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ORIGINAL RESEARCH

Umbilical cord blood stem cells transplantation as an adjunctive treatment strategy for liver cirrhosis in Chinese population: a meta-analysis of effectiveness and safety

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Objective: The aim of the study was to evaluate the efficacy and safety of umbilical cord blood stem cells (USCs) transplantation combined with routine supportive therapy (RST) for liver cirrhosis (LC).

Materials and methods: Clinical trials involved in this research were searched from Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database. Treatment effects, quality of life (QoL), adverse events and other outcome measures were extracted and evaluated.

Results: A total of 10 trials including 616 LC patients were involved in this study. Based on our analysis, the liver function of LC patients was significantly improved after USCs transplantation and RST combined therapy, indicated by decreased total bilirubin, alanine aminotransferase, aspartate aminotransferase levels and prothrombin time and increased serum albumin level and prothrombin activity. Compared to those treated by RST alone, patients treated by combined therapy showed more satisfied treatment effects, improved QoL reflected by improved appetite (odds ratio [OR]=5.43, 95% CI=2.84 to 10.38, $P<0.00001$) and relieved fatigue (OR=4.33, 95% CI=0.87 to 21.60, $P=0.07$), ascetic fluid (OR=4.56, 95% CI=2.69 to 7.74, $P<0.00001$), abdominal distension (OR=4.01, 95% CI=1.34 to 12.02, $P=0.01$) and edema (OR=2.69, 95% CI=0.23 to 31.72, $P=0.43$). No serious adverse events occurred during USCs therapy.

Conclusion: USCs transplantation is a safe and effective adjuvant therapy for RST-treated LC, possibly through improving patients' liver function.

Keywords: umbilical cord blood stem cells, routine supportive therapy, liver cirrhosis, meta-analysis

Introduction

Liver cirrhosis (LC) is a common chronic progressive liver disease with diffuse liver damage, which usually results from prolonged or repeated alcohol excess, viral hepatitis and other etiologies.[1,2] LC is characterized as reduced liver regeneration and hepatic dysfunction, which can lead to portal hypertension with serious complications including ascites, hepatic encephalopathy, secondary infection and so on.[3,4] Incidence of LC and mortality caused by LC had risen remarkably in the past few decades, and the patients were usually diagnosed at the irreversible state.[1] Although survival has been improved due to effective LC management, it still ranks high among the world's leading causes of death.[2,5] Liver transplantation is the only curative treatment for patients with decompensated LC,[5] but it confronts with problems such as donor shortage,

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high medical costs, surgical complications, immunological rejection and ethical restraints.[3,5] Liver transplantation failure may cause extensive and progressive fibrosis, which restrains liver regeneration and causes irreversible cirrhosis.[3]

Researchers have been exploring new approaches to promote liver regeneration,[3] and stem cell therapy was considered as a promising treatment strategy.[6,7] Preclinical LC studies on stem cell transplantation have shown beneficial effects, and the most commonly used cells were mesenchymal stem cells (MSCs),[8–10] hepatic progenitor cells (HPCs)[11,12] and hematopoietic stem cells (HSCs),[13,14] which were usually obtained from autologous or allogeneic bone marrow.[4,12] However, the procedure of bone marrow aspiration was invasive, and quantity and quality of bone marrow stem cells (BMSCs) are age-dependent, which limit their clinical potentiality.[15–18] As an alternative source of BMSCs, umbilical cord blood stem cells (USCs) showed promising clinical application prospects. USCs are composed of immature immune cells and multipotent stem cells such as MSCs, endothelial progenitor cells (EPCs) and HSCs.[16,17] They can migrate to injury sites due to chemotaxis, differentiate into various types of cells such as osteoblasts, chondrocytes and hepatocytes cells and secrete various cytokines and growth factors.[19] Compared to BMSCs, USCs are more accessible with fewer ethical constraints.[17,18,20]

Clinical trials reported that USCs transfusion could ameliorate liver fibrosis and improve liver functions without significant side effects.[21,22] In comparison with LC patients treated by routine supportive therapy (RST), those who underwent RST and USCs combined therapy exhibited more prominent therapeutic effects. In this study, we conducted a meta-analysis to systematically evaluate the therapeutic efficacy and safety of USCs and RST combined therapy in comparison with RST alone for LC, in order to provide scientific basis for future research and clinical application.

Materials and methods

Search strategy and selection criteria

We performed literature search across Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database with key terms "stem cells" OR "umbilical cord blood stem cells", AND "liver cirrhosis" OR "hepatocirrhosis", without language restriction. Literature studies published before April 2017 were involved in this analysis.

The selection criteria are listed as follows: case-controlled trials involving >30 LC patients; participants diagnosed with LC, without malignant tumor and not pregnant or lactating; patients in the experimental group who received USCs and RST combined therapy, and those in the control group who were treated by RST alone.

Data extraction and quality assessment

Two authors (Huimin Tao and Yafeng Li) collected and summarized data independently, including author's names, years of publication, locations, patients' ages and LC stages, samples sizes, causes of LC, therapeutic regimens, administration routes, number of USCs and study parameter types. Trials' quality was evaluated by following the instructions of Cochrane Handbook.[23]

Outcome definition

Clinical responses evaluated in this research included treatment efficacy, quality of life (QoL) and adverse events. Treatment efficacy was assessed in terms of levels of total bilirubin (TBIL), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), prothrombin activity (PTA) and Child–Pugh score. Patients' QoL covered the following indicators: fatigue, appetite, abdominal distension, ascitic fluid and edema.

Statistical analysis

We performed analysis using Review Manager 5.2 (Cochrane Collaboration). $P<0.05$ indicates differences with statistical significance. Appropriate analysis model was determined by heterogeneity according to Cochran's Q test.[24] Studies with $I^2<50\%$ or $P>0.1$ was considered homogenous, and fixed-effects model was applied; otherwise a random-effects model was applied.[25] Therapeutic efficacy was evaluated by odds ratio (OR) and presented with 95% CI.

Publication bias was evaluated based on the funnel plot. Sensitivity analyses were also performed to assess the impact of number of infused cells ($>1\times10^8$ or $<1\times10^8$) and routes of cell administration (intravenous or hepatic artery infusion).

Results

Search results

A total of 5,323 articles were initially identified, and 5,227 were excluded due to the lack of clinical trials (n=4,876), duplication and repetition (n=187) or were unrelated studies (n=164). After full-text assessment, 18 reviews or meta-analyses, 12 articles without control group, 48 studies without USCs transplantation and 8 with insufficient data were also excluded. After selection, 10 trials[26–35] with 616 LC patients were included in this meta-analysis (Figure 1).

Characteristics of patients

All trials that met our selection criteria were conducted in People's Republic of China. In total, 327 LC patients accepted USCs and RST combined therapy, and 289 patients were treated by RST alone.

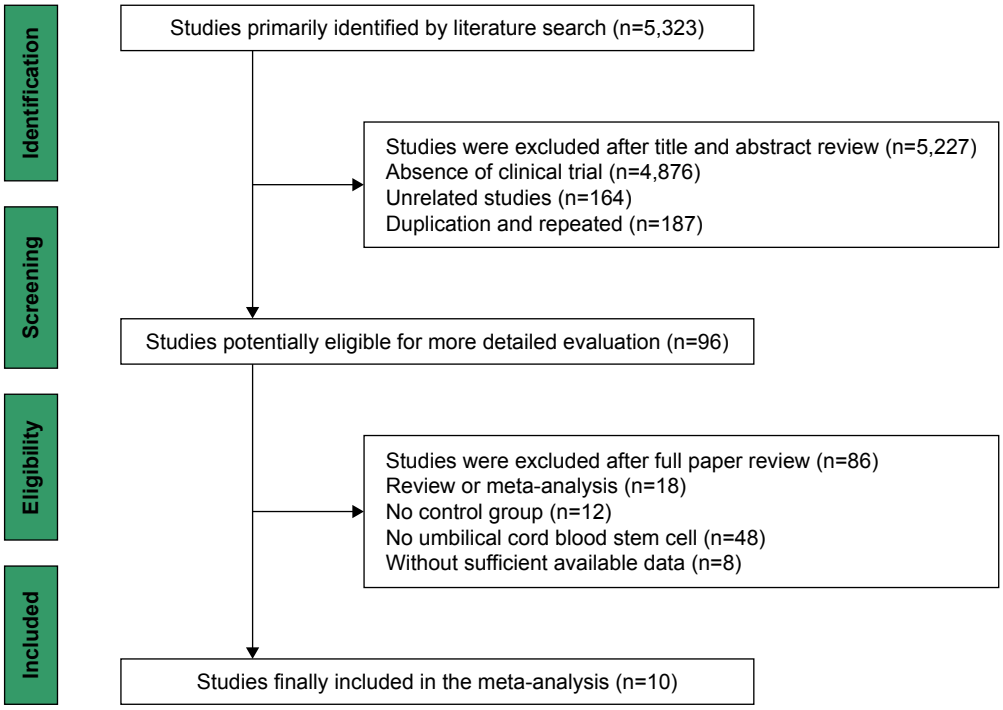

Figure 1 Flow diagram of the selection process.

USCs were obtained from healthy full-term infant's umbilical cord blood and were infused to LC patients through hepatic artery (n=6), portal vein (n=1) or peripheral vein (n=3), respectively. Detailed information of the involved studies and participants is summarized in Tables 1 and 2.

Quality assessment

Risk of bias assessment is shown in Figure 2. Six studies had low risk and the other 4 studies did not have clear description of randomization process. All studies had low risk of bias on allocation, performance and detection. One trial missing follow-up study and 1 trial missing primary outcome data had high risk of bias, and 2 studies with selective reporting had unclear risk of bias.

Therapeutic efficacy assessments

Random-effects meta-analysis was used to analyze the OR rate of the following descriptive indicators because of their high heterogeneity.

Effectiveness of USCs on TBIL, ALB, ALT, AST and coagulation function

As shown in Figure 3A, the TBIL level was reduced after combined therapy. This reduction was statistically significant

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

Included studies	Nation	Stage of LC	No of patients Con/Exp	Age (years)		Causes of LC
				Con	Exp	
Li et al (2013)[26]	People's Republic of China	Child–Pugh C	48/61	ND	ND	HBV
Li and Zhang (2016)[27]	People's Republic of China	Child–Pugh A–C	21/29	19.2±5.3 (mean)	18.5±6.9 (mean)	HDC
Tan et al (2012)[28]	People's Republic of China	Child–Pugh A–C	20/22	ND	56 (mean)	ND
Wang et al (2012)[29]	People's Republic of China	Child–Pugh B–C	31/30	50±20 (mean)	48±22 (mean)	HBV (43), HCV (13) and alcohol (5)
Wang et al (2014)[30]	People's Republic of China	Child–Pugh B–C	20/30	52 (median)	53 (median)	HBV (35), HCV (5), alcohol (6) and BC (4)
Zhang et al (2015)[31]	People's Republic of China	Child–Pugh A–C	23/25	56.1±9.5 (mean)	55.6±10.7 (mean)	HBV
Zhou et al (2013)[32]	People's Republic of China	Child–Pugh B–C	26/30	42.8±5.1 (mean)	44.1±3.9 (mean)	HBV
Zhou et al (2016)[33]	People's Republic of China	Child–Pugh B–C	30/30	46±25 (mean)	45±26 (mean)	PBC
Zhou et al (2017)[34]	People's Republic of China	Child–Pugh B–C	40/40	ND	ND	Alcohol
Zhu and Han (2014)[35]	People's Republic of China	Child–Pugh B–C	30/30	55.2±14.1 (mean)	54.3±12.4 (mean)	PC (49) and alcohol (11)

Notes: Con, control group (RST alone group); Exp, experimental group (RST plus USCs therapy).
Abbreviations: LC, liver cirrhosis; ND, non-determined; HBV, hepatitis B virus; HDC, hepatolenticular degeneration cirrhosis; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; BC, biliary cirrhosis; PC, post-hepatitic cirrhosis; RST, routine supportive treatment; USCs, umbilical cord blood stem cells.

Table 2 Information of USCs therapy

Included studies	Therapeutic regimen		Administration route	Cell dose	Parameter types
	Exp group	Con group			
Li et al (2013)[26]	Con Reg + USCs	RST	1×10^9	1×10^9	TBIL, ALT, PT and QoL
Li and Zhang (2016)[27]	Con Reg + USCs	RST	$1.6–7.3\times10^7$	$1.6–7.3\times10^7$	TBIL, ALB, ALT, AST and PT
Tan et al (2012)[28]	Con Reg + USCs	RST	3.3×10^8 to 8.7×10^9	3.3×10^8 to 8.7×10^9	TBIL, ALB, ALT and PT
Wang et al (2012)[29]	Con Reg + USCs	RST	$1–5\times10^7$	$1–5\times10^7$	TBIL, ALB, ALT, AST and PTA
Wang et al (2014)[30]	Con Reg + USCs	RST	$1.6–7.3\times10^9$	$1.6–7.3\times10^9$	TBIL, ALB, ALT, AST and PTA
Zhang et al (2015)[31]	Con Reg + USCs	RST	$0.2–2\times10^7$	$0.2–2\times10^7$	TBIL, ALT, AST and PT
Zhou et al (2013)[32]	Con Reg + USCs	RST	$>2\times10^9$	$>2\times10^9$	TBIL, ALB, ALT, AST, PT and QoL
Zhou et al (2016)[33]	Con Reg + USCs	RST	$1–5\times10^7$	$1–5\times10^7$	TBIL, ALB, ALT, AST and PTA
Zhou et al (2017)[34]	Con Reg + USCs	RST	$1–5\times10^7$	$1–5\times10^7$	TBIL, ALB, ALT, AST and PTA
Zhu and Han (2014)[35]	Con Reg + USCs	RST	$1.7–7.5\times10^7$	$1.7–7.5\times10^7$	TBIL, ALB, ALT, PT and QoL

Notes: Con, control group (RST alone group); Exp, experimental group (RST plus USCs therapy).
Abbreviations: Con Reg, Control group regimen; USCs, umbilical cord blood stem cells; RST, routine supportive treatment; TBIL, total bilirubin; ALT, alanine aminotransferase; PT, prothrombin time; QoL, quality of life; ALB, albumin; AST, aspartate aminotransferase; PTA, prothrombin activity.

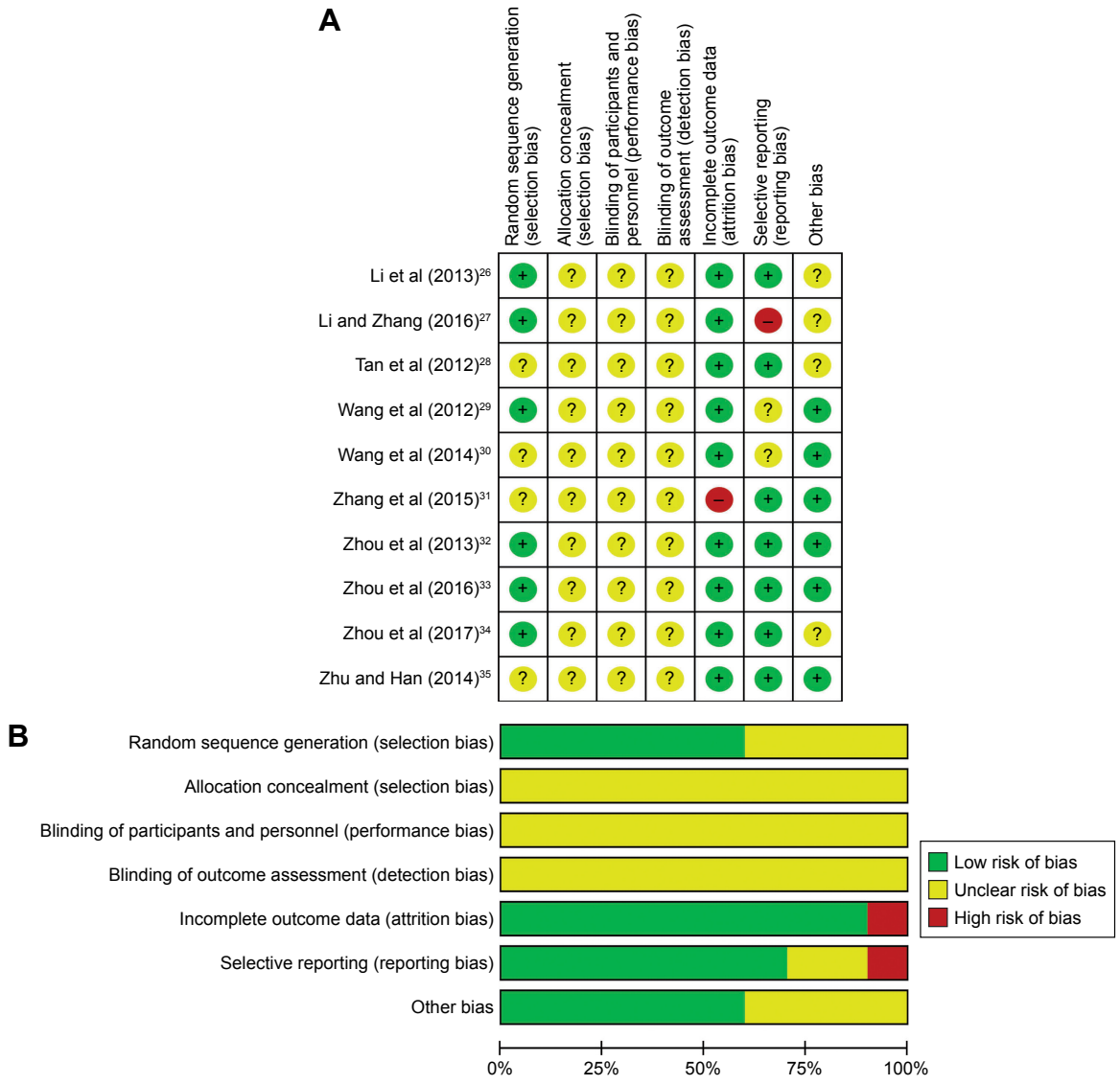

Figure 2 (**A**) Risk of bias summary: review of authors' judgments about each risk of bias item for the included studies. (**B**) Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all the included studies. Each color represents a different level of bias: red for high risk, green for low risk and yellow for unclear risk of bias.

A

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
TBIL at 1st week								
Tan et al (2012)[28]	41.2	13.2	22	43.6	12.3	22	5.1	−2.40 (−9.94 to 5.14)
Wang et al (2014)[30]	43.6	12.3	30	46.6	12	30	5.2	−3.00 (−9.15 to 3.15)
Subtotal (95% CI)			**52**			**52**	**10.4**	**−2.76 (−7.53 to 2.00)**
Heterogeneity: τ^2=0.00; χ^2=0.01, *df*=1 (*P*=0.90); I^2=0%								
Test for overall effect: *Z*=1.14 (*P*=0.26)								
TBIL at 4th week								
Li et al (2013)[26]	68	10	61	79	11	61	5.3	−11.00 (−14.73 to −7.27)
Li and Zhang (2016)[27]	20.5	8.5	29	65.3	21.6	29	5.1	−44.80 (−53.25 to −36.35)
Tan et al (2012)[28]	34.5	10.4	22	43.6	12.3	22	5.2	−9.10 (−15.83 to −2.37)
Zhang et al (2015)[31]	36.3	19.7	25	36.4	22	25	4.9	−0.10 (−11.68 to 11.48)
Zhou et al (2013)[32]	57.9	15	30	63.4	18.5	30	5.1	−5.50 (−14.02 to 3.02)
Zhu and Han (2014)[35]	91.7	46.6	30	107.3	53.2	30	3.6	−15.60 (−40.91 to 9.71)
Subtotal (95% CI)			**197**			**197**	**29.2**	**−14.37 (−26.15 to −2.58)**
Heterogeneity: τ^2=184.44; χ^2=64.59, *df*=5 (*P*<0.00001); I^2=92%								
Test for overall effect: *Z*=2.39 (*P*=0.02)								
TBIL at 8th week								
Li et al (2013)[26]	50	10	61	79	11	61	5.3	−29.00 (−32.73 to −25.27)
Wang et al (2012)[29]	30.1	12	30	37.4	14.5	30	5.2	−7.30 (−14.04 to −0.56)
Zhou et al (2013)[32]	38.5	9.2	30	63.4	18.5	30	5.1	−24.90 (−32.29 to −17.51)
Zhou et al (2016)[33]	38.3	12.2	30	50.3	16.5	30	5.2	−12.00 (−19.34 to −4.66)
Zhou et al (2017)[34]	38.5	12.2	40	51.3	16.5	40	5.2	−12.80 (−19.16 to −6.44)
Zhu and Han (2014)[35]	71.3	37.8	30	107.3	53.2	30	3.8	−36.00 (−59.35 to −12.65)
Subtotal (95% CI)			**221**			**221**	**29.8**	**−18.92 (−27.74 to −10.10)**
Heterogeneity: τ^2=99.77; χ^2=48.37, *df*=5 (*P*<0.00001); I^2=90%								
Test for overall effect: *Z*=4.21 (*P*<0.0001)								
TBIL at 12th week								
Li et al (2013)[26]	31	8	61	79	11	61	5.3	−48.00 (−51.41 to −44.59)
Tan et al (2012)[28]	25.5	9.5	22	43.6	12.3	22	5.2	−18.10 (−24.59 to −11.61)
Zhang et al (2015)[31]	34.1	20.2	25	36.4	22	25	4.9	−2.30 (−14.01 to 9.41)
Subtotal (95% CI)			**108**			**108**	**15.4**	**−23.21 (−50.11 to 3.68)**
Heterogeneity: τ^2=548.56; χ^2=104.24, *df*=2 (*P*<0.00001); I^2=98%								
Test for overall effect: *Z*=1.69 (*P*=0.09)								
TBIL at 24th week								
Li et al (2013)[26]	30	6	61	79	11	61	5.3	−49.00 (−52.14 to −45.86)
Tan et al (2012)[28]	26.5	13.5	22	43.6	12.3	22	5.1	−17.10 (−24.73 to −9.47)
Zhang et al (2015)[31]	36.2	20	25	36.4	22	25	4.9	−0.20 (−11.85 to 11.45)
Subtotal (95% CI)			**108**			**108**	**15.3**	**−22.48 (−52.22 to 7.26)**
Heterogeneity: τ^2=673.23; χ^2=109.32, *df*=2 (*P*<0.00001); I^2=98%								
Test for overall effect: *Z*=1.48 (*P*=0.14)								
Total (95% CI)			**686**			**686**	**100**	**−17.42 (−25.89 to −8.94)**
Heterogeneity: τ^2=348.79; χ^2=712.83, *df*=19 (*P*<0.00001); I^2=97%								
Test for overall effect: *Z*=4.03 (*P*<0.0001)								
Test for subgroup differences: χ^2=13.80, *df*=4 (*P*=0.008); I^2=71.0%								

Mean difference IV, random, 95% CI

−100 −50 0 50 100

Favors (post-therapy) Favors (pre-therapy)

Figure 3 (*Continued*)

B

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
ALB at 1st week								
Tan et al (2012)[28]	29.1	10.5	22	28.6	9.4	22	3.8	0.50 (–5.39 to 6.39)
Wang et al (2014)[30]	27.1	4.8	30	25.6	8.2	30	5.9	1.50 (–1.90 to 4.90)
Subtotal (95% CI)			**52**			**52**	**9.6**	**1.25 (–1.69 to 4.19)**
Heterogeneity: τ^2=0.00; χ^2=0.08, *df*=1 (*P*=0.77); I^2=0%								
Test for overall effect: *Z*=0.83 (*P*=0.41)								
ALB at 4th week								
Li et al (2013)[26]	28.6	2.6	61	22.8	5.8	61	7.5	5.80 (4.20 to 7.40)
Li and Zhang (2016)[27]	37.2	3.4	29	29.9	2.8	29	7.5	7.30 (5.70 to 8.90)
Tan et al (2012)[28]	33.5	11.8	22	28.6	9.4	22	3.5	4.90 (–1.40 to 11.20)
Zhou et al (2013)[32]	35.2	3.3	30	29.8	3.6	30	7.4	5.40 (3.65 to 7.15)
Zhu and Han (2014)[35]	28.2	6.3	30	27.5	5.1	30	6.4	0.70 (–2.20 to 3.60)
Subtotal (95% CI)			**172**			**172**	**32.3**	**5.09 (3.14 to 7.04)**
Heterogeneity: τ^2=3.26; χ^2=15.42, *df*=4 (*P*=0.004); I^2=74%								
Test for overall effect: *Z*=5.12 (*P*<0.00001)								
ALB at 8th week								
Li et al (2013)[26]	30.1	5.4	61	22.8	5.8	61	7.2	7.30 (5.31 to 9.29)
Wang et al (2012)[29]	36.4	7.8	30	26.9	9.3	30	5.0	9.50 (5.16 to 13.84)
Zhou et al (2013)[32]	35	3.4	30	29.8	3.6	30	7.4	5.20 (3.43 to 6.97)
Zhou et al (2016)[33]	33.1	8.3	30	24.9	7.8	30	5.2	8.20 (4.12 to 12.28)
Zhou et al (2017)[34]	32.3	8.3	40	25.9	7.8	40	5.7	6.40 (2.87 to 9.93)
Zhu and Han (2014)[35]	30.1	4.9	30	27.5	5.1	30	6.7	2.60 (0.07 to 5.13)
Subtotal (95% CI)			**221**			**221**	**37.3**	**6.16 (4.34 to 7.99)**
Heterogeneity: τ^2=2.96; χ^2=12.97, *df*=5 (*P*=0.02); I^2=61%								
Test for overall effect: *Z*=6.63 (*P*<0.00001)								
ALB at 12th week								
Li et al (2013)[26]	33.4	8.9	61	22.8	5.8	61	6.6	10.60 (7.93 to 13.27)
Tan et al (2012)[28]	36.6	12.4	22	28.6	9.4	22	3.4	8.00 (1.50 to 14.50)
Subtotal (95% CI)			**83**			**83**	**9.9**	**10.23 (7.76 to 12.69)**
Heterogeneity: τ^2=0.00; χ^2=0.53, *df*=1 (*P*=0.47); I^2=0%								
Test for overall effect: *Z*=8.13 (*P*<0.00001)								
ALB at 24th week								
Li et al (2013)[26]	34.6	3.8	61	22.8	5.8	61	7.4	11.80 (10.06 to 13.54)
Tan et al (2012)[28]	37.3	11.7	22	28.6	9.4	22	3.5	8.70 (2.43 to 14.97)
Subtotal (95% CI)			**83**			**83**	**10.9**	**11.58 (9.90 to 13.26)**
Heterogeneity: τ^2=0.00; χ^2=0.87, *df*=1 (*P*=0.35); I^2=0%								
Test for overall effect: *Z*=13.53 (*P*<0.00001)								
Total (95% CI)			**611**			**611**	**100**	**6.21 (4.65 to 7.76)**
Heterogeneity: τ^2=7.68; χ^2=90.79, *df*=16 (*P*<0.00001); I^2=82%								
Test for overall effect: *Z*=7.84 (*P*<0.00001)								
Test for subgroup differences: χ^2=52.61, *df*=4 (*P*<0.00001); I^2=92.4%								

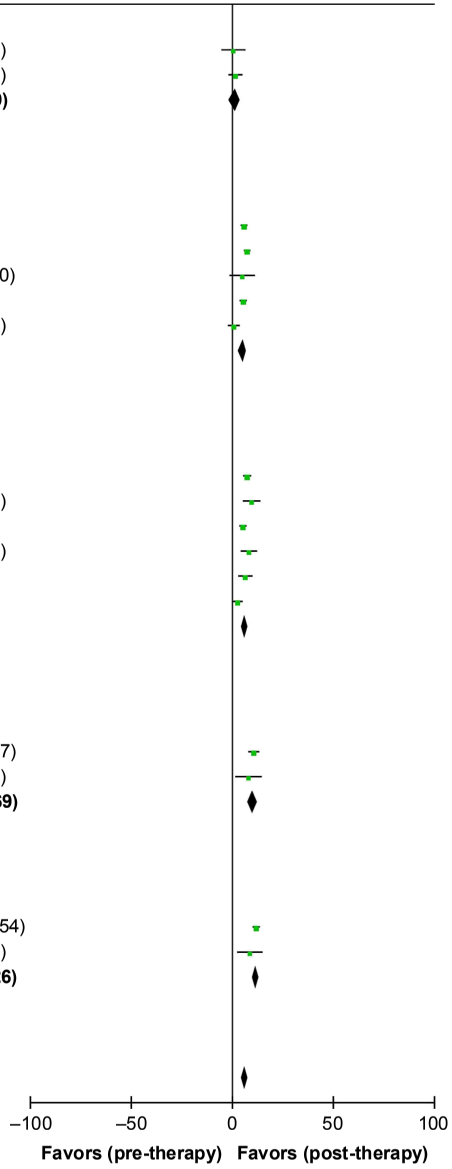

Figure 3 (*Continued*)

Figure 3 (*Continued*)

D

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
AST at 1st week								
Wang et al (2014)[30]	51.2	10.8	30	55.6	12.5	30	11.8	–4.40 (–10.31 to 1.51)
Subtotal (95% CI)			**30**			**30**	**11.8**	**–4.40 (–10.31 to 1.51)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.46 (P=0.14)								
AST at 4th week								
Li and Zhang (2016)[27]	54.3	16.2	29	78.3	54.7	29	8.8	–24.00 (–44.76 to –3.24)
Zhang et al (2015)[31]	36.3	16.7	25	37.2	21.6	25	11.0	–0.90 (–11.60 to 9.80)
Zhou et al (2013)[32]	42.3	12.7	30	79.7	16.1	30	11.6	–37.40 (–44.74 to –30.06)
Subtotal (95% CI)			**84**			**84**	**31.4**	**–20.79 (–46.96 to 5.37)**
Heterogeneity: τ^2=485.94; χ^2=30.42, df=2 (P<0.00001); I^2=93%								
Test for overall effect: Z=1.56 (P=0.12)								
AST at 8th week								
Wang et al (2012)[29]	53.6	15.4	30	68.1	17	30	11.5	–14.50 (–22.71 to –6.29)
Zhou et al (2013)[32]	41.5	9.9	30	79.7	16.1	30	11.7	–38.20 (–44.96 to –31.44)
Zhou et al (2016)[33]	33.6	14.5	30	72.6	16.9	30	11.5	–39.00 (–46.97 to –31.03)
Subtotal (95% CI)			**90**			**90**	**34.6**	**–30.66 (–45.80 to –15.52)**
Heterogeneity: τ^2=163.69; χ^2=23.64, df=2 (P<0.00001); I^2=92%								
Test for overall effect: Z=3.97 (P<0.0001)								
AST at 12th week								
Zhang et al (2015)[31]	33.8	14.9	25	37.2	21.6	25	11.1	–3.40 (–13.69 to 6.89)
Subtotal (95% CI)			**25**			**25**	**11.1**	**–3.40 (–13.69 to 6.89)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.65 (P=0.52)								
AST at 24th week								
Zhang et al (2015)[31]	35.4	15.6	25	37.2	21.6	25	11.1	–1.80 (–12.24 to 8.64)
Subtotal (95% CI)			**25**			**25**	**11.1**	**–1.80 (–12.24 to 8.64)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.34 (P=0.74)								
Total (95% CI)			**254**			**254**	**100**	**–18.24 (–29.97 to –6.52)**
Heterogeneity: τ^2=294.92; χ^2=133.78, df=8 (P<0.00001); I^2=94%								
Test for overall effect: Z=3.05 (P=0.002)								
Test for subgroup differences: χ^2=12.54, df=4 (P=0.01); I^2=68.1%								

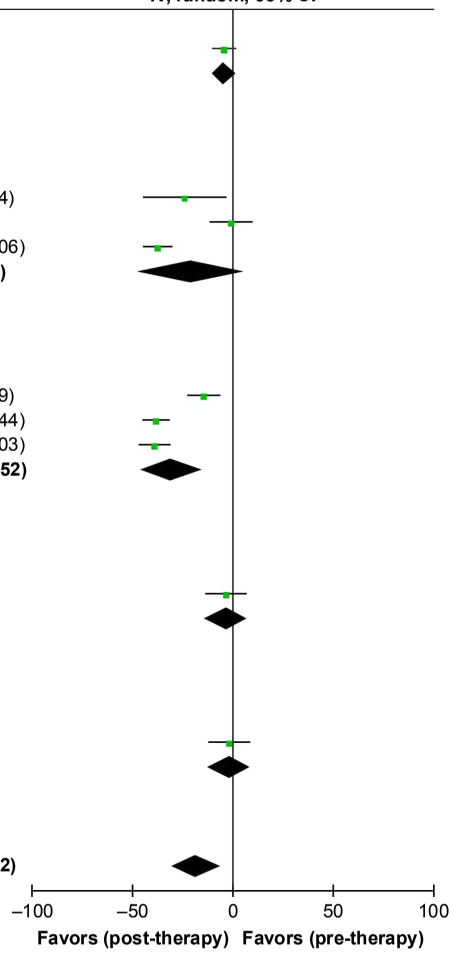

Figure 3 (*Continued*)

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Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
PT at 1st week								
Tan et al (2012)[28]	25.5	10.4	22	26.4	11.7	22	2.6	–0.90 (–7.44 to 5.64)
Wang et al (2014)[30]	22.7	5.5	30	23.5	4.3	30	7.1	–0.80 (–3.30 to 1.70)
Subtotal (95% CI)			**52**			**52**	**9.7**	**–0.81 (–3.15 to 1.52)**
Heterogeneity: τ^2=0.00; χ^2=0.00, *df*=1 (*P*=0.98); I^2=0%								
Test for overall effect: *Z*=0.68 (*P*=0.49)								
PT at 4th week								
Li et al (2013)[26]	18.6	1.6	61	20.1	3.2	61	9.5	–1.50 (–2.40 to –0.60)
Li and Zhang (2016)[27]	15.5	3.7	29	18.8	4.7	29	7.6	–3.30 (–5.48 to –1.12)
Tan et al (2012)[28]	18.6	8.4	22	26.4	11.7	22	3.0	–7.80 (–13.82 to –1.78)
Zhou et al (2013)[32]	17.6	2	30	22.3	3.7	30	8.7	–4.70 (–6.21 to –3.19)
Zhu and Han (2014)[35]	15.1	2.1	30	16.7	3.9	30	8.6	–1.60 (–3.19 to –0.01)
Subtotal (95% CI)			**172**			**172**	**37.5**	**–3.01 (–4.66 to –1.37)**
Heterogeneity: τ^2=2.38; χ^2=17.55, *df*=4 (*P*=0.002); I^2=77%								
Test for overall effect: *Z*=3.59 (*P*=0.0003)								
PT at 8th week								
Li et al (2013)[26]	17.4	0.8	61	20.1	3.2	61	9.6	–2.70 (–3.53 to –1.87)
Zhou et al (2013)[32]	15.9	1	30	22.3	3.7	30	8.9	–6.40 (–7.77 to –5.03)
Zhu and Han (2014)[35]	15	2.9	30	16.7	3.9	30	8.4	–1.70 (–3.44 to 0.04)
Subtotal (95% CI)			**121**			**121**	**26.9**	**–3.61 (–6.21 to –1.02)**
Heterogeneity: τ^2=4.80; χ^2=24.80, *df*=2 (*P*<0.00001); I^2=92%								
Test for overall effect: *Z*=2.73 (*P*=0.006)								
PT at 12th week								
Li et al (2013)[26]	15.2	1.4	61	20.1	3.2	61	9.6	–4.90 (–5.78 to –4.02)
Tan et al (2012)[28]	16.4	5.2	22	26.4	11.7	22	3.5	–10.00 (–15.35 to –4.65)
Subtotal (95% CI)			**83**			**83**	**13.0**	**–6.74 (–11.54 to –1.94)**
Heterogeneity: τ^2=9.18; χ^2=3.40, *df*=1 (*P*=0.07); I^2=71%								
Test for overall effect: *Z*=2.75 (*P*=0.006)								
PT at 24th week								
Li et al (2013)[26]	14.1	0.9	61	20.1	3.2	61	9.6	–6.00 (–6.83 to –5.17)
Tan et al (2012)[28]	15.7	6.8	22	26.4	11.7	22	3.2	–10.70 (–16.35 to –5.05)
Subtotal (95% CI)			**83**			**83**	**12.8**	**–7.48 (–11.77 to –3.20)**
Heterogeneity: τ^2=6.79; χ^2=2.60, *df*=1 (*P*=0.11); I^2=61%								
Test for overall effect: *Z*=3.43 (*P*=0.0006)								
Total (95% CI)			**511**			**511**	**100**	**–3.97 (–5.20 to –2.73)**
Heterogeneity: τ^2=3.94; χ^2=111.99, *df*=13 (*P*<0.00001); I^2=88%								
Test for overall effect: *Z*=6.31 (*P*<0.00001)								
Test for subgroup differences: χ^2=10.08, *df*=4 (*P*=0.04); I^2=60.3%								

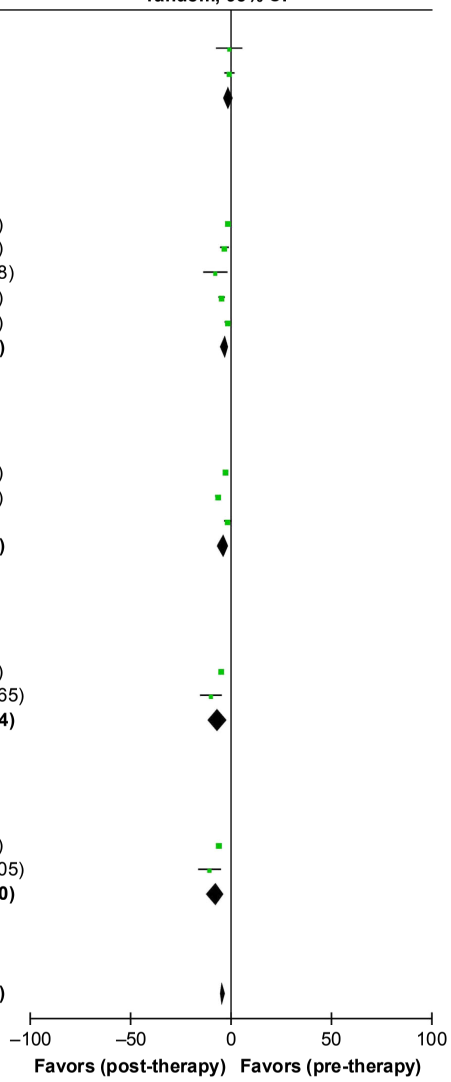

Figure 3 (*Continued*)

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Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
PTA at 2nd week								
Zhang et al (2015)[31]	67.4	25.5	25	62.2	22	25	5.4	5.20 (–8.00 to 18.40)
Subtotal (95% CI)			**25**			**25**	**5.4**	**5.20 (–8.00 to 18.40)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.77 (P=0.44)								
PTA at 4th week								
Zhang et al (2015)[31]	68.4	23.7	25	62.2	22	25	5.8	6.20 (–6.48 to 18.88)
Subtotal (95% CI)			**25**			**25**	**5.8**	**6.20 (–6.48 to 18.88)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.96 (P=0.34)								
PTA at 8th week								
Wang et al (2012)[29]	57.2	11.8	30	47.4	10.1	30	30.3	9.80 (4.24 to 15.36)
Zhou et al (2016)[33]	43	11.4	30	37.5	14.5	30	21.5	5.50 (–1.10 to 12.10)
Zhou et al (2017)[34]	74	12.4	40	60.5	14.5	40	26.8	13.50 (7.59 to 19.41)
Subtotal (95% CI)			**100**			**100**	**78.7**	**9.79 (5.46 to 14.13)**
Heterogeneity: τ^2=5.32; χ^2=3.13, df=2 (P=0.21); I^2=36%								
Test for overall effect: Z=4.43 (P<0.00001)								
PTA at 12th week								
Zhang et al (2015)[31]	71.3	27.4	25	62.2	22	25	4.9	9.10 (–4.67 to 22.87)
Subtotal (95% CI)			**25**			**25**	**4.9**	**9.10 (–4.67 to 22.87)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.29 (P=0.20)								
PTA at 24th week								
Zhang et al (2015)[31]	70.9	26.3	25	62.2	22	25	5.2	8.70 (–4.74 to 22.14)
Subtotal (95% CI)			**25**			**25**	**5.2**	**8.70 (–4.74 to 22.14)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.27 (P=0.20)								
Total (95% CI)			**200**			**200**	**100**	**9.32 (6.26 to 12.38)**
Heterogeneity: τ^2=0.00; χ^2=3.85, df=6 (P=0.70); I^2=0%								
Test for overall effect: Z=5.97 (P<0.00001)								
Test for subgroup differences: χ^2=0.64, df=4 (P=0.96); I^2=0%								

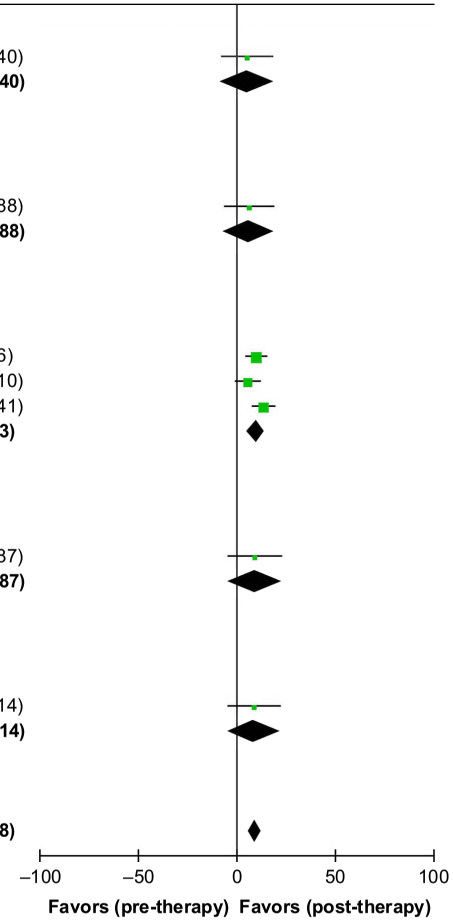

Figure 3 Forest plot of the comparison of TBIL (**A**), ALB (**B**), ALT (**C**), AST (**D**), PT (**E**) and PTA (**F**) in pre- and post-therapy.
Note: The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance method; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PTA, prothrombin activity.

in the 4th and 8th week (4th: OR=−14.37, CI=−26.15 to −2.58, P=0.02; 8th: OR=−18.92, CI=−27.74 to −10.10, P<0.0001), but not in the 1st, 12th and 24th week after treatment (1st: OR=−2.76, CI=−7.53 to 2.00, P=0.26; 12th: OR=−23.21, CI=−50.11 to 3.68, P=0.09; 24th: OR=−22.48, CI=−52.22 to 7.26, P=0.14). No statistical differences were observed in the TBIL level between experimental and control groups (Figure S1A).

The ALB level was increased after combined therapy, especially in the 4th, 8th, 12th and 24th week (Figure 3B, 1st: OR=1.25, CI=−1.69 to 4.19, P=0.41; 4th: OR=5.09, CI=3.14 to 7.04, P<0.00001; 8th: OR=6.16, CI=4.34 to 7.99, P<0.00001; 12th: OR=10.23, CI=7.76 to 12.69, P<0.00001; 24th: OR=11.58, CI=9.90 to 13.26, P<0.00001). The ALB level in the combined therapy group was also higher than that of the control group in the 4th, 8th, 12th and 24th week after therapy (Figure S1B).

After combined therapy, the ALT level was significantly reduced in the 4th and 8th week (Figure 3C, 1st: OR=−14.98, CI=−52.73 to 22.77, P=0.44; 4th: OR=−62.91, CI=−90.38 to −35.43, P<0.00001; 8th: OR=−38.84, CI=−63.80 to −13.87, P=0.002; 12th: OR=−97.79, CI=−173.60 to −21.98, P=0.01; 24th: OR=−101.28, CI=−179.48 to −23.08, P=0.01). No statistical differences were observed in the ALT level between the 2 groups (Figure S1C).

As shown in Figure 3D, the AST level was significantly reduced only in the 8th week after combined therapy (1st: OR=−4.40, CI=−10.31 to 1.51, P=0.14; 4th: OR=−20.79, CI=−46.96 to 5.37, P=0.12; 8th: OR=−30.66, CI=−45.80 to −15.52, P<0.0001; 12th: OR=−3.40, CI=−13.69 to 6.89, P=0.52; 24th: OR=−1.80, CI=−12.24 to 8.64, P=0.74). Comparison between the 2 groups indicated that the AST level significantly decreased in the 8th week in the combined therapy group (Figure S1D).

The blood coagulation was evaluated in terms of PT and PTA. After combined therapy, PT was reduced in the 4th, 8th, 12th and 24th week (Figure 3E, 1st: OR=−0.81, CI=−3.15 to 1.52, P=0.49; 4th: OR=−3.01, CI=−4.66 to −1.37, P=0.0003; 8th: OR=−3.61, CI=−6.21 to −1.02, P=0.006; 12th: OR=−6.74, CI=−11.54 to −1.94, P=0.006; 24th: OR=−7.48, CI=−11.77 to −3.20, P=0.0006). Compared with patients treated by RST alone, shorter PT were observed in combined therapy-treated patients in the 8th, 12th and 24th week after treatment (Figure S1E).

As shown in Figure 3F, in the 8th week after combined therapy, PTA was statistically increased (2nd: OR=5.20, CI=−8.00 to 18.40, P=0.44; 4th: OR=6.20, CI=−6.48 to 18.88, P=0.34; 8th: OR=9.79, CI=5.46 to 14.13, P<0.00001; 12th: OR=9.10, CI=−4.67 to 22.87, P=0.20; 24th: OR=8.70, CI=−4.74 to 22.14, P=0.20). Meanwhile, the pooled results showed that in the 8th week after treatment, patients who underwent combined therapy had more significantly increased PTA compared with patients who received RST alone (Figure S1F).

All the abovementioned results indicated that the combination of USCs and RST had better therapeutic effects for LC patients than RST alone.

QoL assessment

QoL of patients who received combined therapy was significantly improved compared to those treated by RST alone, indicated by better appetite, relieved ascitic fluid and abdominal distension after USCs treatment (Figure 4, appetite: OR=5.43, CI=2.84 to 10.38, P<0.00001; ascitic fluid: OR=4.56, CI=2.69 to 7.74, P<0.00001; abdominal distension: OR=4.01, CI=1.34 to 12.02, P=0.01), whereas the improvements in fatigue and edema were not significant (Figure 4, fatigue: OR=4.33, CI=0.87 to 21.60, P=0.07; edema: OR=2.69, CI=0.23 to 31.72, P=0.43). Appetite and ascitic fluid were not heterogeneous among the studies, so the fixed-effects model was used for analyzing their OR. Otherwise, random-effects model was used.

Adverse events assessment

We evaluated safety of USCs therapy in this meta-analysis. The most common side effect during treatment was fever, which usually subsided within 24 hours without treatment. No serious adverse events or death were reported after USCs therapy (Table 3). However, all trials did not compare the incidence of side effects in experimental and control groups.

Publication bias

Funnel plots of TBIL, ALB, ALT and PT data were symmetrical in general, indicating small publication bias (Figures 5 and S2).

Sensitivity analysis

Subgroup analyses were performed to evaluate the effects of cell numbers ($>1\times10^8$ or $<1\times10^8$) and administration routes (through intravenous or hepatic artery) on clinical efficacy. Results showed that a larger number of infused USCs (cell numbers $>1\times10^8$) were associated with improved liver function, indicated by decreased TBIL and ALT levels and PT and increased ALB level (Tables 4 and S1). Moreover, compared to intravenous USCs perfusion, USCs transplantation

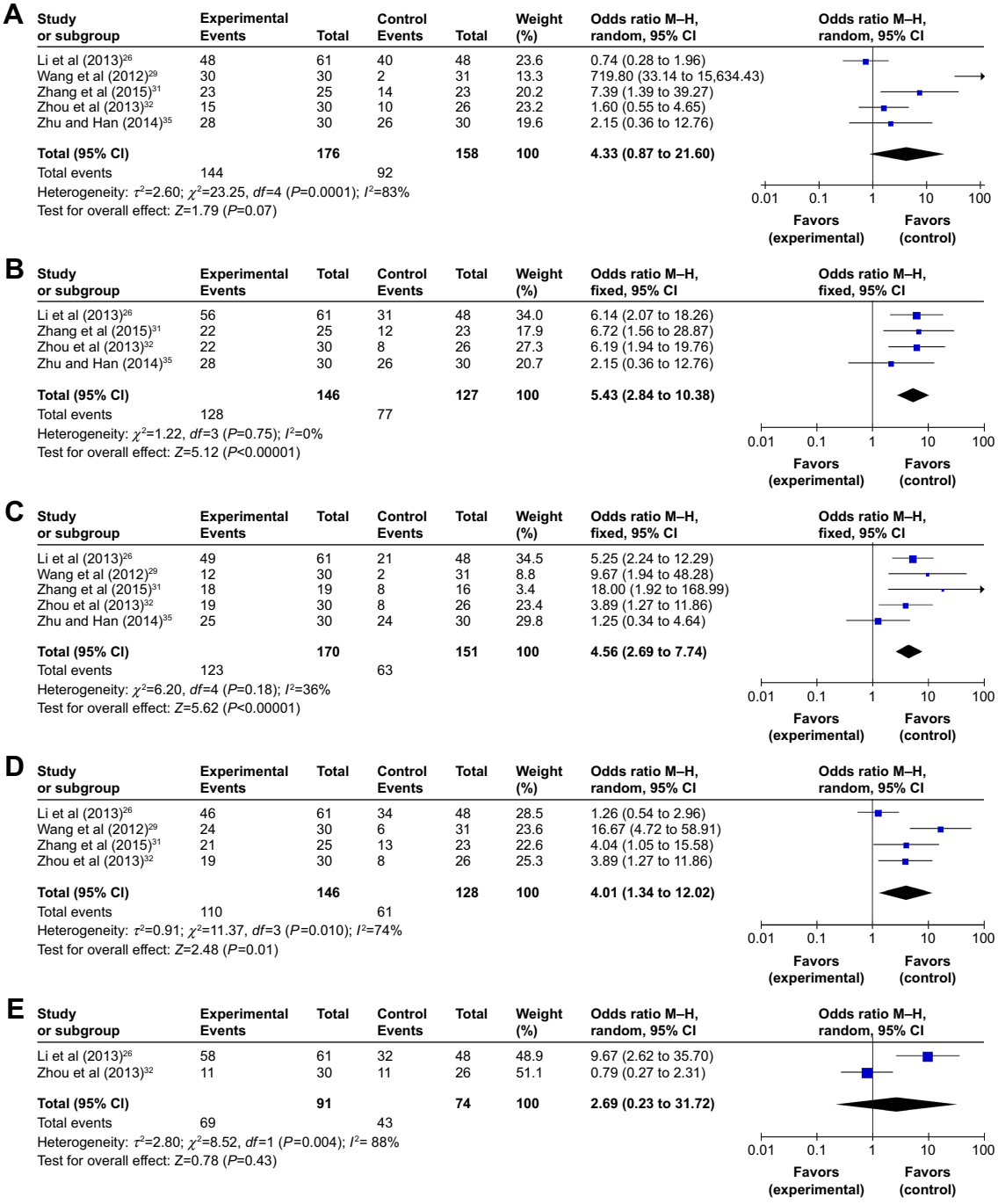

Figure 4 Forest plot of the comparison of QoL including fatigue (**A**), appetite (**B**), abdominal distension (**C**), ascitic fluid (**D**) and edema (**E**) between the experimental and control groups.

Notes: Control group, RST alone group; experimental group, RST plus USCs therapy.

Abbreviations: M–H, Mantel–Haenszel method; QoL, quality of life; USCs, umbilical cord blood stem cells; RST, routine supportive treatment.

through hepatic artery was more effective in reducing the TBIL level and PT, but less valid in increasing the ALB level (Tables 4 and S1).

Discussion

Stem cells derived from umbilical cord blood are mainly composed of HSCs, MSCs, EPCs and immature immunological cells.[16] HSCs and MSCs can differentiate into functional hepatocyte-like cells both in vitro and in vivo.[36,37] Their anti-inflammatory and paracrine function can affect liver function.[5] MSCs can migrate and home to injured liver tissue,[38] differentiate into hepatocytes, inhibit hepatocytes death,[39] stimulate endogenous hepatocyte regeneration and promote the secretion of HGF, epidermal growth factor

Table 3 Information of adverse events during the USCs therapy

Included studies	Adverse events (number)
Li et al (2013)[26]	No obvious adverse reactions; excitement (12)
Li and Zhang (2016)[27]	Fever (1)
Tan et al (2012)[28]	No obvious adverse reactions
Wang et al (2012)[29]	No obvious adverse reactions
Wang et al (2014)[30]	No obvious adverse reactions
Zhang et al (2015)[31]	No obvious adverse reactions
Zhou et al (2013)[32]	No obvious adverse reactions; low-grade fever (3)
Zhou et al (2016)[33]	No obvious adverse reactions
Zhou et al (2017)[34]	No obvious adverse reactions
Zhu and Han (2014)[35]	Low-grade fever (1); tension, pain (1)

Abbreviation: USCs, umbilical cord blood stem cells.

(EGF) and vascular endothelial growth factor (VEGF),[40] thereby enhance liver regeneration. van Poll et al[39] and Parekkadan et al[41] reported that MSCs can upregulate anti-inflammatory cytokine IL-10 and downregulate pro-inflammatory cytokines such as TNF-α and IL-6, by which they alleviate liver fibrosis. Moreover, MSCs can alleviate cirrhosis through inhibiting hepatic stellate cells' proliferation, promoting their apoptosis and inhibiting extracellular matrix (ECM) accumulation.[3,42,43] Research of Higashiyama et al[44] indicated that MSCs can alleviate cirrhosis through expressing matrix metalloproteinase-2 (MMP-2) and MMP-9, which had antifibrotic effect by degrading the ECM. Pan et al[45] demonstrated that MSCs can attenuate liver fibrosis by specifically downregulating Dlk-1 expression through FGF2 secretion. Chen et al[46] found that MSCs remarkably inhibited the proliferation of hepatic stellate cells through activation of Notch and PI3K/Akt signaling pathways. EPCs have potential to regenerate the vascular endothelium in liver.[5,47] Therefore, USCs were considered with promising prospective to treat LC.

In recent years, several studies have shown that USCs were safe and feasible treatment for LC. However, the different clinical protocols among those studies may lead to different therapeutic effects. In this study, we investigated published clinical trials extensively to achieve high statistical reliability. Our meta-analysis revealed that compared to LC patients who received RST alone, those treated by USCs and RST combined therapy exhibited more favorable efficacy,

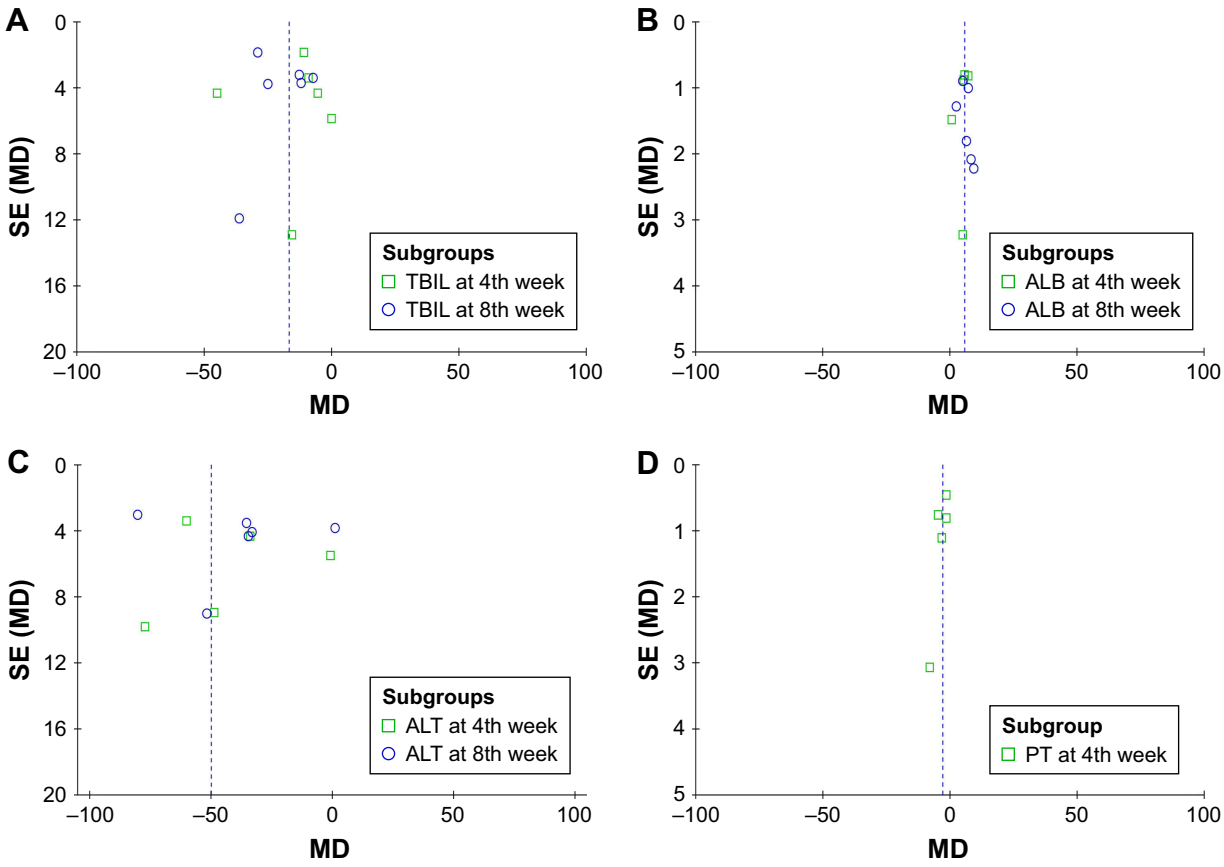

Figure 5 Funnel plot of percentage of TBIL (**A**), ALB (**B**), ALT (**C**) and PT (**D**) in pre- and post-therapy.
Note: Bias analyses were conducted for parameters discussed in >6 papers.
Abbreviations: TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time.

Table 4 Subgroup analyses of TBIL, ALB, ALT and PT in pre- and post-therapy

Parameters	Time point (after therapy)	Factors at study level	Pre-therapy	Post-therapy	Analysis method	Heterogeneity		OR	95% CI	*P*-value
			No of patients	No of patients		I^2 (%)	*P*-value			
TBIL	4th week	CN>1×10⁸	113	113	Random	0	0.49	−9.91	−12.95 to −6.86	<0.00001
		CN<1×10⁸	84	84	Random	95	<0.00001	−20.56	−53.73 to 12.61	0.22
		Hepatic artery	82	82	Random	0	0.68	−8.05	−13.22 to −2.88	0.002
		Intravenous	115	115	Random	97	<0.00001	−18.77	−42.39 to 4.85	0.12
	8th week	CN>1×10⁸	91	91	Random	0	0.33	−28.17	−31.50 to −24.84	<0.00001
		CN<1×10⁸	130	130	Random	49	0.12	−12.14	−18.01 to −6.26	<0.0001
ALB	4th week	CN>1×10⁸	113	113	Random	0	0.92	5.59	4.44 to 6.75	<0.00001
		CN<1×10⁸	59	59	Random	93	<0.0001	4.12	−2.35 to 10.58	0.21
		Hepatic artery	82	82	Random	73	0.02	3.57	0.02 to 7.11	0.05
		Intravenous	90	90	Random	41	0.19	6.55	5.08 to 8.02	<0.00001
	8th week	CN>1×10⁸	91	91	Random	58	0.12	6.20	4.14 to 8.26	<0.00001
		CN<1×10⁸	130	130	Random	71	0.02	6.37	3.10 to 9.64	0.0001
ALT	4th week	CN>1×10⁸	113	113	Random	97	<0.00001	−84.81	−122.71 to −46.90	<0.0001
		CN<1×10⁸	84	84	Random	96	<0.00001	−41.59	−88.74 to 5.56	0.08
		Hepatic artery	82	82	Random	97	<0.00001	−85.80	−142.84 to −28.76	0.003
		Intravenous	115	115	Random	98	<0.00001	−45.52	−89.67 to −1.37	0.04
	8th week	CN>1×10⁸	91	91	Random	99	<0.00001	−57.36	−101.95 to −12.77	0.01
		CN<1×10⁸	130	130	Random	96	<0.00001	−29.02	−49.72 to −8.33	0.006
PT	4th week	CN>1×10⁸	113	113	Random	87	0.0003	−3.81	−6.82 to −0.80	0.01
		CN<1×10⁸	59	59	Random	35	0.22	−2.28	−3.91 to −0.65	0.006
		Hepatic artery	82	82	Random	80	0.007	−3.88	−6.75 to −1.00	0.008
		Intravenous	90	90	Random	55	0.13	−2.12	−3.79 to −0.44	0.01

Note: Subgroup analyses were conducted in parameters discussed in >6 papers.
Abbreviations: CN, cell number; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; OR, odds ratio.

including increased ALB and PTA levels, and decreased TBIL, ALT, AST levels and PT, although changes in TBIL and ALT levels did not show statistical significance. Patients' QoL was remarkably improved after USCs therapy, including improved appetite and relieved fatigue, abdominal distension, ascitic fluid and edema. These results indicated that the combination of USCs transplantation and RST had more satisfied therapeutic effects for LC patients than those treated by RST alone.

USCs have been clinically applied to treat hematological malignancies for more than 2 decades with a good safety record. In this research, our analyses showed that USCs were also safe to treat LC. Fever was the most common side effect during USCs therapy, which in most cases resolved naturally, and no serious adverse events or death occurred during therapy.

Some factors may influence the therapeutic effects of USCs therapy, such as USCs dosages and infusion routes. Number of infused USCs is one of the primary determinations in therapeutic strategy optimization. Nakamura et al found that human $CD34^+$ cell transplantation after chronic liver injury aroused functional regeneration in a dose-dependent manner.[48] Our analysis also revealed that a larger number of infused USCs were associated with more satisfied efficacy. Moreover, we found that USCs infusion through hepatic artery was more effective in reducing TBIL and PT but not in increasing ALB compared to intravenous perfusion. However, currently available publications probing the impact of administration routes on USCs' curative effect are still insufficient, and more data will be needed to perform convincible statistical analysis. We expect our study will be valuable for the design of upcoming comprehensive clinical trials.

Our study has some limitations. The numbers of LC patients included in this study was not big enough and the follow up periods was short. Although the effectiveness of USCs therapy on hematological, nerve and other system diseases have been reported,[49–52] but its application on LC was still mainly performed in People's Republic of China. This may be because there are a large number of Chinese LC patients and many Chinese research studies were focused on it, therefore abundant papers were generated. Moreover, the therapeutic effects of USCs therapy are affected by multiple factors, such as injection modes, infused USCs numbers and LC stages. Further detailed analyses need to be conducted based on research studies with sufficient information, standardized therapeutic regimens and strict patients inclusion criteria. Although the therapeutic effects of USCs for LC were satisfied, which

population of cells among USCs was mainly responsible for these effects was unclear, and the underlying mechanism remained elusive. Qi et al[5] assumed that the improved liver microenvironments and/or the increased hepatocytes number may help liver function recovery after stem cell therapy.

Conclusion

This study confirmed the efficacy and safety of USCs transplantation and RST combined therapy for LC patients. USCs therapy greatly enhanced the improvement in liver function after RST and improved QoL of LC patients. Therefore, USCs transplantation and RST combined therapy is a promising treatment option for LC patients.

Acknowledgment

Huimin Tao and Yafeng Li are the co-first authors.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
TBIL at 1st week								
Tan et al (2012)[1]	41.2	13.2	22	43.2	11.4	20	5.1	–2.00 (–9.44 to 5.44)
Wang et al (2014)[2]	43.6	12.3	30	43.2	11.3	20	5.2	0.40 (–6.23 to 7.03)
Subtotal (95% CI)			**52**			**40**	**10.4**	**–0.66 (–5.61 to 4.29)**
Heterogeneity: τ^2=0.00; χ^2=0.22, *df*=1 (*P*=0.64); I^2=0%								
Test for overall effect: *Z*=0.26 (*P*=0.79)								
TBIL at 4th week								
Li et al (2013)[3]	68	10	61	74	13	48	5.5	–6.00 (–10.45 to –1.55)
Li and Zhang (2016)[4]	20.5	8.5	29	22.8	9.5	21	5.4	–2.30 (–7.41 to 2.81)
Tan et al (2012)[1]	34.5	10.4	22	33.4	12.7	20	5.2	1.10 (–5.96 to 8.16)
Zhang et al (2015)[5]	36.3	19.7	25	30.2	17.3	23	4.7	6.10 (–4.37 to 16.57)
Zhou et al (2013)[6]	57.9	15	30	55.8	14.9	26	5.1	2.10 (–5.75 to 9.95)
Zhu and Han (2014)[7]	91.7	46.6	30	102.3	53.4	30	2.6	–10.60 (–35.96 to 14.76)
Subtotal (95% CI)			**197**			**168**	**28.4**	**–1.44 (–5.11 to 2.23)**
Heterogeneity: τ^2=6.79; χ^2=7.63, *df*=5 (*P*=0.18); I^2=34%								
Test for overall effect: *Z*=0.77 (*P*=0.44)								
TBIL at 8th week								
Li et al (2013)[3]	50	10	61	66	9	48	5.5	–16.00 (–19.57 to –12.43)
Wang et al (2012)[8]	30.1	12	30	31.6	10.8	31	5.3	–1.50 (–7.24 to 4.24)
Zhou et al (2013)[6]	38.5	9.2	30	39.2	10	26	5.4	–0.70 (–5.76 to 4.36)
Zhou et al (2016)[9]	38.3	12.2	30	40.6	13.3	30	5.3	–2.30 (–8.76 to 4.16)
Zhou et al (2017)[10]	38.5	12.2	40	40.8	13.5	40	5.4	–2.30 (–7.94 to 3.34)
Zhu and Han (2014)[7]	71.3	37.8	30	99.8	43.6	30	3.1	–28.50 (–49.15 to –7.85)
Subtotal (95% CI)			**221**			**205**	**30.1**	**–6.51 (–13.57 to 0.55)**
Heterogeneity: τ^2=62.66; χ^2=42.58, *df*=5 (*P*<0.00001); I^2=88%								
Test for overall effect: *Z*=1.81 (*P*=0.07)								
TBIL at 12th week								
Li et al (2013)[3]	31	8	61	63	10	48	5.6	–32.00 (–35.47 to –28.53)
Tan et al (2012)[1]	25.5	9.5	22	27.4	9.4	20	5.3	–1.90 (–7.62 to 3.82)
Zhang et al (2015)[5]	34.1	20.2	25	28.7	18.8	23	4.6	5.40 (–5.63 to 16.43)
Subtotal (95% CI)			**108**			**91**	**15.5**	**–9.82 (–34.50 to 14.85)**
Heterogeneity: τ^2=461.49; χ^2=103.03, *df*=2 (*P*<0.00001); I^2=98%								
Test for overall effect: *Z*=0.78 (*P*=0.44)								
TBIL at 24th week								
Li et al (2013)[3]	30	6	61	50	8	48	5.6	–20.00 (–22.72 to –17.28)
Tan et al (2012)[1]	26.5	13.5	22	25.4	10.4	20	5.2	1.10 (–6.15 to 8.35)
Zhang et al (2015)[5]	36.2	20	25	30.6	13.6	23	4.8	5.60 (–4.01 to 15.21)
Subtotal (95% CI)			**108**			**91**	**15.6**	**–4.82 (–22.76 to 13.12)**
Heterogeneity: τ^2=238.45; χ^2=49.07, *df*=2 (*P*<0.00001); I^2=96%								
Test for overall effect: *Z*=0.53 (*P*=0.60)								
Total (95% CI)			**686**			**595**	**100**	**–4.92 (–10.42 to 0.57)**
Heterogeneity: τ^2=138.41; χ^2=341.03, *df*=19 (*P*<0.00001); I^2=94%								
Test for overall effect: *Z*=1.76 (*P*=0.08)								
Test for subgroup differences: χ^2=2.41, *df*=4 (*P*=0.66); I^2=0%								

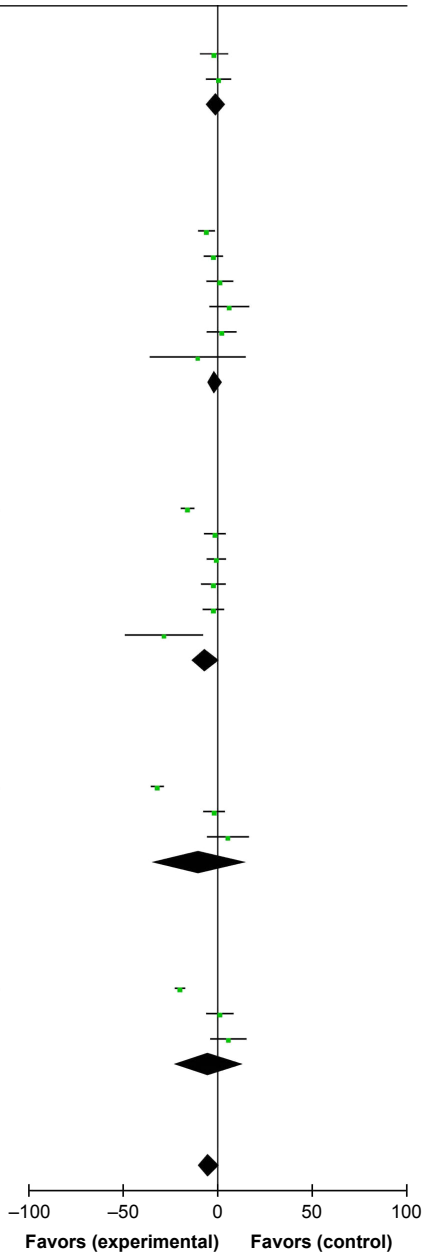

Figure S1 (*Continued*)

B

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
ALB at 1st week								
Tan et al (2012)[1]	29.1	10.5	22	30.1	10.5	20	2.7	–1.00 (–7.36 to 5.36)
Wang et al (2014)[2]	27.1	4.8	30	28.1	10.5	20	3.9	–1.00 (–5.91 to 3.91)
Subtotal (95% CI)			**52**			**40**	**6.6**	**–1.00 (–4.89 to 2.89)**
Heterogeneity: τ^2=0.00; χ^2=0.00, *df*=1 (*P*=1.00); I^2=0%								
Test for overall effect: *Z*=0.50 (*P*=0.61)								
ALB at 4th week								
Li et al (2013)[3]	28.6	2.6	61	23.8	3.5	48	9.3	4.80 (3.61 to 5.99)
Li and Zhang (2016)[4]	37.2	3.4	29	32.4	3.6	21	8.1	4.80 (2.82 to 6.78)
Tan et al (2012)[1]	33.5	11.8	22	30.4	12.4	20	2.2	3.10 (–4.24 to 10.44)
Zhou et al (2013)[6]	35.2	3.3	30	28	3.3	26	8.5	7.20 (5.47 to 8.93)
Zhu and Han (2014)[7]	28.2	6.3	30	28.1	4.9	30	6.6	0.10 (–2.76 to 2.96)
Subtotal (95% CI)			**172**			**145**	**34.7**	**4.39 (2.32 to 6.46)**
Heterogeneity: τ^2=3.77; χ^2=17.88, *df*=4 (*P*=0.001); I^2=78%								
Test for overall effect: *Z*=4.16 (*P*<0.0001)								
ALB at 8th week								
Li et al (2013)[3]	30.1	5.4	61	25.2	4.5	48	8.3	4.90 (3.04 to 6.76)
Wang et al (2012)[2]	36.4	7.8	30	26.4	8.2	31	4.9	10.00 (5.98 to 14.02)
Zhou et al (2013)[6]	35	3.4	30	29.8	3.9	26	8.2	5.20 (3.27 to 7.13)
Zhou et al (2016)[9]	33.1	8.3	30	25.6	7.6	30	4.9	7.50 (3.47 to 11.53)
Zhou et al (2017)[10]	32.3	8.3	40	24.6	7.7	40	5.6	7.70 (4.19 to 11.21)
Zhu and Han (2014)[2]	30.1	4.9	30	28.3	5.2	30	7.1	1.80 (–0.76 to 4.36)
Subtotal (95% CI)			**221**			**205**	**38.8**	**5.77 (3.79 to 7.75)**
Heterogeneity: τ^2=3.91; χ^2=15.58, *df*=5 (*P*=0.008); I^2=68%								
Test for overall effect: *Z*=5.71 (*P*<0.00001)								
ALB at 12th week								
Li et al (2013)[3]	33.4	8.9	61	26.2	6.1	48	6.6	7.20 (4.38 to 10.02)
Tan et al (2012)[1]	36.6	12.4	22	31.2	9.3	20	2.6	5.40 (–1.19 to 11.99)
Subtotal (95% CI)			**83**			**68**	**9.2**	**6.92 (4.33 to 9.52)**
Heterogeneity: τ^2=0.00; χ^2=0.24, *df*=1 (*P*=0.62); I^2=0%								
Test for overall effect: *Z*=5.23 (*P*<0.00001)								
ALB at 24th week								
Li et al (2013)[3]	34.6	3.8	61	26.7	6	48	8.1	7.90 (5.95 to 9.85)
Tan et al (2012)[1]	37.3	11.7	22	29.7	10.5	20	2.5	7.60 (0.89 to 14.31)
Subtotal (95% CI)			**83**			**68**	**10.6**	**7.88 (6.01 to 9.75)**
Heterogeneity: τ^2=0.00; χ^2=0.01, *df*=1 (*P*=0.93); I^2=0%								
Test for overall effect: *Z*=8.26 (*P*<0.00001)								
Total (95% CI)			**611**			**526**	**100**	**5.15 (3.92 to 6.38)**
Heterogeneity: τ^2=3.87; χ^2=53.35, *df*=16 (*P*<0.00001); I^2=70%								
Test for overall effect: *Z*=8.20 (*P*<0.00001)								
Test for subgroup differences: χ^2=18.99, *df*=4 (*P*=0.0008); I^2=78.9%								

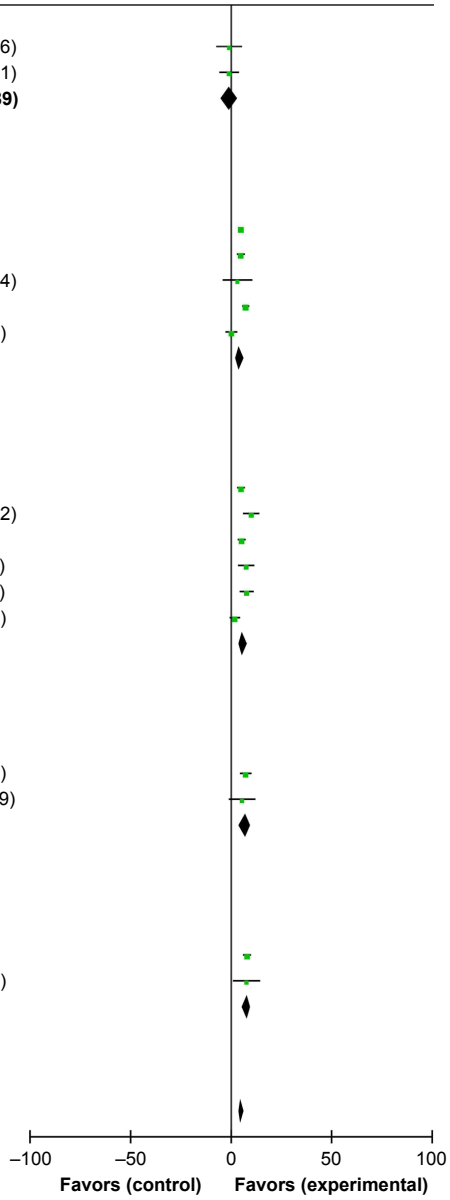

Figure S1 (*Continued*)

C

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
ALT at 1st week								
Tan et al (2012)[1]	212.4	67.4	22	221.3	86.4	20	0.4	–8.90 (–56.09 to 38.29)
Wang et al (2014)[2]	52.1	9.8	30	50.2	9.9	20	6.2	1.90 (–3.68 to 7.48)
Subtotal (95% CI)			**52**			**40**	**6.6**	**1.75 (–3.79 to 7.29)**
Heterogeneity: τ^2=0.00; χ^2=0.20, *df*=1 (*P*=0.66); I^2=0%								
Test for overall effect: *Z*=0.62 (*P*=0.54)								
ALT at 4th week								
Li et al (2013)[3]	66	15	61	73	21	48	5.5	–7.00 (–14.03 to 0.03)
Li and Zhang (2016)[4]	39.8	25.2	29	49.5	42.9	21	1.7	–9.70 (–30.21 to 10.81)
Tan et al (2012)[1]	67.2	23.5	22	87.3	32.4	20	2.2	–20.10 (–37.36 to –2.84)
Zhang et al (2015)[5]	31.5	16.7	25	31	12.9	23	4.9	0.50 (–7.91 to 8.91)
Zhou et al (2013)[6]	37.8	13.7	30	51.6	14.2	26	5.4	–13.80 (–21.14 to –6.46)
Zhu and Han (2014)[7]	58.7	18.3	30	48.2	12.9	30	5.1	10.50 (2.49 to 18.51)
Subtotal (95% CI)			**197**			**168**	**24.9**	**–5.44 (–14.27 to 3.39)**
Heterogeneity: τ^2=89.23; χ^2=24.85, *df*=5 (*P*=0.0001); I^2=80%								
Test for overall effect: *Z*=1.21 (*P*=0.23)								
ALT at 8th week								
Li et al (2013)[3]	46	9	61	52	8	48	7.2	–6.00 (–9.20 to –2.80)
Wang et al (2012)[8]	46.2	14.6	30	44.8	15.1	31	5.3	1.40 (–6.05 to 8.85)
Zhou et al (2013)[6]	36.9	14	30	49.9	14.3	26	5.4	–13.00 (–20.44 to –5.56)
Zhou et al (2016)[9]	36.3	13.5	30	39.2	13.3	30	5.7	–2.90 (–9.68 to 3.88)
Zhou et al (2017)[10]	37.3	13.5	40	39.4	13.3	40	6.1	–2.10 (–7.97 to 3.77)
Zhu and Han (2014)[7]	55.6	19.3	30	49.1	16.8	30	4.6	6.50 (–2.66 to 15.66)
Subtotal (95% CI)			**221**			**205**	**34.2**	**–3.20 (–7.55 to 1.14)**
Heterogeneity: τ^2=18.29; χ^2=14.64, *df*=5 (*P*=0.01); I^2=66%								
Test for overall effect: *Z*=1.45 (*P*=0.15)								
ALT at 12th week								
Li et al (2013)[3]	36	7	61	50	15	48	6.7	–14.00 (–18.59 to –9.41)
Tan et al (2012)[1]	46.3	12.5	22	48.2	13.9	20	5.1	–1.90 (–9.92 to 6.12)
Zhang et al (2015)[5]	29.2	13.8	25	27.3	17.5	23	4.7	1.90 (–7.07 to 10.87)
Subtotal (95% CI)			**108**			**91**	**16.4**	**–5.20 (–15.72 to 5.32)**
Heterogeneity: τ^2=72.55; χ^2=13.23, *df*=2 (*P*=0.001); I^2=85%								
Test for overall effect: *Z*=0.97 (*P*=0.33)								
ALT at 24th week								
Li et al (2013)[3]	34	6	61	42	14	48	6.8	–8.00 (–12.24 to –3.76)
Tan et al (2012)[1]	37.4	12.3	22	41.4	11.7	20	5.4	–4.00 (–11.26 to 3.26)
Zhang et al (2015)[5]	29.7	13.1	25	26.6	11.4	23	5.6	3.10 (–3.83 to 10.03)
Subtotal (95% CI)			**108**			**91**	**17.8**	**–3.37 (–10.03 to 3.29)**
Heterogeneity: τ^2=24.88; χ^2=7.22, *df*=2 (*P*=0.03); I^2=72%								
Test for overall effect: *Z*=0.99 (*P*=0.32)								
Total (95% CI)			**686**			**595**	**100**	**–3.68 (–6.74 to –0.62)**
Heterogeneity: τ^2=31.16; χ^2=70.60, *df*=19 (*P*<0.00001); I^2=73%								
Test for overall effect: *Z*=2.36 (*P*=0.02)								
Test for subgroup differences: χ^2=3.09, *df*=4 (*P*=0.54); I^2=0%								

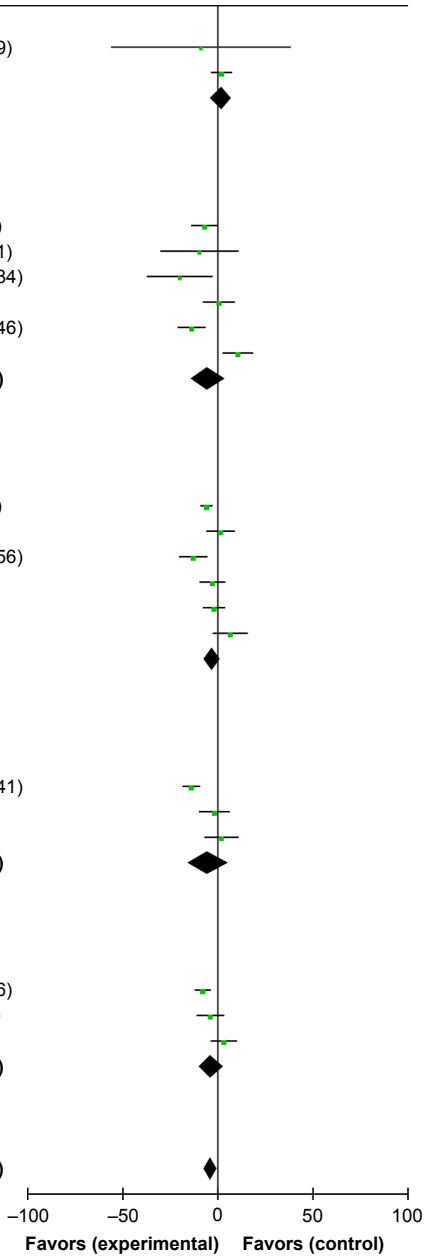

Figure S1 (*Continued*)

D

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
AST at 1st week								
Wang et al (2014)[2]	51.2	10.8	30	53.6	13.3	20	12.8	–2.40 (–9.39 to 4.59)
Subtotal (95% CI)			**30**			**20**	**12.8**	**–2.40 (–9.39 to 4.59)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.67 (P=0.50)								
AST at 4th week								
Li and Zhang (2016)[4]	54.3	16.2	29	61.2	17.7	21	9.6	–6.90 (–16.50 to 2.70)
Zhang et al (2015)[5]	36.3	16.7	25	41.6	23.5	23	7.6	–5.30 (–16.92 to 6.32)
Zhou et al (2013)[6]	42.3	12.7	30	55.7	12.9	26	13.2	–13.40 (–20.13 to –6.67)
Subtotal (95% CI)			**84**			**70**	**30.4**	**–10.16 (–15.15 to –5.17)**
Heterogeneity: τ^2=0.07; χ^2=2.01, df=2 (P=0.37); I^2=0%								
Test for overall effect: Z=3.99 (P<0.0001)								
AST at 8th week								
Wang et al (2012)[8]	53.6	15.4	30	55.7	14.7	31	12.0	–2.10 (–9.66 to 5.46)
Zhou et al (2013)[6]	41.5	9.9	30	57.9	14.1	26	13.6	–16.40 (–22.87 to –9.93)
Zhou et al (2016)[9]	33.6	14.5	30	38.6	13.8	30	12.6	–5.00 (–12.16 to 2.16)
Subtotal (95% CI)			**90**			**87**	**38.2**	**–8.00 (–16.82 to 0.83)**
Heterogeneity: τ^2=47.80; χ^2=9.38, df=2 (P=0.009); I^2=79%								
Test for overall effect: Z=1.78 (P=0.08)								
AST at 12th week								
Zhang et al (2015)[5]	33.8	14.9	25	41.8	24.2	23	7.7	–8.00 (–19.49 to 3.49)
Subtotal (95% CI)			**25**			**23**	**7.7**	**–8.00 (–19.49 to 3.49)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.37 (P=0.17)								
AST at 24th week								
Zhang et al (2015)[5]	35.4	15.6	25	35.6	14.5	23	10.8	–0.20 (–8.72 to 8.32)
Subtotal (95% CI)			**25**			**23**	**10.8**	**–0.20 (–8.72 to 8.32)**
Heterogeneity: not applicable								
Test for overall effect: Z=0.05 (P=0.96)								
Total (95% CI)			**254**			**223**	**100**	**–6.89 (–10.92 to –2.87)**
Heterogeneity: τ^2=20.10; χ^2=17.65, df=8 (P=0.02); I^2=55%								
Test for overall effect: Z=3.36 (P=0.0008)								
Test for subgroup differences: χ^2=5.66, df=4 (P=0.23); I^2=29.4%								

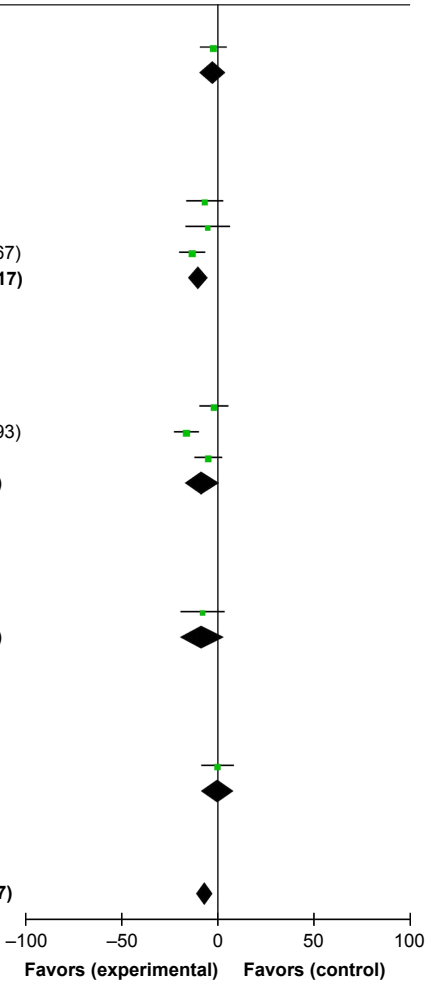

Figure S1 (*Continued*)

E

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
PT at 1st week								
Tan et al (2012)[1]	25.5	10.4	22	24.8	9.7	20	2.4	0.70 (–5.38 to 6.78)
Wang et al (2014)[2]	22.7	5.5	30	20.6	5.5	20	5.5	2.10 (–1.01 to 5.21)
Subtotal (95% CI)			**52**			**40**	**7.9**	**1.81 (–0.96 to 4.58)**
Heterogeneity: τ^2=0.00; χ^2=0.16, *df*=1 (*P*=0.69); I^2=0%								
Test for overall effect: *Z*=1.28 (*P*=0.20)								
PT at 4th week								
Li et al (2013)[3]	18.6	1.6	61	18.2	2.1	48	10.2	0.40 (–0.32 to 1.12)
Li and Zhang (2016)[4]	15.5	3.7	29	16.9	4.4	21	7.1	–1.40 (–3.71 to 0.91)
Tan et al (2012)[1]	18.6	8.4	22	22.5	11.5	20	2.3	–3.90 (–10.04 to 2.24)
Zhou et al (2013)[6]	17.6	2	30	19.5	2.7	26	9.3	–1.90 (–3.16 to –0.64)
Zhu and Han (2014)[7]	15.1	2.1	30	16.3	3.8	30	8.7	–1.20 (–2.75 to 0.35)
Subtotal (95% CI)			**172**			**145**	**37.4**	**–1.03 (–2.33 to 0.28)**
Heterogeneity: τ^2=1.31; χ^2=13.20, *df*=4 (*P*=0.01); I^2=70%								
Test for overall effect: *Z*=1.54 (*P*=0.12)								
PT at 8th week								
Li et al (2013)[3]	17.4	0.8	61	17.8	4.6	48	9.1	–0.40 (–1.72 to 0.92)
Zhou et al (2013)[6]	15.9	1	30	18.3	2	26	10.0	–2.40 (–3.25 to –1.55)
Zhu and Han (2014)[7]	15	2.9	30	16.1	2.9	30	8.8	–1.10 (–2.57 to 0.37)
Subtotal (95% CI)			**121**			**104**	**27.9**	**–1.39 (–2.68 to –0.10)**
Heterogeneity: τ^2=0.92; χ^2=7.00, *df*=2 (*P*=0.03); I^2=71%								
Test for overall effect: *Z*=2.11 (*P*=0.04)								
PT at 12th week								
Li et al (2013)[3]	15.2	1.4	61	18.6	3.4	48	9.7	–3.40 (–4.42 to –2.38)
Tan et al (2012)[1]	16.4	5.2	22	21.5	8.3	20	3.9	–5.10 (–9.34 to –0.86)
Subtotal (95% CI)			**83**			**68**	**13.6**	**–3.49 (–4.49 to –2.50)**
Heterogeneity: τ^2=0.00; χ^2=0.58, *df*=1 (*P*=0.44); I^2=0%								
Test for overall effect: *Z*=6.88 (*P*<0.00001)								
PT at 24th week								
Li et al (2013)[3]	14.1	0.9	61	17.6	1.8	48	10.3	–3.50 (–4.06 to –2.94)
Tan et al (2012)[1]	15.7	6.8	22	21.8	10.7	20	2.8	–6.10 (–11.58 to –0.62)
Subtotal (95% CI)			**83**			**68**	**13.1**	**–3.53 (–4.08 to –2.97)**
Heterogeneity: τ^2=0.00; χ^2=0.85, *df*=1 (*P*=0.36); I^2=0%								
Test for overall effect: *Z*=12.47 (*P*<0.00001)								
Total (95% CI)			**511**			**425**	**100**	**–1.73 (–2.79 to –0.67)**
Heterogeneity: τ^2=2.74; χ^2=99.34, *df*=13 (*P*<0.00001); I^2=87%								
Test for overall effect: *Z*=3.20 (*P*=0.001)								
Test for subgroup differences: χ^2=30.54, *df*=4 (*P*<0.00001); I^2=86.9%								

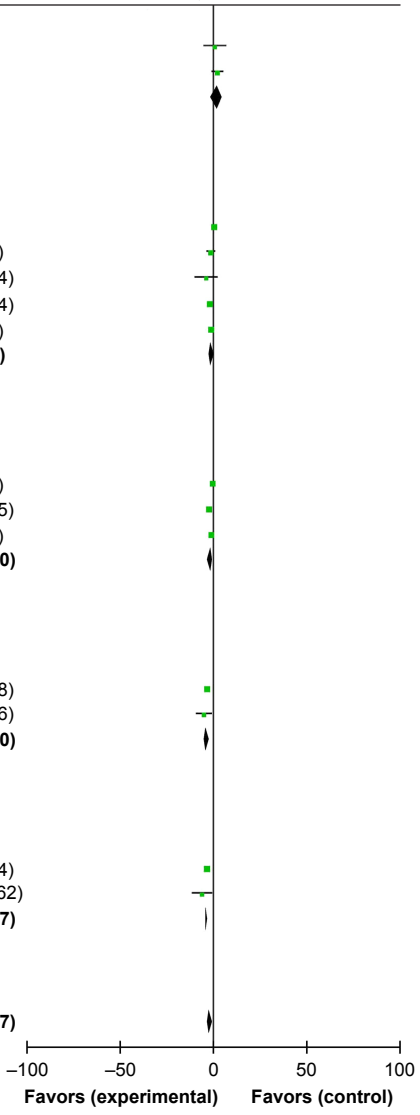

Figure S1 (*Continued*)

F

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
PTA at 2nd week								
Zhang et al (2015)[5]	67.4	25.5	25	58.6	17.9	23	6.6	8.80 (–3.59 to 21.19)
Subtotal (95% CI)			**25**			**23**	**6.6**	**8.80 (–3.59 to 21.19)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.39 (P=0.16)								
PTA at 4th week								
Zhang et al (2015)[5]	68.4	23.7	25	59.3	19.4	23	6.8	9.10 (–3.11 to 21.31)
Subtotal (95% CI)			**25**			**23**	**6.8**	**9.10 (–3.11 to 21.31)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.46 (P=0.14)								
PTA at 8th week								
Wang et al (2012)[8]	57.2	11.8	30	46.8	10.7	31	25.1	10.40 (4.74 to 16.06)
Zhou et al (2016)[9]	43	11.4	30	38.2	12.5	30	22.7	4.80 (–1.25 to 10.85)
Zhou et al (2017)[10]	74	12.4	40	58.3	12.3	40	26.8	15.70 (10.29 to 21.11)
Subtotal (95% CI)			**100**			**101**	**74.5**	**10.42 (4.28 to 16.55)**
Heterogeneity: τ^2=20.90; χ^2=6.94, df=2 (P=0.03); I^2=71%								
Test for overall effect: Z=3.33 (P=0.0009)								
PTA at 12th week								
Zhang et al (2015)[5]	71.3	27.4	25	60.9	19.1	23	5.8	10.40 (–2.88 to 23.68)
Subtotal (95% CI)			**25**			**23**	**5.8**	**10.40 (–2.88 to 23.68)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.54 (P=0.12)								
PTA at 24th week								
Zhang et al (2015)[5]	70.9	26.3	25	60.3	18.9	23	6.2	10.60 (–2.88 to 23.48)
Subtotal (95% CI)			**25**			**23**	**6.2**	**10.60 (–2.88 to 23.48)**
Heterogeneity: not applicable								
Test for overall effect: Z=1.61 (P=0.11)								
Total (95% CI)			**200**			**193**	**100**	**10.36 (7.05 to 13.68)**
Heterogeneity: τ^2=3.05; χ^2=7.08, df=6 (P=0.31); I^2=15%								
Test for overall effect: Z=6.13 (P<0.00001)								
Test for subgroup differences: χ^2=0.09, df=4 (P=1.00); I^2=0%								

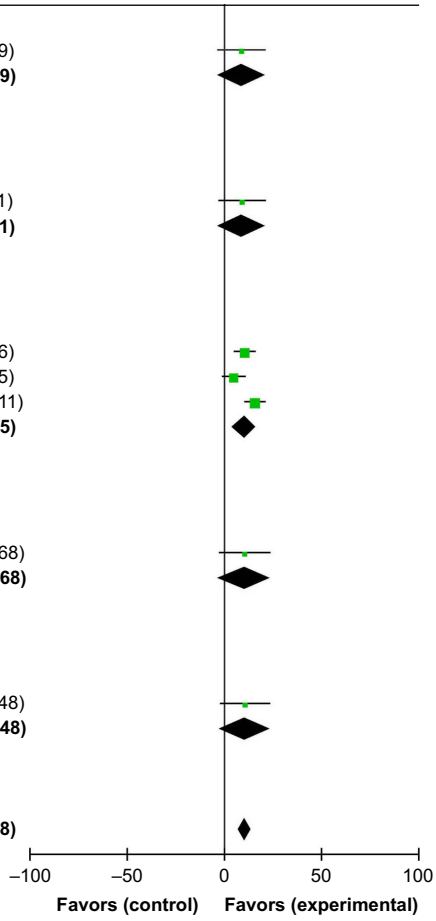

Figure S1 Forest plot of the comparison of TBIL (**A**), ALB (**B**), ALT (**C**), AST (**D**), PT (**E**) and PTA (**F**) between the experimental and control groups.
Notes: Control group, RST alone group; experimental group, RST plus USCs therapy.
Abbreviations: IV, inverse variance method; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PTA, prothrombin activity; USCs, umbilical cord blood stem cells; RST, routine supportive treatment.

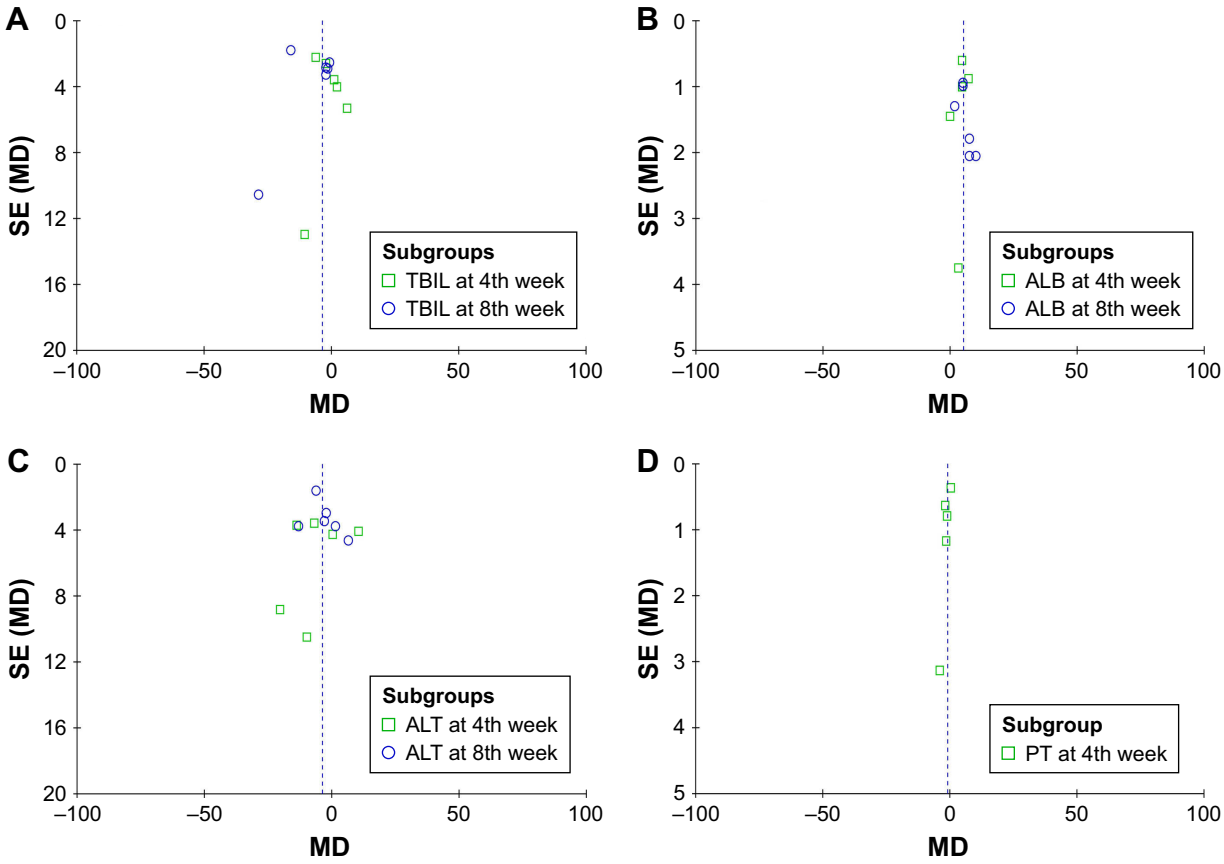

Figure S2 Funnel plot of percentage of total bilirubin (TBIL, **A**), albumin (ALB, **B**), alanine aminotransferase (ALT, **C**) and prothrombin time (PT, **D**) between the experimental and control groups.

Notes: Subgroup analyses were conducted in parameters discussed in >6 papers. Control group, routine supportive therapy alone group; experimental group, RST plus umbilical cord blood stem cell therapy.

Table S1 Subgroup analyses of TBIL, ALB, ALT and PT between the experimental and control groups

Parameters	Time point (after therapy)	Factors at study level	Exp group No of patients	Con group No of patients	Analysis method	Heterogeneity I^2 (%)	Heterogeneity *P*-value	OR	95% CI	*P*-value
TBIL	4th week	CN>1×10⁸	113	94	Random	57	0.10	−1.66	−7.24 to 3.93	0.56
		CN<1×10⁸	84	74	Random	22	0.28	−0.47	−6.73 to 5.79	0.88
		Hepatic artery	82	76	Random	0	0.64	1.05	−4.09 to 6.19	0.69
		Intravenous	115	92	Random	57	0.10	−2.35	−7.70 to 3.01	0.39
	8th week	CN>1×10⁸	91	74	Random	96	<0.00001	−8.46	−23.45 to 6.53	0.27
		CN<1×10⁸	130	131	Random	52	0.10	−3.56	−8.84 to 1.71	0.19
ALB	4th week	CN>1×10⁸	113	94	Random	63	0.07	5.70	3.62 to 7.78	<0.00001
		CN<1×10⁸	59	51	Random	86	0.008	2.57	−2.03 to 7.17	0.27
		Hepatic artery	82	76	Random	89	0.0001	3.60	−1.95 to 9.16	0.20
		Intravenous	90	69	Random	0	1.00	4.80	3.78 to 5.82	<0.00001
	8th week	CN>1×10⁸	91	74	Random	0	0.83	5.04	3.71 to 6.38	<0.00001
		CN<1×10⁸	130	131	Random	80	0.002	6.56	2.65 to 10.48	0.001
ALT	4th week	CN>1×10⁸	113	94	Random	30	0.24	−11.45	−17.68 to −5.22	0.0003
		CN<1×10⁸	84	74	Random	59	0.09	3.08	−6.63 to 12.79	0.53
		Hepatic artery	82	76	Random	91	<0.0001	−7.01	−26.09 to 12.06	0.47
		Intravenous	115	92	Random	4	0.35	−4.27	−9.67 to 1.13	0.12
	8th week	CN>1×10⁸	91	74	Random	65	0.09	−8.66	−15.32 to −2.00	0.01
		CN<1×10⁸	130	131	Random	8	0.36	−0.20	−3.88 to 3.48	0.91
PT	4th week	CN>1×10⁸	113	94	Random	82	0.004	−1.00	−3.14 to 1.14	0.36
		CN<1×10⁸	59	51	Random	0	0.89	−1.26	−2.55 to 0.03	0.06
		Hepatic artery	82	76	Random	0	0.61	−1.68	−2.65 to −0.71	0.0007
		Intravenous	90	69	Random	53	0.15	−0.15	−1.78 to 1.48	0.86

Notes: Subgroup analyses were conducted in parameters discussed in >6 papers. Control group, RST alone group; experimental group, RST plus USCs therapy.
Abbreviations: Exp, experimental; Con, control; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; OR, odds ratio; RST, routine supportive therapy; USCs, umbilical cord blood stem cells.

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