Comparative Efficacy of Stem Cells on Chronic Decompensated Cirrhosis: A Network Meta-analysis

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Abstract: Currently, liver transplantation is the best way to improve the survival rate of decompensated cirrhosis, but its application is limited due to the shortage of donors and high cost. In the recent two decades, stem cell therapy is becoming a promising frontier alternative treatment. However, because various stem cell types, sources, and routes of administration can affect the therapeutic effect, we conducted this network meta-analysis to compare the efficacy of stem cells of different types, sources and delivery routes in the treatment of chronic decompensated cirrhosis. We retrieved the literature from PubMed, Embase, Cochrane Library, Web of Science from their establishment to December 2022. Additionally, clinicaltrials.gov was looked through for trials that had not yet been published or supplemental information that had been released as of December 2022. Only randomised controlled studies were included and patients must be aged at least 18 years and older with chronic decompensated liver cirrhosis but not acute-on-chronic liver failure. The included studies could be treated with stem cells of any source, type and route of administration. The primary outcome of measurement is the model of end-stage liver disease (MELD) score. This study has been registered with INPLASY (Registration number INPLASY202310050). From 2,374 articles, we included 18 studies with 936 patients. Our analysis showed no publication bias and revealed that human umbilical cord mesenchymal stem cells administered by artery and vein (hUCMSCsAV) can significantly improve MELD score of patients with chronic decompensated cirrhosis (SUCRA: 81.7%). Other effective stem cell approaches included ABMSCsA (SCURA：65.7%), ABMSCsSH (SUCRA: 64.5%), ABMSCsGV (SUCRA: 63.5%), APBSCsGA (SUCRA: 58.7%), ABMNCsV (SUCRA: 54.9%), ABMSCsV (47.9%), and hUCMSCsV (46%). hUCMSCsAV was identified as the superior choice, followed by ABMSCsA. While these findings are promising, further high-quality research is necessary to confirm these results.

Keywords: Stem Cells; Comparative Efficacy; Decompensated Liver Cirrhosis; Network Meta-Analysis

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1 Introduction

Liver cirrhosis is an important public health problem that puzzles the world. There are about 2millions of people die of advanced liver disease every year around the world, accounting for about 3.5% of all death in the world [1]. About one million of them died of liver cirrhosis, which is the third leading cause of death in people aged 45-65 [2]. Cirrhosis is the final common pathological stage of persistent liver injury caused by various causes (e.g. alcoholic, nonalcoholic fatty liver, chronic viral hepatitis, etc.). It is divided into compensatory stage and decompensated stage. Once the patient enters decompensated stage, the median survival time is only 2-3 years. At present, the treatment of decompensated cirrhosis is very limited, and liver transplantation is actually the best and only approach to improve the survival rate of decompensated cirrhosis [3]. Liver transplantation should be considered when the expected survival time of liver transplantation is higher than that of non-liver transplantation [2]. The four-year survival rate after liver transplantation is over 70% [4]. However, liver transplantation is difficult to be widely applied due to the lack of donor organs and high cost [5]. Therefore, it is very important to study the alternative treatment of liver transplantation.

In 1999, Petersen etc. published the first animal experimental research paper on the application of stem cells to treat liver injury [6]. Stem cell therapy as a promising frontier treatment for decompensated cirrhosis, is becoming one of the feasible alternatives to liver transplantation in recent 20 years [7]. Stem cells are undifferentiated cells in the human body. They can differentiate into any cell in any organ of the human body and have the ability to renew themselves [7]. Therefore, it is a promising tool for tissue regeneration. According to the origin of stem cells, they are divided into embryonic stem cells, umbilical cord blood stem cells, fetal stem cells, adult stem cells and induced pluripotent stem cells [8]. Each kind of stem cells can be further subdivided into several types [8]. People have tried different types and sources of stem cells to trigger liver regeneration [9].

It is very important and necessary to optimize the factors such as cell sources, types, and delivery route, etc. before taking stem cell therapy as a routine clinical treatment [10]. This is because different types and sources of stem cells and the choice of delivery route will affect the therapeutic efficacy [11]. For example, Deng, et al. found that direct intravenous administration of adipose-derived mesenchymal stem cells is more effective than intrasplenic injection through animal studies [12]. However, the current studies on stem cell therapy for liver diseases are mostly small sample studies, non-randomised controlled studies, and the quality of evidence is not high [13]. In order to explore the effect of various stem cell types, sources, and routes of administration on chronic decompensated cirrhosis, we think it is necessary to conduct a network meta-analysis. The Model of end-stage liver disease (MELD) score is a reliable and decisive predictor of the prognosis of decompensated cirrhosis by incorporating serum bilirubin, creatinine and international normalized ration (INR) into a formula [14, 15]. So as in Sun's network meta-analysis, we chose MELD as the outcomes of interest for our network meta-analysis [16]. ACLF is considered to be a clinical syndrome different from the general decompensated cirrhosis [17, 18]. Because of its particularity, the studies on ACLF were not included in our analysis. It is believed that our network meta-analysis of the efficacy of various types of stem cells from different sources and routes of administration in the treatment of chronic decompensated cirrhosis can provide useful clues for clinical practice.

2 Methods

2.1 Search Strategy and Selection Criteria

The network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analysis (PRISMA-NMA) statement, and the protocol was registered and made available on the INPLASY website at https://inplasy.com/inplasy-2023-1-0050/ (Registration number INPLASY202310050).

We searched four databases (PubMed, Embase, Cochrane Library, and Web of Science) from their establishment until December 2nd, 2022 with no language restrictions. Furthermore, trials that had not been published or supplemental data as of December 2022 were searched for on clinicaltrials.gov. In addition, the search was updated on January 2nd, 2023 across all four database. PICOS tool is the basis of our literature search: (P) Participants: People diagnosed with chronic decompensated cir-

rhosis as previously described; (I) Interventions: Various stem cells types, sources, and delivery routes including totally 10 different combinations, i.e. autologous bone marrow CD133+ cells delivered by vein (AB-CD133V), autologous bone marrow mesenchymal stem cells delivered by artery (ABMSCsA), Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells (ABMSCsSH), autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment (ABMSCsGV), autologous peripheral blood stem cells delivered by artery (APBSCsGA) after G-CSF pretreatment, autologous bone marrow mononuclear cells delivered by vein (ABMNCsV), autologous bone marrow mesenchymal stem cells delivered by vein (ABMSCsV), human umbilical cord mesenchymal stem cells delivered by vein (hUCMSCsV), human umbilical cord mesenchymal stem cells delivered by artery and vein (hUCMSCsAV), human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery (hUCMSCs+ABSCsA); (C) Comparator: The control group was treated with any other treatment matched with the experimental group or the other stem cell approach of different stem cell type, source or delivery route; (O) Outcome: MELD score; (S) Study type: Randomised controlled trials. The following MeSH terms were used to search studies on chronic decompensated cirrhosis: “Liver cirrhosis”, “Liver diseases”, “Hepatitis, Chronic”, “End Stage Liver Disease”, “End-stage liver disease”, “Human Liver Disease”, “Liver Failure”, “Hepatic Insufficiency”, “Hepatic Encephalopathy”, “liver cirrhosis”. Using the set operator AND, these terms were merged with stem cell research identified by the following MeSH terms: “Stem Cells”, “Stem Cell Research”, “Mesenchymal Stem Cell Transplantation”, “Peripheral Blood Stem Cell Transplantation”, “Cord Blood Stem Cell Transplantation”, “Stem Cell Transplantation”, “Hematopoietic Stem Cell Mobilization”, “Hematopoietic Stem Cell Transplantation”, “Mesenchymal Stem Cells”, “Oogonial Stem Cells”, “Adult Stem Cells”, “Peripheral Blood Stem Cells”, “Neural Stem Cells”, “Induced Pluripotent Stem Cells”, “Fetal Stem Cells”, “Embryonic Stem Cells”, “Pluripotent Stem Cells”, “Multipotent Stem Cells”, “Totipotent Stem Cells”, “Myeloid Progenitor Cells”, “Hematopoietic Stem Cells”, “Human Embryonic Stem Cells”. We also searched identified studies for randomized controlled trials. The complete search strategy in PubMed has been deposited in figshare as an example (10.6084/m9. figshare. 26295739).

The following were the criteria for inclusion: (1) Study subjects: patients who have been diagnosed with chronic decompensated cirrhosis meeting the clinical practice guidelines from the European Association for the Study of the Liver [19]; (2) Interventions: at least one of the intervention arms include stem cells of various types, sources, and delivery routes; (3) Control group: patients received matched medical therapy, placebo, or stem cells of different types, sources or delivery routes; (4) Study design: randomised controlled trial (RCT); (5) Outcome index: the research reported the model of end-stage liver disease (MELD) score [20]; (6) There are no language restrictions; (7) Patients are at least 18 years old. Studies that matched one or more of the following criteria were ruled ineligible: incomplete data; non-randomised controlled trials; animal models; duplicate articles; cross-sectional studies; retrospective analyses and reviews. Participants are under 18 years of age.

2.2 Data Analysis

Using the literature management software Endnote, the literature was screened and excluded. The titles of the literature were initially examined for duplication, non-randomised controlled trial studies, review papers, protocols, and correspondence by two researchers. Both researchers studied the abstracts of the literature in full and identified additional papers for inclusion. Both researchers independently reviewed the literature during this process, and then they compared the remaining literature to determine whether it was identical or different. If it was identical, it was incorporated. If it was different, the issue was then discussed and resolved in a group setting.

Using a seven-item, standardized and pre-selected data extraction form was used to record data for inclusion under the following headings in the study. (1) author (year/country), (2) sample size, (3) Enrollment period, (4) disease, (5) intervention, (6) delivery route, (7) Follow-up.

Table 1 Characteristics of the studies included in the network meta-analysis

Author (Year/Country)	Entry no (T/F/M)	Age (mean+SD)	Final No	Enrollment period	Disease	Intervention		Delivery route	Follow-up
						Experiment	Control		
Esmaeilzadeh [21]	T:10/1/9	45.2±7.5	T:10	Sep. 2014- June. 2016	DC	ABMNCs	GMT	Vein	6m
(2019, Iran)	C:10/2/8	46±10.25	C:10						
Fang [22]	T:50/NA/NA	NA	T:50	May 2013- Mar. 2017	DC	hUCMSCs	GMT	Vein	48w
(2018, China)	C:53/NA/NA	NA	C:53						
Wu [23]	T:42/NA/NA	NA	T:42	Mar. 2014-Feb. 2016	DC	ABMSCs	GMT	Artery	24w
(2017, China)	C:42/NA/NA	NA	C:42						
Fang [24]	T:59/NA/NA	NA	T:47	Jan. 2013-May 2016	DC	hUCMSCs	GMT	Artery, vein	12w
(2017, China)	C:59/NA/NA	NA	C:38						
Suk [25]	T:18/NA/NA	NA	T:18	Jan. 2013-Nov. 2015	DC	ABCD133	GMT	Vein	12m
(2016, Korea)	C:19/NA/NA	NA	C:19						
Mohamadnejad [26]	T1:8/NA/NA	NA	T1:4	Mar. 2010-Jun. 2012	DC	ABCD133			
(2016, Iran)	T2:10/NA/NA	NA	T2:8			ABMNCs	GMT	Vein	6m
	C:9/NA/NA	NA	C:6						
Zeng [27]	T:13/NA/NA	NA	T:13	Feb. 2010-Feb. 2013	DC	G-CSF+	GMT	Artery, Vein (7 days later)	1y
(2015, China)	C:19/NA/NA	NA	C:19			hUCMSCs+ABSCs			
Zekr [28]	T:30/5/25	50.97±4.15	T:30	May 2010-May 2012	DC	G-CSF+	GMT	Vein	12m
(2015, Egypt)	C:30/4/26	49.43±4.53	C:30			ABMSCs			
Deng [29]	T:33/13/20	49.48±11.07	T:33	Jul. 2011-Dec. 2013	DC	APBSCs	GMT	Artery	48w
(2015, China)	C:35/12/23	50.20±10.64	C:35						
Xu [30]	T:27/13/14	44±12	T:20	Mar. 2012-Dec. 2012	DC	ABMSCs	GMT	Artery	24w
(2014, China)	C:29/11/18	45±10	C:19						
Wang [31]	T:9/NA/NA	NA	T:9	Nov. 2011-May 2012	DC	hUCMSCs	GMT	Vein	4w
(2013, China)	C:9/NA/NA	NA	C:9						
Mohamadnejad [32]	T:14/7/7	43.1±17.6	T:11	NA	DC	ABMSCs	GMT	Vein	12m
(2013, Iran)	C:11/5/6	34.6±13.8	C:11						
Zhang [33]	T:30/4/26	48±9.75	T:30	NA	DC	hUCMSCs	GMT	Vein	50w
(2012, China)	C:15/1/14	47±8.75	C:15						
Lin [34]	T:38/4/34	47±12.25	T:38	NA	DC	hUCMSCs	GMT	Vein	48w
(2012, China)	C:16/1/15	48±8.75	C:16						
El-Ansary [35]	T:15/4/11	48±7.4	T:15	Oct. 2008-Jun. 2009	DC	ABMSCs	GMT	Vein	6m
(2012, Egypt)	C:10/2/8	51.6±7.2	C:10						
Amer [36]	T:20/4/16	NA	T:20	May 2005-Jun. 2009	DC	ABMSCs	GMT	Intrasplenic /Intrahepatic	6m
(2011, Egypt)	C:203/17	NA	C:20						
Peng [37]	T:53/3/50	42.19±10.80	T:6	NA	DC	ABMSCs	GMT	Artery	4w
(2011, China)	C:105/6/99	42.22±11.37	C:16						
Nikeghbalian [38]	T:3/2/1	37±2.65	T:3	NA	DC	ABCD133	AB-MNCs	Vein	3m
(2011, Iran)	C:3/1/2	34.33±5.5	C:3						

ABMNCs: Autologous bone marrow mononuclear cells, ABMSCs: Autologous bone marrow mesenchymal stem cells, ABCD133: Autologous bone marrow $CD133^+$ cells, ABSCs: Autologous bone marrow stem cells, hUCMSCs: human umbilical cord mesenchymal stem cells, APBSCs: Autologous peripheral blood stem cells, G-CSF: Granulocyte colony- stimulating factor, T: Experimental group, C: Control group, GMT: General medical treatment, DC: Decompensated cirrhosis, NA: not available, w: week(s), m: month(s), y: year(s)

The consistency and inconsistency of the network were analyzed using a loop specific method that compared intervention effects derived from direct and indirect evidence. Each intervention's relative ranking probability was calculated using surface under the cumulative ranking (SURCA) curves and displayed using rankograms. Pair-

wise and network meta-analysis were carried out in Stata with the use of the network command and procedures that were self-programmed in Stata.

Utilizing RoB2 to calculate the risk of bias, two researchers independently evaluated the risk of bias of individual studies. This tool uses five domains to assess the risk of bias. The following areas were taken into account: the randomised process, deviations from intended interventions, missing outcome data, outcome measurement, and choice of the reported result. The definition of overall bias was "low risk of bias" if all domains were rated as low risk, "some concerns" if at least one domain was rated as having some concerns, and "high risk of bias" if one or more domains were rated as high risk or multiple domains were rated as having some concerns that could impair the validity of the results.

Changes in MELD score were the outcome of interest in our network meta-analysis. MELD scores are continuous and reported as means with standard deviations (SD) when a combination of stem cell type and delivery route constitutes the intervention in a study. Confidence intervals (Cls) at the 95% level will be supplied for all continuous variables. We chose a random effects model of analysis over a fixed effects model because of the likelihood of heterogeneity among studies.

Stata (version 15.1) was used to perform an aggregation and analysis of NMA data following the protocol laid out in the PRISMA NMA user's guide via Markov chain Monte Carlo simulation chains with a Bayesian framework. The Stata software was used to check for consistency; if the P value was more than 0.05, the test was considered successful. Stata was used to visualize and characterize network diagrams of different interventions. Each node in the generated network diagrams stands for a unique stem cell intervention and a different control condition, and the lines linking the nodes indicate direct head-to-head comparisons between interventions. The number of studies is represented visually by a graph in which the width of the connecting lines and the size of each node increase with study count [39].

The intervention hierarchy was described and summarized using a P score. The P score, which is a weighted average of all competing therapies, is a frequentist counterpart to SUCRA values and measures how confident one can be that one treatment is superior to all others. The P score can be between 0 and 1, where 0 indicates the very worst treatment and 1 the absolute greatest therapy. Such assessments should be considered skeptically unless there are true clinically significant variations between interventions, despite the fact that the P score or SUCRA can be advantageously translated into the proportion of effectiveness or acceptability of the interventions. To detect possible publication bias in NMA due to the effects of small-scale studies on the overall results, a network funnel plot was constructed and visually inspected using the symmetry criterion. Egger's test and Begg's test were also used to examine the potential influence of publication bias on the study's results.

3 Results

The manual search pulled up eleven more items in addition to the 2,374 documents that the electronic database search yielded. The remaining 791 papers were examined once the duplicates had been removed, and another 674 papers were disqualified from consideration by reading their titles and abstracts. Only 18 papers were taken into consideration for this study after carefully reading the full texts of the remaining 117 papers, as 99 of them were once more eliminated (due to factors like non-randomised controlled trials, conference abstracts, insufficient data, and failure to meet the interventions and/or outcome of interest covered in this review). (Figure 1)

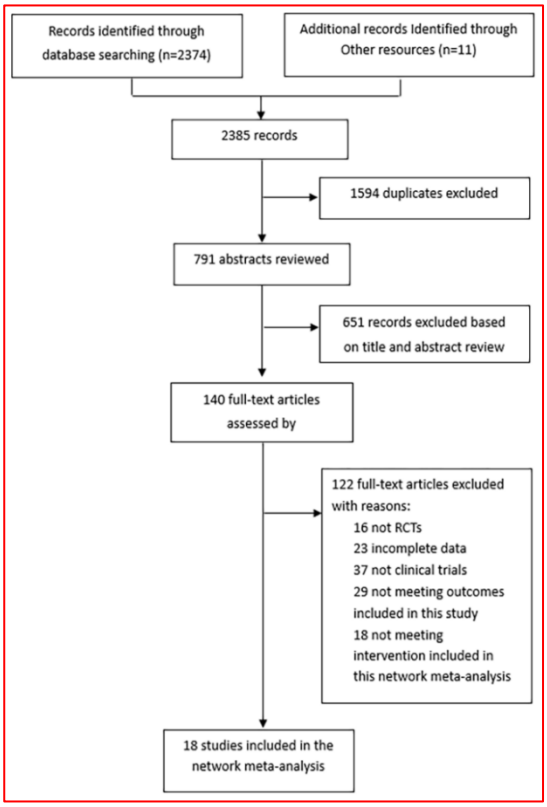

Figure 1 Flowchart of literature evaluation and selection. The diagram depicted the steps needed to incorporate randomised controlled trials including people with chronic decompensated cirrhosis.

The majority of the studies were graded as having a low or uncertain risk of bias across the five areas by the Revised Cochrane risk-of-bias test for randomised trials. The high risk of bias was found in two trials because they have missing outcome data and possible bias in the measurement of the outcome respectively [27, 34]. The trials included in this study's evaluation ofthe risk of bias are shown in Figure A1 and Figure A2.

As for characteristics of the included studies in our analysis, we looked at papers from 18 randomised controlled trials with a total of 936 people with non-diabetic NAFLD. All of them came out between 2011 and 2019. AB-CD133 (vein) and ABMSCs (vein) was used in two studies [26, 32, 35, 38], ABMSCs (G-CSF, vein), ABMSCs (Intrasplenic/Intrahepatic injection), APBSCs (G-CSF, Artery), hUCMSCs (Artery+vein), hUCMSCs+ABSCs (Artery) were used in one study [24, 27, 29, 36, 40], ABMNCs (Vein) and ABMSCs (Vein) were used in two studies [21, 32, 35, 38]. All studies used MELD as a measure of success. There were ten studies from East Asia (686 patients) [22-24, 27, 29-31, 33, 34, 37], one from northeast Asia (37 patients) [25], four from southwest Asia (66 patients) [21, 26, 32, 38], and three from northeast Africa (125 patients) [26, 32, 36]. The features of the included studies are shown in Table 1.

The NMA figure of MELD was displayed in Figure 2. The lines show which therapies were compared, and the nodes reflect comparative therapy. The size of each node was based on the number of participants. The thickness of the connecting line was based on how many times each comparison was done. We can see that most comparisons re indirect comparisons. The 95% prediction intervals shown in Figure 3 provide a prediction of effect estimates from future studies, indicating that future randomised controlled trials comparing efficacy with various stem cell types, sources and administration routes on chronic decompensated cirrhosis.

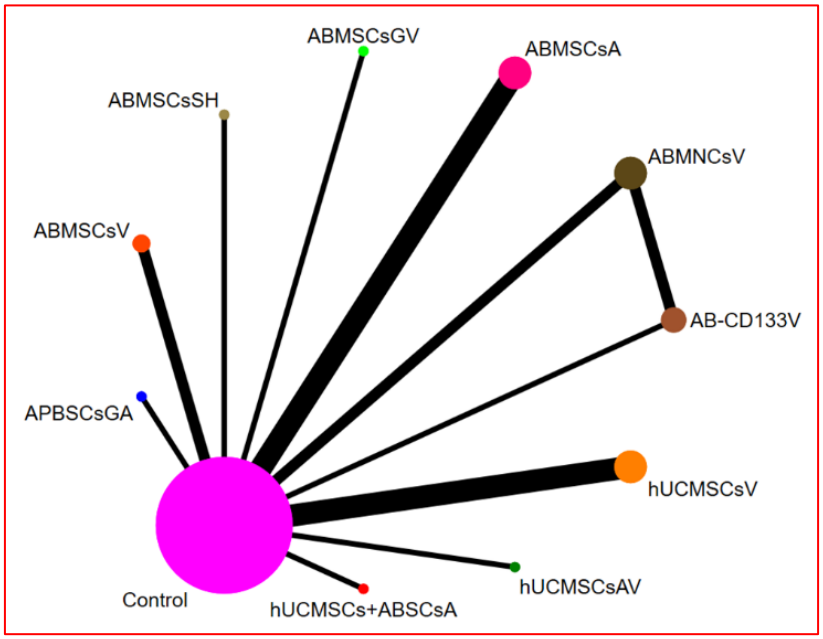

Figure 2 NMA figure for MELD score. In this diagram, each node represents a possible therapeutic strategy. The number of patients who received a certain treatment determines the size of the corresponding node. The lines provide a direct comparison, with the line width according to the number of tests conducted. Indirect comparisons were calculated using common nodes. AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery

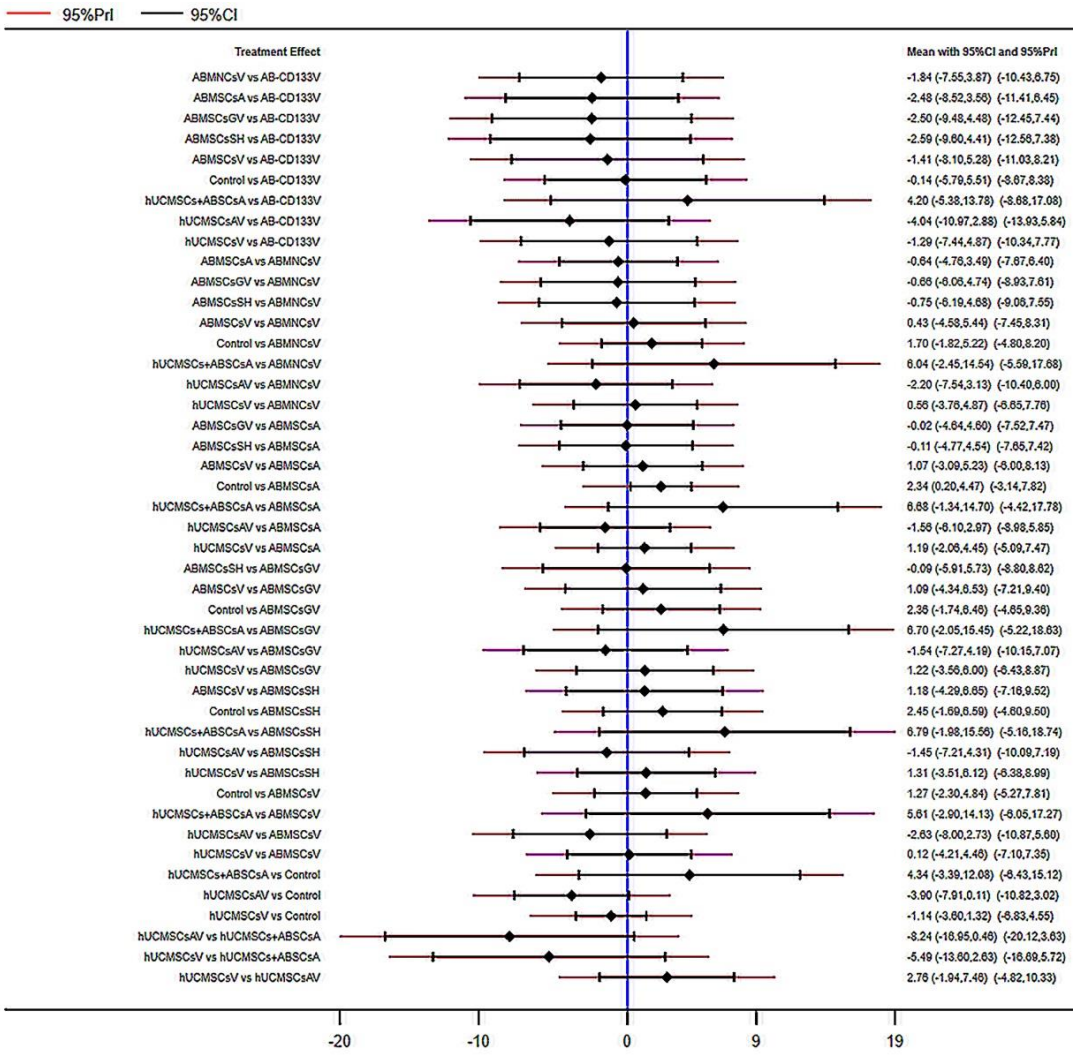

Figure 3 Interval plot for MELD score. As opposed to the estimated 95% Cls, the 95% prediction intervals (95% Prl) for comparative efficacy of various stem cell types, sources and delivery routes on chronic decompensated cirrhosis including the null value (ie, 1). AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery

All P-values were more than 0.05, showing that the effect of study consistency was acceptable, and all P-values were consistent with one another when comparing studies indirectly and directly. Table A1 and Table A2 show results of testing for consistency and inconsistency. The results of the network meta-analysis showed that hUCMSCsAV [MD = -3.90, 95% Cl = (-7.90, 0.10)], ABMSCsA [MD = -2.34, 95% Cl = (-4.48, -0.19)], ABMSCsSH [MD = -2.45, 95% Cl = (-6.61, 1.71)], ABMSCsGV [MD = -2.36, 95% Cl = (-6.48, 1.76)], APBSCsGA [MD = -2.01, 95% Cl = (-6.09, 2.07)], ABMNCsV [MD = -1.69, 95% Cl = (-5.23, 1.84)], ABMSCsV [MD = -1.22, 95% Cl = (-4.77, 2.34)], hUCMSCsV [MD = -1.14, 95% Cl = (-3.62, 1.33)] were all superior to the control group in loweringMELD scores (Table A3). When compared to the control group, AB-CD133V [MD = 0.14, 95% Cl = (-5.52, 5.80)] and hUCMSCs+ABSCsA [MD = 4.34, 95% Cl = (-3.40, 12.09)] did not show as much improvement in MELD score (Table A3). Figure A3 shows that the SUCRA, which evaluates the potential of different stem cell types, sources and routes of administration on chronic decom-

pensated cirrhosis to reduce MELD scores, gave hUCMSCsAV preference. Table 2 summarized the improvement of MELD score of each different stem cell therapeutic approach compared with the control group on chronic decompensated cirrhosis. The 95% prediction interval shown in Figure 3 provides predictions for future studies to estimate the effectiveness of comparing different stem cell types, sources and delivery routes in reducing MELD scores in patients with chronic decompensated cirrhosis.

Table 2 Network estimates comparative efficacy of various stem cell types, sources and delivery routes on chronic decompensated liver to reduce MELD score

	Intervention	Comparator	Network estimate effect size (95%CI)
First	hUCMSCsAV	Control	-3.90 (-7.90 to 0.47)
Second	ABMSCsA	Control	-2.34 (-4.48 to 0.19)
Third	ABMSCsSH	Control	-2.45 (-6.61 to 1.71)
Fourth	ABMSCsGV	Control	-2.36 (-6.48 to 1.78)
Fifth	APBSCsGA	Control	-2.01 (-6.09 to 2.07)
Sixth	ABMNCsV	Control	-1.69 (-5.23 to 1.84)
Seventh	ABMSCsV	Control	-1.22 (-4.77 to 2.34)
Eighth	hUCMSCsV	Control	-1.14 (-3.62 to 1.33)
Ninth	AB-CD133V	Control	0.14 (5.52 to 5.80)
Tenth	hUCMSCs+ABSCsA	Control	4.34 (-3.40 to 12.09)

AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = G-CSF given and autologous bone marrow mesenchymal stem cells delivered by vein, APBSCsGA = G-CSF given and autologous peripheral blood stem cells delivered by artery, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery

For the outcome variable, we made a funnel plot in order to look into any possible publication bias (Figure 4). No discernible publication bias was visible in the funnel plot with specifications shown in Figure 4. Additionally, the results of the Egger's and Begg's tests for the MELD score were 0.210 and 0.948 respectively. There was no proof of publication bias.

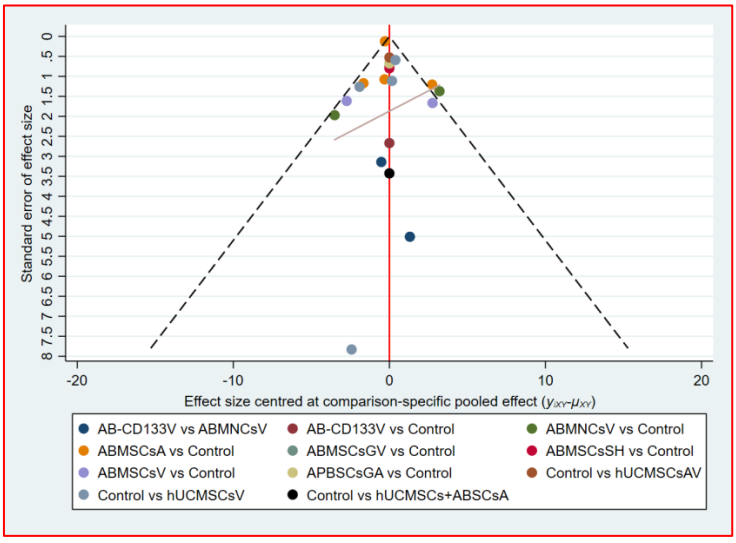

Figure 4 A funnel plot illustrating the publication bias in MELD. A graph with an asymmetrical layout suggested that there might be publication bias, whereas a graph with a symmetrical layout reveals that there was no obvious publication bias. AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery

4 Discussion

In this study, we compared the efficacy of ten different combinations of stem cell types, sources, and routes of administration in the treatment of decompensated cirrhosis. A total of 936 patients were included in 18 studies, which can be said to be a large sample study. It can be seen from the NMA diagram that the most research is about human UCMSCs and autologous bone marrow MSCs. Our study shows that human UCMSCs delivered by artery and vein simultaneously is the best stem cell approach for improving MELD. The second choice is autologous bone marrow MSCs administered by hepatic artery. As in previous similar analysis, we chose MELD as our outcome of interest [16]. The MELD score was first developed in 2001 to predict mortality in patients with cirrhosis treated with transjugular intrahepatic portosystemic stent shunt (TIPSS) [14, 41]. Since 2002, it has been used to predict the death risk of patients with liver cirrhosis and assess the severity of liver cirrhosis [14, 42]. MELD is a reliable and decisive predictor of prognosis [14]. It is generally considered to be superior to other prognostic models for end-stage liver disease such as the Child-Turcotte-Pugh score (CTP score) because it is more accurate and using only objective indicators (i.e. the international normalized ratio, serum bililrubin, creatinine and the cause of cirrhosis) [43]. The MELD score for decompensated cirrhosis, regardless of etiology, is a very useful clinical tool for assessing disease progression and predicting prognosis [43]. Therefore, it is considered to be the most suitable index for evaluating the condition of patients after stem cell transplantation in our study.

In order to solve the shortage of liver donors, people have tried to use different kinds and sources of stem cells to trigger liver regeneration [9]. The study on the therapeutic potential of UCMSCs began in 2009 [44]. According to previous studies, UCMSCs is more effective and efficient than bone marrow MSCs in the treatment of liver fibrosis and cirrhosis [8, 45]. Although the short-term efficacy of BM-MSCs is good, UCMSCs improve the long-term prognosis of patients with liver cirrhosis better [46]. This is consistent with our conclusion that human UCMSC is the best stem cell type for improving the condition of patients with decompensated cirrhosis in our study. Liver cirrhosis and fibrosis are related to the gene expression of many cytokines, such as TGF-β/Smad signaling pathway, which is the most important one in liver fibrosis. Activation of TGF-β/Smad signal transduction pathway induces collagen deposition. Previous studies have shown that UCMSCs can inhibit TGF-β/Smad signal pathway, thus inhibiting the proliferation of hepatic stellate cells and promoting their apoptosis, thus inhibiting the formation of liver fibrosis and cirrhosis [47]. In addition, Baksh et al. showed that UCMSCs showed more beneficial immunogenicity and stronger overall immunosuppressive potential than BMMSCs [46, 48]. Moreover, UCMSCs have more stable biological characteristics and no substantial ethical problems, all of which make UCMSCs the first choice other stem cell types and sources in the treatment of liver fibrosis and cirrhosis [45].

Stem cell therapy for the treatment of decompensated cirrhosis is still in the early stage of clinical translational application, and selection of stem cell types, sources, the route of administration, the frequency and time point of cell administration, etc. are all unsolved problems [49]. As we know, different stem cell types, sources and administration routes will affect the therapeutic efficacy [11]. For example, Deng et al. found that direct intravenous administration of adipose derived MSCs is more effective than intrasplenic injection [12]. A present, the most commonly used administration routes of stem cells mainly include proper hepatic artery, portal vein or peripheral vein injection, intrasplenic or intrahepatic injection, etc. [4]. Previous studies have suggested that hepatic arterial injection is a better way to deliver stem cells because fewer stem cells could be intercepted in circulation and more stem cells remain the damaged liver to differentiate [50]. It has been pointed out that the homing efficiency of MSCs delivered through portal vein or hepatic artery is less than 5% and 20-30% respectively, which also proves that hepatic artery administration may be a more efficient delivery route [46]. Although the peripheral vein route is the most convenient route, however, many stem cells in this case will stay mainly in the lungs and only a few can enter the liver [51]. Portal vein infusion is relatively better than peripheral vein infusion [52]. The results of our analysis are consistent with previous findings that the best therapeutic effect can be obtained by infusing human UCMSCs into hepatic artery and vein simultaneously.

In our study, bone marrow MSCs transplanted via hepatic artery is the second most effective treatment for decompensated cirrhosis after UCMSCs delivered via artery and vein simultaneously. It is well known that bone marrow MSCs is also a proven stem cell therapy for decompensated cirrhosis, but there is a problem of inconsistent

efficacy compared with umbilical cord MSCs [53]. There are also several limiting factors, such as obtaining bone marrow through an invasive procedure, which may lead to injury and inflammation. The proportion of MSCs in bone marrow may not be very high sometimes. In addition, it is difficult to obtain young and healthy bone marrow donors, most of bone marrow MSCs are autologous transplantations. However, bone marrow MSCs in elderly patients may have poor ability to proliferate and differentiate. This is because the ability of stem cells is hindered and their ability to self-renew decreases as people age [54]. The reason is that the immortality of stem cells is related to telomere length and telomerase activity. The telomere length of stem cells decreases with age, so transplantation of stem cells from older donors can affect their clinical efficacy [54, 55]. The patients' condition also limits the number and potential of MSCs available. For example, studies have shown that bone marrow MSCsfrom hepatitis B infected patients proliferate slowly and prone to aging [56]. Therefore, the characteristics of autologous bone marrow stem cells from different patients may vary greatly. In contrast, the advantages of umbilical cord MSCs are obvious. It is easier to obtain, non-invasive and extra UCMSC can be discarded without involving ethical issues. Moreover, some studies have found that the proliferation ability of UCMSCs is much higher than that of bone marrow MSCs, and the immunogenicity of umbilical cord MSCs is lower than that of bone marrow MSCs [57-61]. Therefore, compared with bone marrow MSCs, umbilical cord MSCs is a better choice for the treatment of decompensated cirrhosis [61]. There is an important measure there that might be beneficial for the treatment with bone marrow MSCs is to administer a mobilizer/proliferator such as G-CSF in advance of bone marrow aspiration. One is enhance the introduction of hematopoietic stem cells into the peripheral blood [62, 63]. In addition, it can promote the activation of endogenous liver stem cells. It can also play a beneficial reverse neutrophil deficiency and immune paralysis associated with severe liver insufficiency [61, 62, 64-66]. Unfortunately, the bone marrow MSCs treatment group included in our study, which used G-CSF in advance, only used peripheral intravenous infusion and the curative effect was not very outstanding. This may be caused by the route of administration or by the characteristics of the cells themselves.

In a word, our research has certain clinical practical value. First of all, our analysis found that human umbilical cord MSCs is the most effective stem cell type and source in the treatment of decompensated cirrhosis, and it needs to be administered simultaneously via hepatic artery and vein. Bone marrow MSCs is second only to human umbilical cord MSCs, but it needs to be administered through hepatic artery.

The strength is that the study is the first network meta-analysis in the world to compare directly and indirectly the efficacy of various stem cell types, sources and routes of administration in the treatment of chronic decompensated cirrhosis. Through direct and indirect comparison, we suggest that human umbilical cord MSCs may be the best choice for chronic decompensated cirrhosis. Because we used strict inclusion criteria to obtain a homogenous sample, checking for consistency revealed no inconsistency among studies included.

However, the study is not without defects. Although we tried our best to control heterogeneity and eliminate non-RCT studies, it is inevitable that there could be some potential inconsistency in this study considering that the study population came from different countries and nationalities, different nutritional status and sex ratios, etc. In addition, 6 kinds of stem cells and 4 routes of administration can have at least 24 different combinations, but the studies included in our analysis covered only 10 combinations and most comparisons were indirect. We look forward to more relevant studies and will make a more comprehensive and objective comparison and analysis in the future. Finally, although all available studies have been included, the number of cases assigned to each group is still not enough considering the combination of different cell types and administration routes, and the number of direct comparison studies is also not big. Therefore, our conclusion still has some limitation. But at least our conclusions can provide some reference for the current practice. When there are more related studies in the future, we will certainly conduct a network meta-analysis again to draw more reliable and comprehensive conclusions. It is believed that stem cell interventions will become more promising and meaningful in the treatment of decompensated cirrhosis in the future [53].

5 Role of the Funding Source

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Appendix

Table A1 Consistency test for MELD score

		Coef.	Std. Err.	z	P>|z|	[95% Conf. Interval]	
_y_B	_cons	-1.840489	2.915433	-0.63	0.528	-7.554633	3.873654
_y_C	_cons	-2.47787	3.080672	-0.80	0.421	-8.515877	3.560137
_y_D	_cons	-2.502401	3.561213	-0.70	0.482	-9.482251	4.477448
_y_E	_cons	-2.592397	3.574418	-0.73	0.468	-9.598128	4.413334
_y_F	_cons	-1.410232	3.411507	-0.41	0.679	-8.096663	5.276198
_y_G	_cons	-2.152412	3.549538	-0.61	0.544	-9.10938	4.804555
_y_H	_cons	-.1424632	2.883516	-0.05	0.961	-5.794051	5.509125
_y_I	_cons	4.201539	4.886064	0.86	0.390	-5.374969	13.77805
_y_J	_cons	-4.04246	3.534268	-1.14	0.253	-10.9695	3.884578
_y_K	_cons	-1.285252	4.140318	-0.41	0.682	-7.440162	4.869659

Note: A: AB-CD133V, B: ABMNCsV, C: ABMSCsA, D: ABMSCsGV, E: ABMSCsSH, F: ABMSCsV, G: APBSCsGA, H: Control, I: hUCMSCs+ABSCsA, J: hUCMSCsAV, K: hUCMSCsV, (AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery)

Table A2 Inconsistency test for MELD score

		Coef.	Std. Err.	z	P>|z|	[95% Conf. Interval]	
_y_B	Des_ABH	-1.825537	6.221879	-0.29	0.769	-14.0202	10.36912
	_cons	1.329641	5.194016	0.26	0.798	-8.850443	11.50973
_y_C	_cons	-4.715574	3.108725	-1.52	0.129	-10.80856	1.377415
_y_D	_cons	-4.445005	3.375352	-1.41	0.157	-11.39057	1.840563
_y_E	_cons	-4.865	3.389281	-1.44	0.151	-11.50787	1.77787
_y_F	_cons	3.690205	3.364992	-1.10	0.273	-10.28547	2.905059
_y_G	Des_BH	-4.425015	3.363032	-1.32	0.188	-11.01644	2.166406
_y_H	Des_BH	8.544704	6.301399	1.36	0.175	-3.805811	20.89522
	_cons	-2.415076	2.996535	-0.81	0.420	-8.288176	3.458024
_y_I	_cons	1.928947	4.752303	-0.41	0.685	-7.385397	11.24329
_y_J	_cons	6.315054	3.346912	-1.89	0.059	-12.87488	.244774
_y_K	_cons	-3.479529	3.150466	-1.10	0.269	-9.65433	2.695272

Note: A: AB-CD133V, B: ABMNCsV, C: ABMSCsA, D: ABMSCsGV, E: ABMSCsSH, F: ABMSCsV, G: APBSCsGA, H: Control, I: hUCMSCs+ABSCsA, J: hUCMSCsAV, K: hUCMSCsV, (AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery)

Table A3 League table of pairwise comparisons in the network meta-analysis for various stem cell therapeutic approaches to achieve an improvement in MELD scores. Stem cell approaches were reported in order of surface under the curve cumulative ranking (SUCRA). (Results of the network meta-analysis are represented in the left lower half and results from pairwise meta-analysis in the upper right half. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. In the left lower half, standard mean differences lower than 0 favour the column-defining treatment and in the upper right half, those lower than 0 favour the row-defining treatment. Cells in bold print indicate significant results.) AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = G-CSF given and autologous bone marrow mesenchymal stem cells delivered by vein, APBSCsGA = G-CSF given and autologous peripheral blood stem cells delivered by artery, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery

hUCM-SCsAV	1.56 (-2.97,6.10)	1.45 (-4.32,7.22)	1.54 (-4.20,7.28)	1.89 (-3.82,7.60)	2.21 (-3.13,7.54)	2.68 (-2.66,8.03)	2.76 (-1.94,7.46)	4.04 (-.89,10.97)	3.90 (-0.10, 7.90)	8.24 (-0.47, 16.96)
-1.56 (-6.10,2.97)	ABMSCsA	-0.11 (-4.80,4.57)	-0.02 (-4.67,4.62)	0.33 (-4.29,4.94)	0.64 (-3.50,4.79)	1.12 (-3.03,5.27)	1.19 (-2.08,4.46)	2.48 (-3.58,8.53)	2.34 (0.19,4.48)	6.68 (-1.36, 14.72)
-1.45 (-7.22,4.32)	0.11 (-4.57,4.80)	ABMSCsSH	0.09 (-5.77,5.95)	0.44 (-5.39,6.27)	0.76 (-4.71,6.22)	1.23 (-4.24,6.71)	1.31 (-3.54,6.15)	2.59 (-4.44,9.62)	2.45 (-1.71, 6.61)	6.79 (-2.00, 15.59)
-1.54 (-7.28,4.20)	0.02 (-4.62,4.67)	-0.09 (-5.95,5.77)	ABMSCsGV	0.35 (-5.45,6.15)	0.67 (-4.76,6.10)	1.14 (-4.30,6.59)	1.22 (-3.59,6.02)	2.50 (-4.50,9.50)	2.36 (-1.76, 6.48)	6.70 (-2.07, 15.48)
-1.89 (-7.60,3.82)	-0.33 (-4.94,4.29)	-0.44 (-6.27,5.39)	-0.35 (-6.15,5.45)	APBSCsGA	0.32 (-5.08,5.72)	0.79 (-4.62,6.21)	0.87 (-3.91,5.64)	2.15 (-4.83,9.13)	2.01 (-2.07, 6.09)	6.35 (-2.40, 15.11)
-2.21 (-7.54,3.13)	-0.64 (-4.79,3.50)	-0.76 (-6.22,4.71)	-0.67 (-6.10,4.76)	-0.32 (-5.72,5.08)	ABMNCsV	0.48 (-4.54,5.49)	0.55 (-3.79,4.88)	1.83 (-3.89,7.56)	1.69 (-1.84, 5.23)	6.04 (-2.48, 14.55)
-2.68 (-8.03,2.66)	-1.12 (-5.27,3.03)	-1.23 (-6.71,4.24)	-1.14 (-6.59,4.30)	-0.79 (-6.21,4.62)	-0.48 (-5.49,4.54)	ABMSCsV	0.07 (-4.26,4.40)	1.35 (-5.33,8.04)	1.22 (-2.34, 4.77)	5.56 (-2.96, 14.08)
-2.76 (-7.46,1.94)	-1.19 (-4.46,2.08)	-1.31 (-6.15,3.54)	-1.22 (-6.02,3.59)	-0.87 (-5.64,3.91)	-0.55 (-4.88,3.79)	-0.07 (-4.40,4.26)	hUCMSCsV	1.28 (-4.89,7.46)	1.14 (-1.33, 3.62)	5.49 (-2.64, 13.62)
-4.04 (-10.97, 2.89)	-2.48 (-8.53,3.58)	-2.59 (-9.62,4.44)	-2.50 (-9.50,4.50)	-2.15 (-9.13,4.83)	-1.83 (-7.56,3.89)	-1.35 (-8.04,5.33)	-1.28 (-7.46,4.89)	AB-CD133 V	-0.14 (-5.80, 5.52)	4.20 (-5.39, 13.80)
-3.90 (-7.90,0.10)	-2.34 (-4.48,-0.19)	-2.45 (-6.61,1.71)	-2.36 (-6.48,1.76)	-2.01 (-6.09,2.07)	-1.69 (-5.23,1.84)	-1.22 (-4.77,2.34)	-1.14 (-3.62,1.33)	0.14 (-5.52, 5.80)	Control	4.34 (-3.40, 12.09)
-8.24 (-16.96, 0.47)	-6.68 (-14.72, 1.36)	-6.79 (-15.59, 2.00)	-6.70 (-15.48, 2.07)	-6.35 (-15.11, 2.40)	-6.04 (-14.55, 2.48)	-5.56 (-14.08, 2.96)	-5.49 (-13.62, 2.64)	-4.20 (-13.80, 5.39)	-4.34 (-12.09, 3.40)	hUCMSCs +ABSCsA

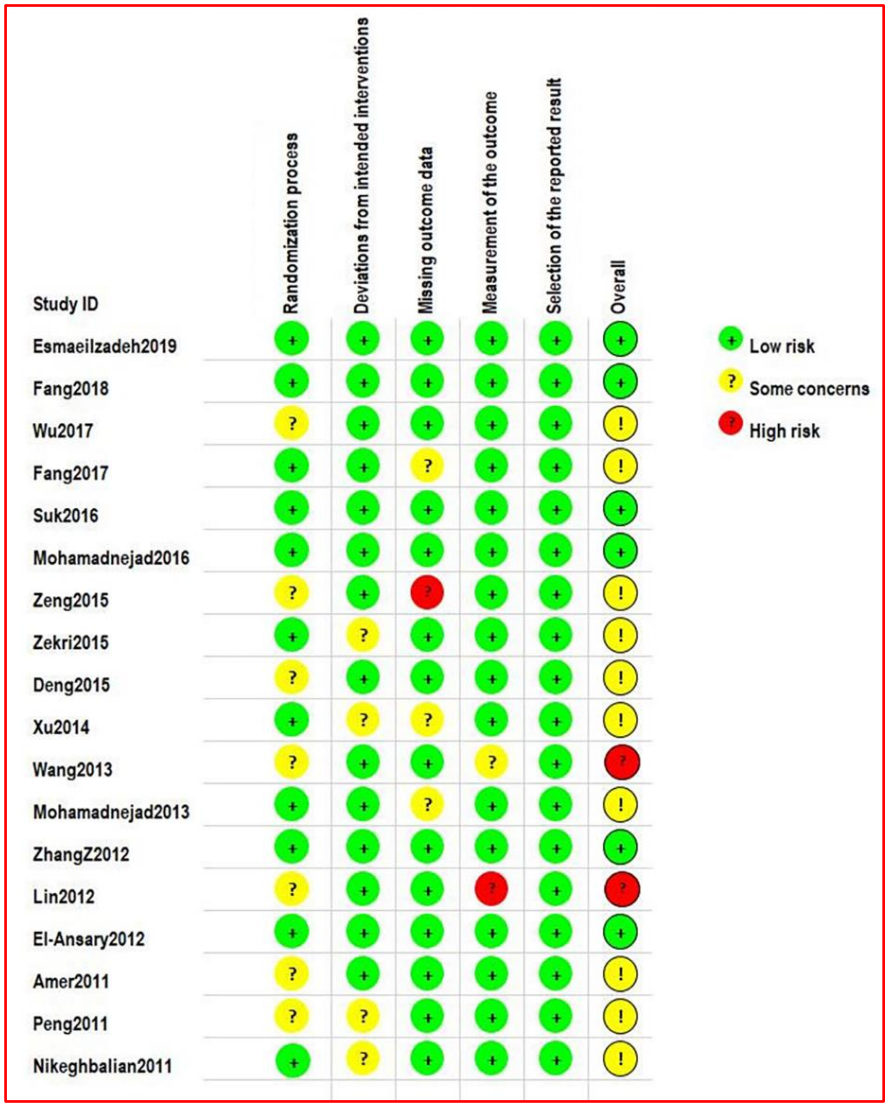

Figure A1 Risk of bias summary assessed with RoB2: Review authors' assessments of each risk of bias item for each study included in this analysis

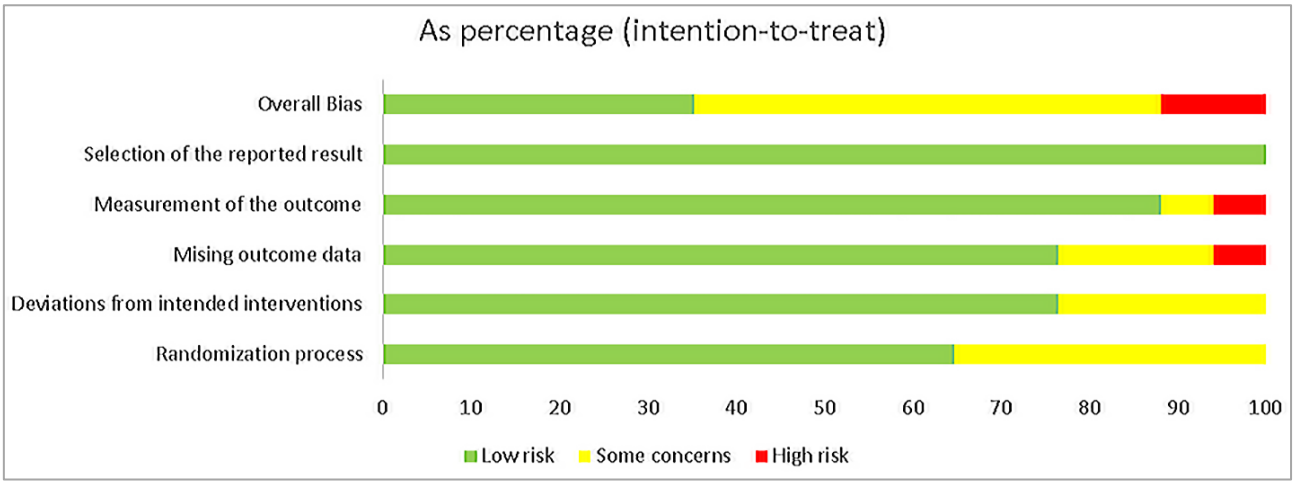

Figure A2 Risk of bias graph assessed with RoB2: percentages representing review authors' assessments of each risk of bias item across all papers included in this analysis.

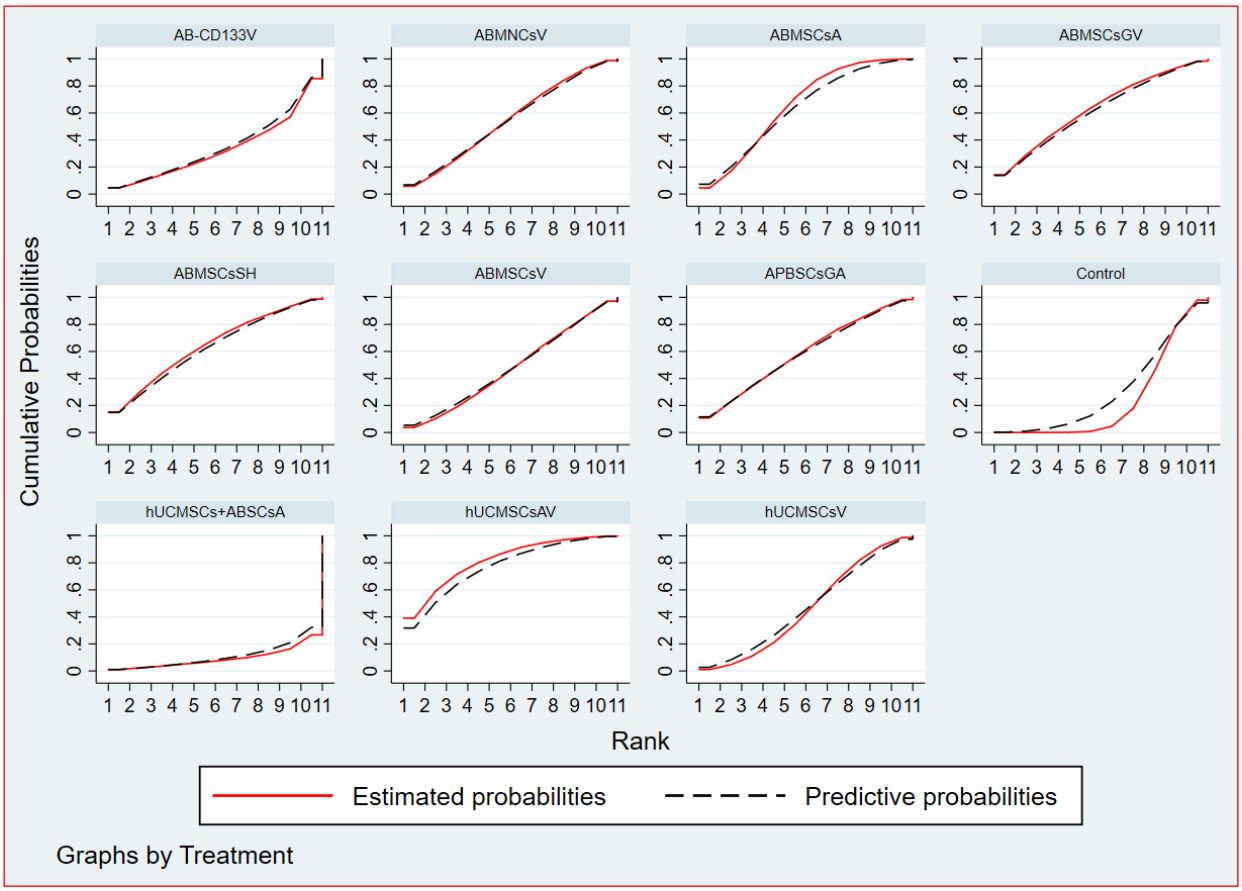

Figure A3 SUCRA plot for MELD. The area beneath each curve represents the cumulative rank likelihood of each treatment, with larger areas indicating greater probabilities. AB-CD133V = Autologous bone marrow CD133+ cells delivered by vein, ABMSCsA = Autologous bone marrow mesenchymal stem cells delivered by artery, ABMSCsSH = Intrasplenic or intrahepatic injected autologous bone marrow mesenchymal stem cells, ABMSCsGV = autologous bone marrow mesenchymal stem cells delivered by vein after G-CSF pretreatment, APBSCsGA = autologous peripheral blood stem cells delivered by artery after G-CSF pretreatment, ABMNCsV = Autologous bone marrow mononuclear cells delivered by vein, ABMSCsV = Autologous bone marrow mesenchymal stem cells delivered by vein, hUCMSCsV = human umbilical cord mesenchymal stem cells delivered by vein, hUCMSCsAV = human umbilical cord mesenchymal stem cells delivered by artery and vein, hUCMSCs+ABSCsA = human umbilical cord mesenchymal stem cells and autologous bone marrow stem cells delivered by artery.

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