Figure 2 Risk of bias summary: review of authors' judgments about each risk of bias item for included studies (A). Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all included studies (B).

$P = 0.0009$; 24th: OR = 905.80, CI = 498.64 to 1312.95, $P = < 0.0001$).

PT and PTA were analyzed to evaluate the coagulation function in patients. PT of combined therapy treated patients was reduced at the 4th and 8th week (Table 3, 2nd: OR = −2.87, CI = −5.92 to 0.18, $P = 0.06$; 4th: OR = −1.46, CI = −2.67 to −0.25, $P = 0.02$; 8th: OR = −4.65, CI = −8.68 to −0.62, $P = 0.02$; 12th: OR = −3.65, CI = −7.51 to 0.21, $P = 0.06$), and PTA was increased at the 4th, 8th 12th and 24th week with statistical significance (Table 3, 2nd: OR = 1.70, CI = −5.66 to 9.06, $P = 0.65$; 4th: OR = 5.56, CI = 1.18 to 9.95, $P = 0.01$; 8th: OR = 17.72, CI = 7.45 to 27.99, $P = 0.0007$; 12th: OR = 9.03, CI = 0.47 to 17.59, $P = 0.04$; 24th: OR = 11.76, CI = 3.06 to 20.46, $P = 0.008$).

In comparison between the two groups of patients, ALB level was significantly higher in combined therapy treated patients than those treated by TST alone, and PTA increase was more significant at the 8th, 12th and 24th week, while no obvious differences were observed in the TBIL, ALT, AST and CHE levels and PT between the two groups (Supplementary Figures 1—6).

The effectiveness of UMSC on liver fibrosis

As shown in Fig. 3, the hepatic fibrosis markers including HA, LN, PC III, CIV and PLD in patients treated by combined therapy were significantly improved compared with those treated by TST alone (HA: OR = −143.20, CI = −181.58 to −104.82, $P < 0.00001$; LN: OR = −50.65, CI = −53.70 to −47.61, $P < 0.00001$; PC III: OR = −8.68, CI = −9.00 to −8.36, $P < 0.00001$; CIV: OR = −105.79, CI = −132.44 to −79.14, $P < 0.00001$; PLD: OR = −876.54, CI = −911.89 to −840.56, $P < 0.00001$).

Clinical symptoms assessment

Analysis on clinical symptoms showed significantly alleviated fatigue, improved appetite, reduced ascites and relieved abdominal distension in patients treated by combined therapy compare to those treated by TST alone (Fig. 4, fatigue: 4th, OR = 2.64, CI = 1.40 to 4.96, $P = 0.003$; 8th, OR = 5.45, CI = 1.45 to 20.50, $P = 0.01$; Appetite: 4th, OR = 4.27, CI = 2.16 to 8.45, $P < 0.0001$; 8th, OR = 3.20, CI = 0.97 to 10.60, $P = 0.06$; ascites: 4th, OR = 3.12, CI = 1.15 to 8.44, $P = 0.03$; 8th, OR = 2.29, CI = 0.70 to 7.43, $P = 0.17$; Abdominal distension: 4th, OR = 5.44, CI = 2.02 to 14.66, $P = 0.0008$; 8th, OR = 1.43, CI = 0.32 to 6.46, $P = 0.64$).

QOL evaluation

The life quality of patients was evaluated before and after combined therapy. The analysis results show that

Table 3 Meta-analysis of TBIL, ALB, ALT, AST, CHE, PT, PTA in pre- and post-therapy.

Parameter	Time point (after therapy)	Pre-therapy	Post-therapy	Analysis method	Heterogeneity		Odds ratio (OR)	95% CI	*P*-value
		No. patients (*n*)	No. patients (*n*)		I^2 (%)	*P*-value			
TBIL	1 week	62	62	Random	0	0.64	1.85	−7.68 to 11.38	0.70
	2 week	154	154	Random	18	0.30	−6.14	−11.73 to −0.54	0.03
	4 week	218	218	Random	91	< 0.00001	−18.53	−33.40 to −3.66	0.01
	8 week	96	96	Random	97	< 0.00001	−26.22	−58.25 to 5.81	0.11
	12 week	167	167	Random	98	< 0.00001	−53.96	−88.04 to −19.88	0.002
	24 week	68	68	Random	0	0.43	−5.75	−13.30 to 1.80	0.14
ALB	1 week	24	24	Random			1.08	−1.71 to 3.87	0.45
	2 week	116	116	Random	65	0.04	2.99	1.06 to 4.92	0.002
	4 week	180	180	Random	59	0.02	4.12	2.43 to 5.81	< 0.00001
	8 week	58	58	Random	10	0.33	4.43	2.83 to 6.03	< 0.00001
	12 week	129	129	Random	59	0.04	3.83	1.96 to 5.69	< 0.0001
	24 week	30	30	Random			4.27	1.35 to 7.19	0.004
ALT	1 week	38	38	Random			−1.68	−9.02 to 5.66	0.65
	2 week	118	118	Random	47	0.15	−4.60	−13.39 to 4.20	0.31
	4 week	182	182	Random	91	< 0.00001	−14.72	−32.21 to 2.78	0.10
	8 week	60	60	Random	85	0.01	−9.41	−31.80 to 12.98	0.41
	12 week	131	131	Random	71	0.02	−11.86	−22.72 to −1.00	0.03
	24 week	68	68	Random	0	0.41	−3.88	−9.45 to 1.68	0.17
AST	1 week	38	38	Random			1.92	−4.11 to 7.95	0.53
	2 week	118	118	Random	0	0.41	2.42	−3.23 to 8.08	0.40
	4 week	147	147	Random	97	< 0.00001	−15.67	−46.48 to 15.14	0.32
	8 week	38	38	Random			6.91	0.54 to 13.28	0.03
	12 week	118	118	Random	93	< 0.00001	−15.34	−40.35 to 9.66	0.23
	24 week	68	68	Random	89	0.003	−0.09	−19.95 to 19.76	0.99
CHE	1 week	38	38	Random			79.00	−320.39 to 478.39	0.70
	2 week	93	93	Random	0	0.50	263.40	13.89 to 512.91	0.04
	4 week	93	93	Random	4	0.35	557.56	294.93 to 820.19	< 0.0001
	8 week	63	63	Random	85	0.01	1020.50	229.16 to 1811.85	0.01
	12 week	68	68	Random	0	0.79	679.20	276.77 to 1081.63	0.0009
	24 week	68	68	Random	0	0.98	905.80	498.64 to 1312.95	< 0.0001
PT	2 week	12	12	Random			−2.87	−5.92 to 0.18	0.06
	4 week	112	112	Random	23	0.27	−1.46	−2.67 to −0.25	0.02
	8 week	20	20	Random	83	0.01	−4.65	−8.68 to −0.62	0.02
	12 week	75	75	Random	88	0.0002	−3.65	−7.51 to 0.21	0.06
PTA	2 week	30	30	Fixed			1.70	−5.66 to 9.06	0.65
	4 week	88	88	Fixed	0	0.79	5.56	1.18 to 9.95	0.01
	8 week	8	8	Fixed			17.72	7.45 to 27.99	0.0007
	12 week	30	30	Fixed			9.03	0.47 to 17.59	0.04
	24 week	30	30	Fixed			11.76	3.06 to 20.46	0.008

TBIL: total bilirubin; ALB: albumin; CHE: cholinesterase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; PTA: prothrombin activity.

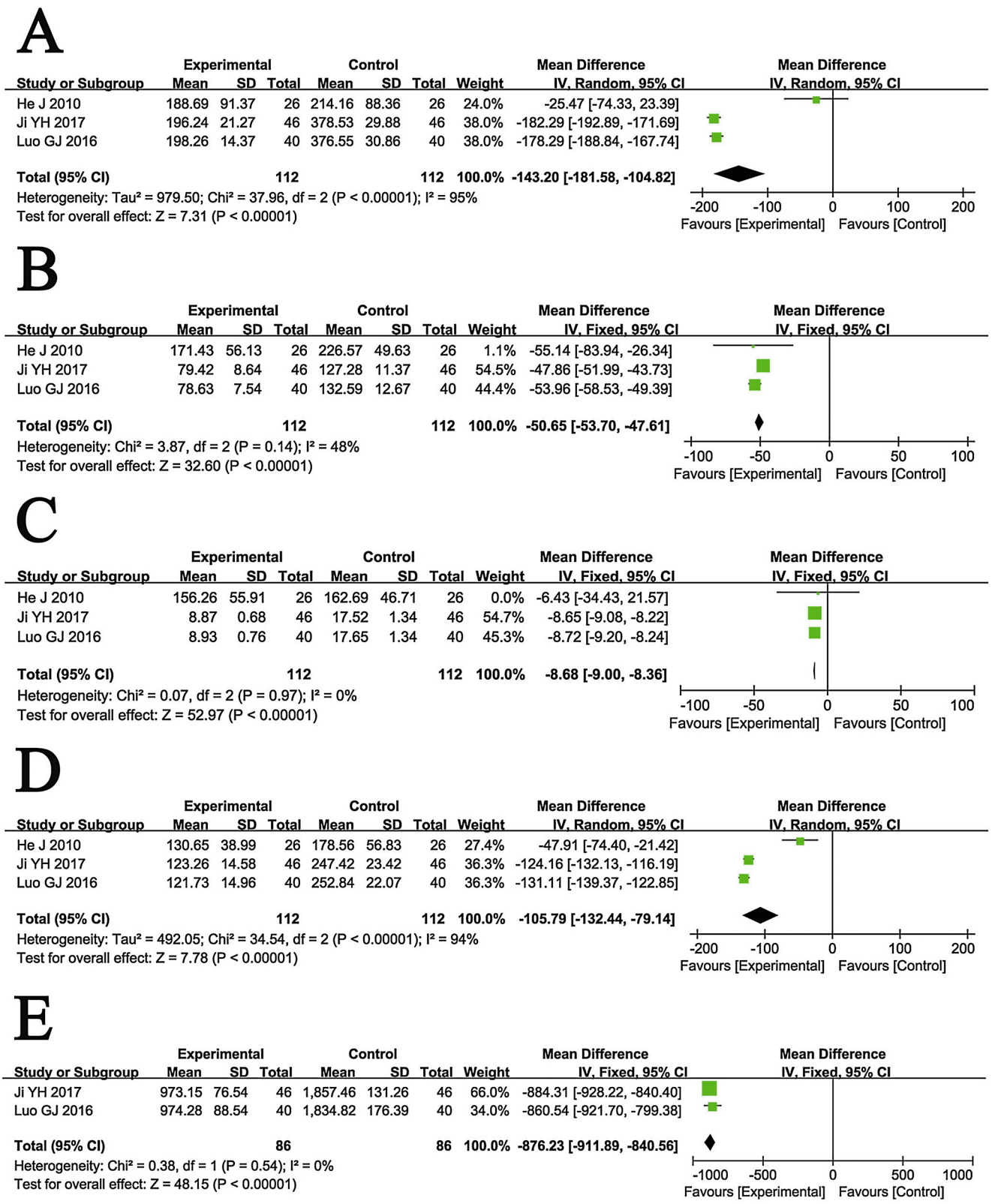

Figure 3 Forest plot of the comparison of serum liver fibrosis markers including hyaluronic acid (HA, A), laminin (LN, B), type III procollagen (PC III, C), type IV collagen (CIV, D) and plasma prolidase (PLD, E) between the experimental and control group. Control group, TST alone group; Experimental group TST plus UMSC therapy; UMSC, umbilical cord mesenchymal stem cells; TST, traditional supportive therapy; CI, confidence interval.

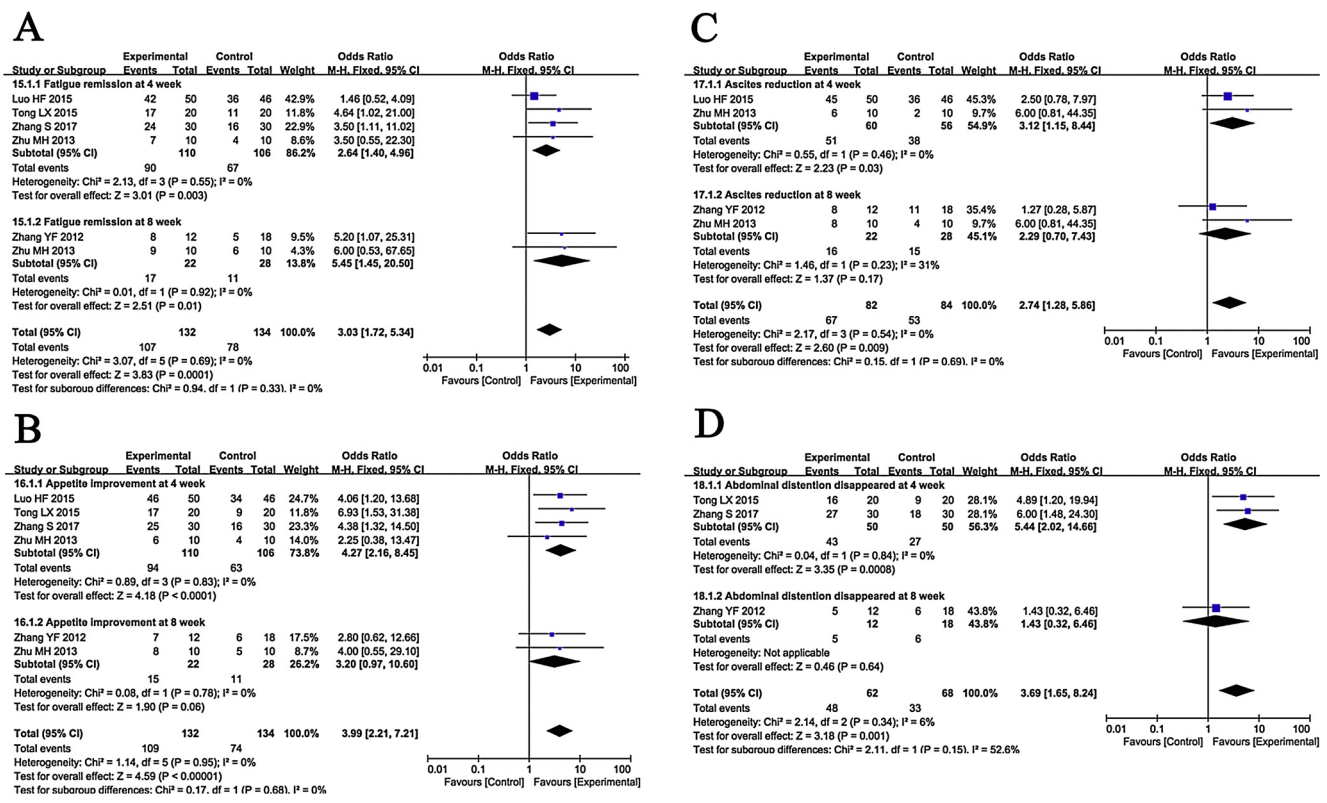

Figure 4 Forest plot of the comparison of clinical symptoms including fatigue (A), appetite (B), abdominal distension (C) and ascetics (D) between the experimental and control group. Control group, TST alone group; Experimental group TST plus UMSC therapy; UMSC: umbilical cord mesenchymal stem cells; TST: traditional supportive therapy; CI: confidence interval.

scores of PF, RP, BP, GH, VT and MH were significantly increased after combined treatment (Fig. 5, PF: OR = 8.54, CI = 2.61 to 14.48, $P = 0.005$; RP: OR = 11.31, CI = 2.14 to 20.47, $P = 0.02$; BP: OR = 13.08, CI = 7.55 to 18.61, $P < 0.0001$; GH: OR = 7.18, CI = 0.07 to 14.30, $P = 0.05$; VT: OR = 11.12, CI = 4.30 to 17.93, $P = 0.001$; MH: OR = 10.02, CI = 5.47 to 14.58, $P < 0.0001$), whereas SF and RE were not changed (SF: OR = 3.36, CI = −3.47 to 10.19, $P = 0.34$; RE: OR = 3.07, CI = −3.67 to 9.82, $P = 0.37$).

Adverse events assessment

Safety was evaluated upon assessing the adverse effects occurred during and after treatment. Adverse effects of interest were rare, and fever was the most common adverse effects, which usually subsided naturally within 24 hours (Table 4).

Sensitivity analysis

Sensitivity analysis was conducted and one trial was excluded because mesenchymal stem cells were isolated from umbilical cord blood [21]. The stability of primary endpoints was numerically verified and the overall results were still reliable when each parameter was excluded or included in sequence.

Discussion

MSC transfusion has been considered as a promising option to treat LC due to its unique biological characteristics. On one hand, the low immunogenicity of MSC reduces the possibility of graft-versus-host reaction [11]. On the other hand, MSC may help with the reparation and reestablishment in liver by inhibiting the death of hepatocytes and stimulating their regeneration [33—35]. Moreover, MSC shows anti-inflammatory effects, substantiated by up-regulated anti-inflammatory cytokine IL-10 and down regulated pro-inflammatory cytokines such as TNF-α and IL-6 [34,35]. In recent years, several preclinical LC studies using MSC have been conducted. MSC's effectiveness in treating LC was demonstrated through promoting the survival and regeneration of functional hepatocytes, reducing collagen deposition, by which slow down or hold up cirrhosis progress [36—38]. There were divers protocols applied in the isolated trials, which may lead to different therapeutic effects. To systematically assess the effectiveness of MSC transfusion in LC treatment, we investigated a host of clinical trials to achieve high statistical reliability.

Liver function can reflect the state of hepatocytes directly. Our meta-analysis showed significantly improved liver function in patients treated by UMSC, indicated by increased ALB level and decreased TBIL and ALT level. CHE and coagulation factors are mainly synthesized in liver, and appropriately reflected the liver reserve function in patients with LC. We also demonstrated significantly improved CHE,

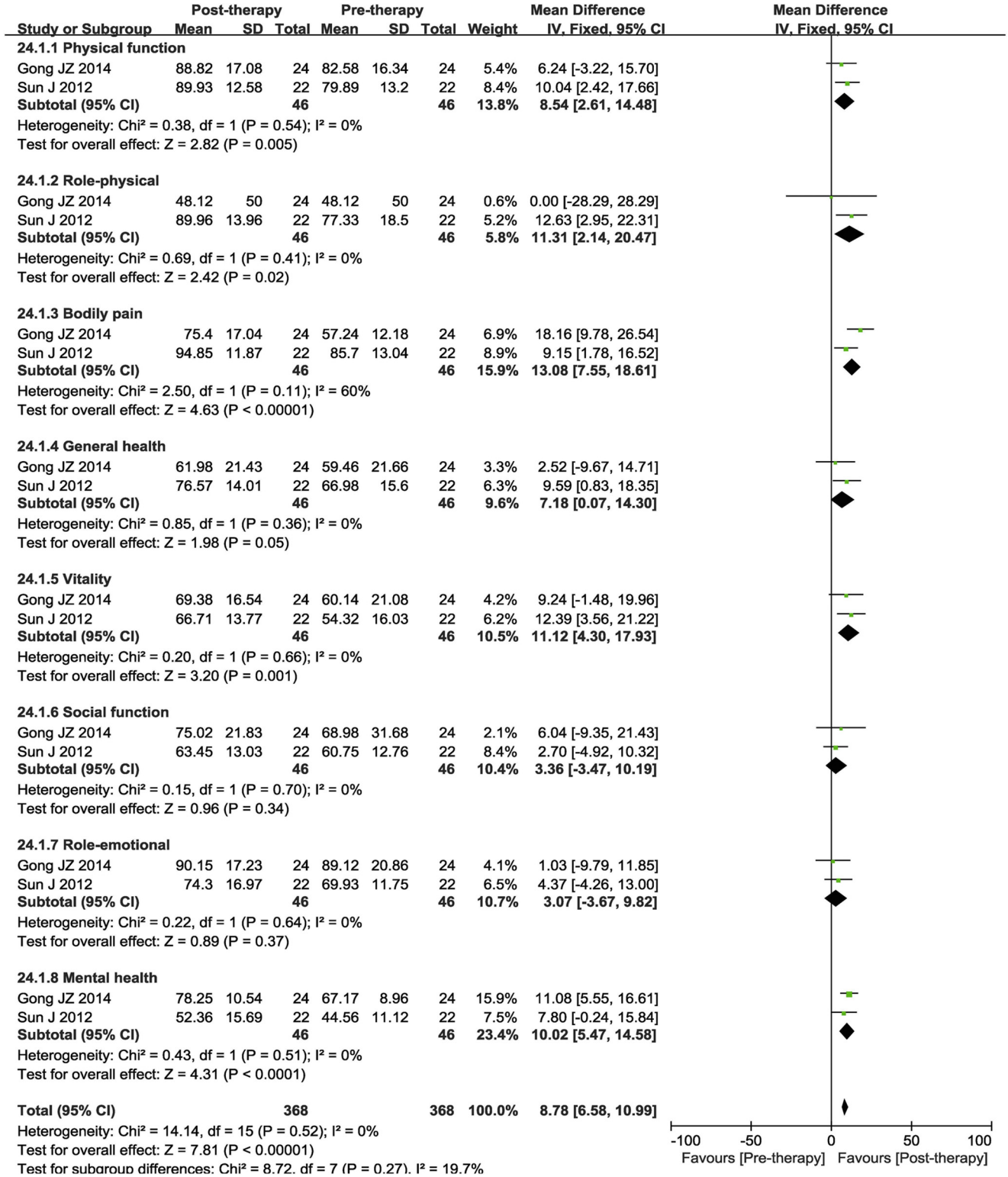

Figure 5 Forest plot of the comparison of quality of life (QOL) including physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE) and mental health (MH) in pre- and post-therapy. CI, confidence interval.

Table 4 Information of adverse effects during the UMSC therapy.

Included studies	Adverse effects (events)
Du et al., 2011 [20]	No obvious adverse reactions; low-grade fever (1)
Gong et al., 2014 [21]	Low-grade fever (3)
He et al., 2010 [22]	No obvious adverse reactions; fever (1)
Ji et al., 2017 [23]	ND
Lin et al., 2012 [16]	Low-grade fever (4)
Luo and Lei, 2016 [24]	ND
Luo et al., 2015 [25]	No obvious adverse reactions
Sun and Pi, 2012 [26]	ND
Sun et al., 2016 [27]	ND
Tong et al., 2015 [28]	No obvious adverse reactions
Zhang et al., 2017 [29]	No obvious adverse reactions
Zhang et al., 2012 [30]	Fever (2).
Zheng et al., 2015 [31]	No obvious adverse reactions; low-grade fever (ND)
Zhu et al., 2013 [32]	No obvious adverse reactions; low-grade fever (1)

UMSC: umbilical cord mesenchymal stem cells; ND: non-determined.

PT and PTA levels in patients underwent combined treatment. The QOL of patients were evaluated with the SF 36 scale in this study, and six of the eight indicators (PF, RP, BP, GH, VT and MH) were significantly improved after UMSC therapy.

Moreover, we revealed the combination of UMSC therapy and TST is associated with a more favorable efficacy than TST alone. Patients treated with combined therapy showed markedly increased ALB and PTA. Liver fibrosis is the one of the most important characteristics of cirrhosis [39]. Serological markers of liver fibrosis were compared between the two different therapy strategies. The degree of hepatic fibrosis was found attenuated more significantly after combined treatment compared with TST alone. We also evaluated the clinical symptoms of LC patients. Our assessment showed that compared to patients treated by TST alone, fatigue, anorexia, abdominal distension and ascites were significantly alleviated after the combined therapy. The results of our meta-analysis indicated that the combination of UMSC and TST had more satisfied therapeutic effects for LC patients than TST alone.

Safety is the top priority of the clinical treatment and it is also key factor for the development of UMSC therapy. UMSC have been applied for clinical use to treat hematological system malignant diseases for more than two decades with a contented safety record [40,41]. Our results further confirmed the safety of UMSC transfusion in LC treatment. Fever was the most common side effects during the UMSC therapy, and no serious adverse events or death occurred during therapy.

There are some limitations in this analysis. First of all, the numbers of involved studies and patients are small, and the follow-up period is short, which may introduce publication bias into conclusions and effect on our data interpretation. Moreover, the 14 included trials were all conducted among Chinese population. Although UMSC therapy has a widely admitted effectiveness on hematological diseases, diseases in nerve system and other systems [42—45], its application in the treatment of LC is not common in other countries apart from China. Despite the assessed data in this meta-analysis, there are other factors, which represent the therapeutic effects of UMSC therapy, such as UMSC infusion methods and cell dosages, and the stages of LC patients. Further analysis based on articles with more completed information may provide more valuable references for clinical trial design in the future.

In summary, this meta-analysis illustrated that UMSC combined with TST was safe and effective in LC therapy. UMSC therapy showed outstanding benefits for LC patients by improving their liver function and QOL, which proved its promising application in LC treatment as an alternative therapeutic strategy in combination with TST.

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Author Contributions

Yan Lu and Ke Li conceived and designed the experiments. Weiwei Sang and Benji Lv performed the experiments, analyzed the data and drafted the manuscript. All authors reviewed and participated in amending the manuscript before submission of the mutually agreed final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2017.11.003.

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