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REVIEW ARTICLE

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Motor functional recovery efficacy of scaffolds with bone marrow stem cells in rat spinal cord injury: a Bayesian network meta-analysis

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STUDY DESIGN: A Bayesian network meta-analysis.
OBJECTIVE: Spinal cord injury (SCI) can profoundly influence human health and has been linked to lifelong disability. More high-level evidence-based medical research is expected to evaluate the value of stem cells and biomaterial scaffold material therapy for SCI.
METHODS: We performed a comprehensive search of Web of Science, Cochrane databases, Embase, and PubMed databases. 18 randomized controlled trials including both scaffolds and BMSCs were included. We performed a Bayesian network meta-analysis to compare the motor functional recovery efficacy of different scaffolds with BMSCs in rat SCI.
RESULTS: In our Bayesian network meta-analysis, the motor functional recovery was found to benefit from scaffolds, BMSCs, and BMSCs combined with scaffolds, but the scaffold and BMSC groups had similar motor functional recovery efficacy, and the BMSCs combined with scaffolds group appeared to show better efficacy than BMSCs and scaffolds alone. Subgroup analysis showed that BMSCs+fibrin, BMSCs+ASC, BMSCs+gelatine, and BMSCs+collagen were the best four treatments for SCI in rat models.
CONCLUSIONS: These Bayesian network meta-analysis findings strongly indicated that BMSCs combined with scaffolds is more effective to improve motor functional recovery than BMSCs and scaffolds alone. The fibrin, gelatine, ASC, and collagen may be favourable scaffolds for the injured spinal cord and that scaffolds with BMSCs could be a promising option in regeneration therapy for patients with SCI.

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INTRODUCTION

Spinal cord injury (SCI) may lead to disastrous consequences for individuals and families, including permanent sensory disturbance, dyskinesia, sphincter dysfunction, dysreflexia, and even complete paralysis [1]. Injured neurons fail to regenerate and repair axons, and glial scar formation in the area can result in irreversible spinal cord damage [2]. Many studies have shown that bone marrow mesenchymal stem cells (BMSCs) are a very promising therapy for targeting SCI by reconstructing the damaged spinal cord and improving functional recovery through angiogenesis, neural and axonal regeneration, and remyelination, preventing glial scar formation [3, 4]. Recently, the encouraging effects of BMSCs on spinal cord regeneration and repair have promoted research interest in using these stem cells for SCI therapy in preclinical studies and clinical trials [5].

Although BMSCs may provide great potential in treating spinal cord injury, the survival rate of the transplanted stem cells in the spinal cord is still very low [6]. Various kinds of scaffolds appear to be able to create a favourable environment and increase the survival chances of stem cells, promote neural reconnection, and reduce the formation of glial scarring. The current research mainly focuses on scaffolds such as acellular spinal cord (ASC), chitosan, collagen, fibrin, gelatine, hydrogel, PLGA poly (lactic-co-glycolic acid) (PLGA), and polyurethane [7]. A systematic review and meta-analysis showed that scaffolds combined with MSCs are more effective than scaffolds or MSCs alone in improving motor function following SCI in animal models. However, there were eight scaffolds, five MSCs, three species of animals (rats, mice, and dogs), and 3 assessments of motor function after SCI in this article, which made the results less persuasive [8]. Therefore, we performed a Bayesian network meta-analysis to compare the motor functional recovery efficacy of different scaffolds with only BMSCs in rat SCI to obtain a convincing result.

MATERIALS AND METHODS

Data sources and search strategy

We searched Web of Science, Cochrane databases, Embase, and PubMed using combinations of the following keywords: 'spinal cord injury (or SCI)', 'scaffolds', Bone marrow mesenchymal stem cells (or BMSCs)', 'motor function', 'Basso, Beattie, Bresnahan locomotor rating scale (or BBB)', and 'rat' (last updated on 31 March 2021). References of identified reports were retrieved and reviewed for other possible related studies. All studies were

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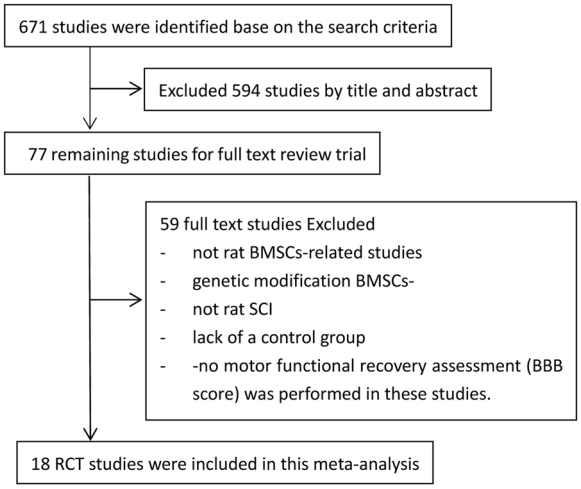

Fig. 1 The study flow diagram.

carefully and repeatedly evaluated. The study period, treatment information, hospital, and any additional inclusion criteria were used to define duplicate or overlapping data.

Inclusion and exclusion criteria

Studies that met the following criteria were eligible for inclusion in this study: (1) original studies specified the topic of rat spinal cord injury; (2) using the Basso, Beattie, and Bresnahan locomotor rating scale (BBB) to assess its efficacy for motor functional recovery; (3) randomised controlled trials, including both scaffolds and rat BMSCs; and (4) publication in English. The exclusion criteria were as follows: (1) the type of literature specified as a talk, review, digest, letter, commentary, digest, or case report; (2) rabbit, canine, or other animal SCI models; (4) Xenotransplantation was performed in the study; (5) studies included stem cells with genetic modification; (6) duplicate or overlapping data; and (4) not case-control studies.

Data extraction and quality assessment

Data from all eligible articles were independently extracted by two authors, who also discussed any disagreements and arrived at a consensus. Data retrieved for each study included the first author's name, publication year, model methods, location of the injury, BBB score (mean), BBB score (standard deviation [std.dev]), sample size, and follow-up time. Two reviewers used the Cochrane Collaboration's tool (RoB 2: a revised tool for assessing the risk of bias in randomised trials) according to the Cochrane Handbook to conduct the quality assessment [9].

Outcome measures and statistical analysis

The BBB was used to assess motor functional recovery efficacy in all the included studies [10]. All BBB scores were presented or measured in the form of mean± std.dev. R 4.0.3 software (University of Science and Technology of China) was used to perform a quality assessment (Rob 2) by using the 'robvis' packages. Our network meta-analysis was conducted based on the Bayesian framework model using R 4.0.3 software with the 'GeMTC' and 'rjags' packages. Continuous data of BBB scores were calculated using the corresponding 95% confidence interval (CI) and mean difference (MD), and the consistency between direct and indirect evidence within treatment loops was assessed by the node-splitting method [11].

RESULTS

Study characteristics

We initially identified 671 studies via a literature search of Embase, CBM databases, Web of Science, and PubMed. A total of 594 reports did not meet the inclusion criteria and were excluded by reviewing the title and abstract. Of the 77 remaining studies that underwent a full-text review, 59 were excluded because they were reviews and not rat BMSCs-related studies, and because of the lack of a control group, no motor functional recovery assessment (BBB score) was performed in these studies. A total of 18 randomised controlled trials (RCTs) involving 541 rats were included in the final network meta-analysis [12–29]. The study flow diagram is shown in Fig. 1. Table 1 summarises the main characteristics of the 18 included studies.

Quality assessment and risk of bias

We used the Cochrane Collaboration tool to assess the quality of the included studies and five aspects of the revised tool RoB 2 to assess the risk of bias in the included randomised trials [9]. In summary, the deviations from intended intervention, outcome measurement, and reporting bias were well-performed in all the enrolled studies; only two studies had high bias due to missing data. In addition, the blindness of the assessor in four studies were not mentioned. The quality assessment of the included studies is summarised in Supplementary Fig. 1A, B.

Network meta-analysis of the motor functional recovery for scaffolds, BMSCs, and BMSCs combined with scaffolds

The network geometry structure diagrams presented a direct association among control, scaffolds, BMSCs, and BMSCs combined with scaffolds (Fig. 2A). In addition, the thicknesses of the lines were proportional to the number of comparisons. Compared with the control group, the motor functional recovery was found to benefit from scaffolds (MD: 2.5, 95% CI: 1.3–3.7), BMSCs (MD: 3.0, 95% CI: 1.2–4.7), and BMSCs combined with scaffolds (MD: 5.3, 95% CI: 4.1–6.4) (Fig. 2B). Compared with the BMSCs group, the scaffold group had similar motor functional recovery efficacy with BMSCs when treating rat SCI (MD: −0.49, 95% CI: −2.2–1.3). Conversely, the BMSCs combined with scaffolds group appeared to show better efficacy than BMSCs alone (MD: 2.2, 95% CI: 0.56–4.0) (Fig. 2C). Furthermore, the rank probabilities tests showed that "BMSCs combined with scaffolds" ranked the first (99.49%) and it was the best treatment, "BMSCs" ranked the second (71.28%), "scaffolds" ranked the third 71.78%), and "control" ranked the fourth (99.91%). The results of the ranking analysis are shown in Fig. 2D. The node-splitting method indicated the consistency of direct and indirect evidence (all p values > 0.05, Fig. 2E).

Subgroup analysis of different scaffolds with BMSCs

These studies covered eight different scaffolds with BMSCs: ASC, chitosan, collagen, fibrin, gelatine, hydrogel, PLGA, and polyurethane. To validate the influences of different scaffolds with BMSCs, we performed a subgroup network meta-analysis. The network geometry structure diagrams presented the direct association among different scaffolds, BMSCs, and BMSCs combined with different scaffolds. We found that BMSCs vs. control, BMSCs_collagen vs. collagen, BMSCs_collagen vs. Control, BMSCs_hydrogel vs. hydrogel, and Collagen vs. Control were the five thickest connecting lines (Fig. 3A). We also found that the following different scaffolds combined with BMSCs appeared to show better efficacy than BMSCs in the treated rats: BMSCs+ASC (MD: 6.6, 95% CI: 2.5–11), BMSCs+Chitosan (MD: 1.1, 95% CI: −1.5–3.7), BMSCs+Collagen (MD: 2.6, 95% CI: 0.037–5.2), BMSCs +Fibrin (MD: 8.8, 95% CI: 3.4–14.0), BMSCs+Gelatine (MD: 4.6, 95% CI: 0.72–8.6), BMSCs+Hydrogel (MD: 0.87, 95% CI: −1.5–3.3), BMSCs+PLGA (MD: 1.2, 95% CI: −1.5–3.9), and BMSCs+Polvurethane (MD: 0.31, 95% CI: −3.5–4.1) (Fig. 3B). The rank probability tests showed that "BMSCs+Fibrin" ranked the first (71.57%) and that it was the best treatment, "BMSCs+ASC" ranked the second (55.31%), "BMSCs+Gelatin" ranked the third (44.01%), "BMSCs +Collagen" ranked the fourth (27.88%), "Control" ranked the last (46.92%).The results of the ranking analysis are shown in Fig. 3C.

Table 1. Main characteristics of all articles included in the meta-analysis.

No	Study and year	Model	Location of injury	Treatment	Sanmple size	Follow up
1	Itosaka 2009	Hemisection	T8	Control	5	4
				BMSCs	5	
				BMSCs+Fibrin	9	
2	Hejcl 2010	Compression	T8-9	Control	15	20
				Hydrogel	13	
				BMSCs+Hydrogel	12	
3	Chen 2011	Transection	T8	Control	10	12
				Chitosan	15	
				BMSCs+Chitosan	15	
4	Cholas 2012	Hemisection	T8-9	Control	6	4
				Collagen	7	
				BMSCs+Collagen	8	
5	Kang 2012	Transection	T8-9	PLGA	4	8
				BMSCs+PLGA	5	
6	Liang 2012	Hemisection	T9-10	Control	6	8
				Hydrogel	6	
				BMSCs+Hydrogel	6	
7	Chen 2014	Hemisection	T8-9	Control	15	8
				ASC	15	
				BMSCs+ASC	15	
8	Ritfeld 2014	Contusion	T10	Control	10	6
				Polyurethane	10	
				BMSCs	10	
				BMSCs+Polyurethane	10	
9	Madigan 2014	Transection	T8-10	Hydrogel	10	4
				BMSCs+Hydrogel	10	
10	Onuma-Ukegawa 2015	Transection	T9	Collagen	18	4
				BMSCs+Collagen	18	
11	Zeng 2015	Transection	T9-10	Control	18	8
				Gelatin	18	
				BMSCs+Gelatin	18	
12	Han 2016	Hemisection	T13-L2	Control	10	8
				Collagen	10	
				BMSCs+Collagen	10	
13	Kim 2016	Contusion	T8-10	Control	12	6
				BMSCs	12	
				BMSCs+PLGA	12	
				BMSCs+Chitosan	12	
14	Li 2017	Transection	T9-10	Control	6	10
				Hydrogel	6	
				BMSCs	6	
				BMSCs+Hydrogel	6	
15	Yang 2017	Transection	T9-10	Control	8	8
				PLGA	8	
				BMSCs+PLGA	8	
16	Ma 2018	Transection	T9-10	Control	6	8
				Gelatin	12	
				BMSCs	12	
17	Wang 2017	Transection	T8-9	Control	8	8
				Collagen	8	
				BMSCs+Collagen	8	
18	Peng 2018	Hemisection	T9	Control	6	8
				Collagen	7	
				BMSCs+Collagen	6	

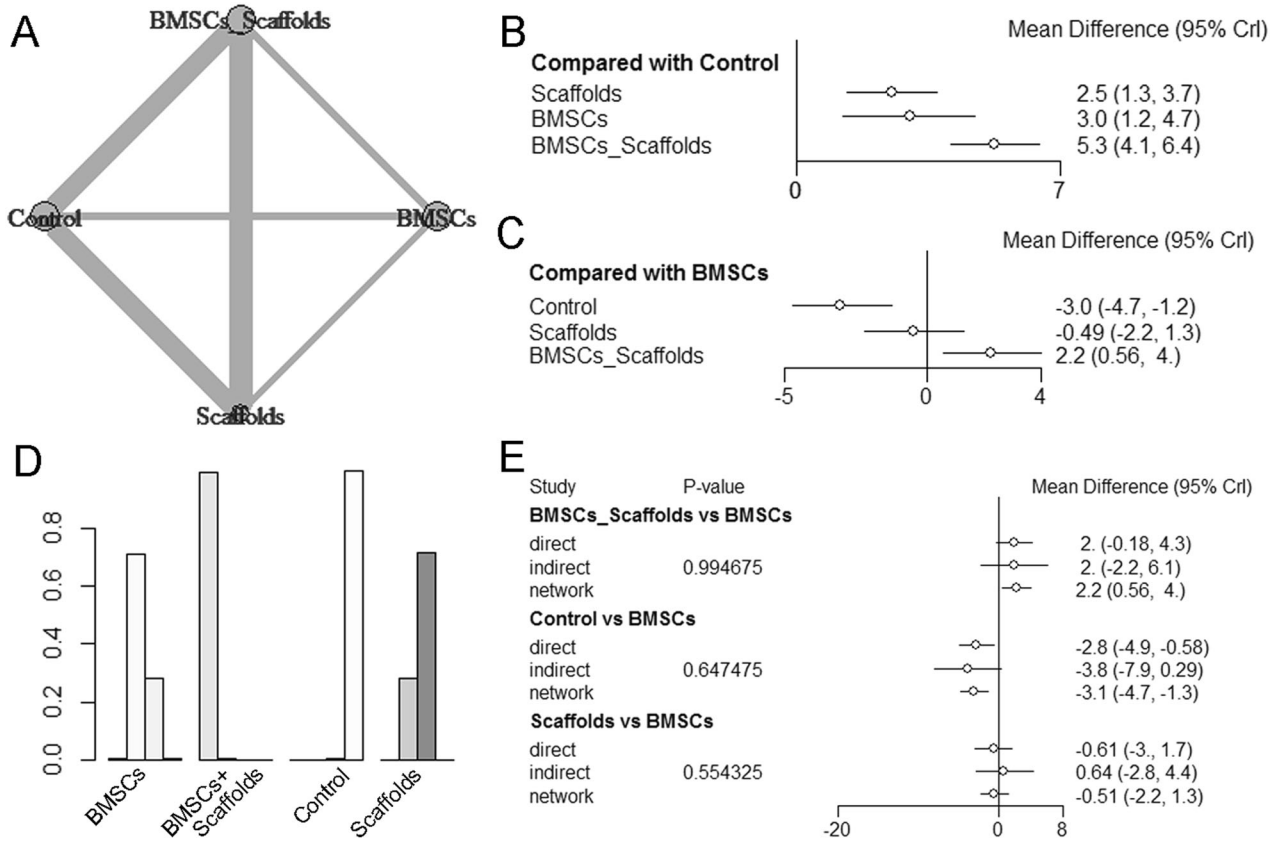

Fig. 2 Network meta-analysis of the motor functional recovery for scaffolds, BMSCs, and BMSCs combined with scaffolds. A The network geometry structure diagrams; **B** The relative forest plots of scaffolds, BMSCs, and BMSCs combined with scaffolds compared with control, **C** scaffolds, and BMSCs combined with scaffolds compared with BMSCs, using mean difference (MD) values and 95% credible intervals (CrIs). **D** Rank of probability for effective outcomes. **E** Node-splitting method in comparison between direct and indirect evidence.

The node-splitting method indicated the consistency of direct and indirect evidence (all p values > 0.05, Supplementary Fig. 2).

DISCUSSION

SCI can profoundly influence human health and has been linked to lifelong disability. More high-level evidence-based medical research is expected to evaluate the value of stem cells and biomaterial scaffold material therapy for SCI [30, 31]. In our Bayesian network meta-analysis, the motor functional recovery was found to benefit from scaffolds, BMSCs, and BMSCs combined with scaffolds, but the scaffold and BMSC groups had similar motor functional recovery efficacy, and the BMSCs combined with scaffolds group appeared to show better efficacy than BMSCs and scaffolds alone. Subgroup analysis showed that BMSCs+fibrin, BMSCs+ASC, BMSCs+gelatine, and BMSCs+collagen were the best four treatments for SCI in rat models.

Compared with other stem cells, BMSCs are abundant across the autologous bone marrow and show lower immunogenicity, which can easily be transplanted and can elude immune surveillance [32]. BMSCs may play a role in the locomotor improvement and tissue repair by secreting numerous neurotrophic factors into the cerebrospinal fluids [3]. Li et al. reported that BMSC transplantation appears to be safe and effective in treating SCI patients in a systematic review and meta-analysis [6]. However, BMSCs did not fare too well in vivo and might survive only 2–3 weeks after transplantation in the injured spinal cord. In addition to the problem, BMSCs are not able to automatically restructure as scaffolds for regenerating axons and neural junctions, much less reduce the gap of the lesion and cavity formation of the injured spinal cord [33]. The combination of BMSCs and biomaterial scaffold materials may be a novel and promising strategy for treating SCI. Biomaterial scaffolds can provide BMSCs with a favourable microenvironment in which cells can achieve long-term and have been used to fill the cord cavity and bridge the gap of the lesion as extracellular matrices (ECM) and cell delivery systems, through which numerous axons extend longitudinally and neuroprotective factors secrete widely [7]. Many studies have claimed that scaffolds markedly improve the survival and migration of transplanted cells. The BMSC-scaffold construct showed significantly more pronounced recovery of neurologic function than scaffolds- or BMSC-treated animals [8]. We also confirmed that the BMSCs combined with the scaffolds group appeared to show better motor functional recovery efficacy than BMSCs and scaffolds alone in our study.

There are several kinds of biomaterials, such as ASC, chitosan, collagen, fibrin, gelatine, hydrogel, PLGA, and polyurethane, that we considered being ideal scaffolds for carrying stem cells and repairing an injured spinal cord. The network meta-analysis revealed that there were no obvious motor functional recovery efficacy differences between the different scaffolds, and the best scaffolds to carry BMSCs were fibronectin, gelatine, ASC, and collagen. Fibrin is a fibrous biopolymer scaffold that has favourable features, including low immunological rejection, good plasticity, and binding capacity to the tissue, which enhances neural fibre sprouting and promotes the survival and migration of BMSCs transplanted into the damaged spinal cord [12]. The biomaterial gelatine fabricated an alternative 3D gelatine sponge (GS) scaffold with excellent bio-affinity to deliver BMSCs that induced the recovery of cortical motor evoked potential (CMEP) and the regeneration of neurons [22]. The ASC scaffold is made up of thin fibres and mimics the native

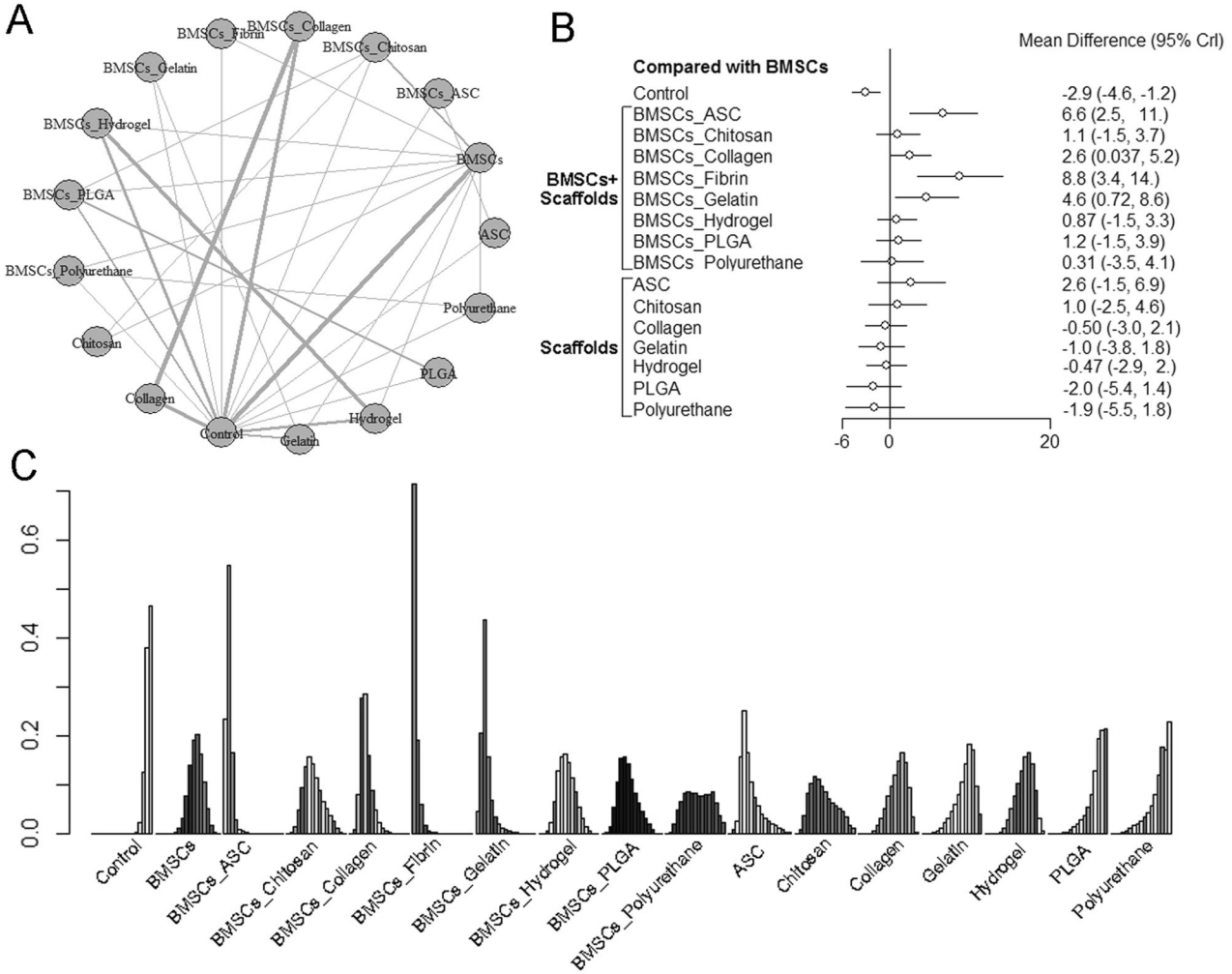

Fig. 3 Subgroup analysis of different scaffolds with BMSCs. A The network geometry structure diagrams; **B** The relative forest plots of different scaffolds, different scaffolds with BMSCs compared with BMSCs, using mean difference (MD) values and 95% credible intervals (CI); **C** Rank of probability for effective outcomes.

extracellular matrix of the spinal cord in favour of BMSC adsorption and host neural induction and conduction [26]. Collagen is a natural polymer-based scaffold that can be made into aligned collagen filaments and collagen tubes that help bridge the gap of the defect, promote axon regeneration, and reduce glial scar formation when grafted into the injured spinal cord [29].

The present meta-analysis, however, is limited in that few small-sized specified treatments for SCI were included, and future large-scale studies should therefore aim to establish a universal standard for evaluating the efficacy of both treatments in this SCI population. All the included studies were limited to the English literature; therefore, some related published studies in other languages that might have met the inclusion criteria might have been missed. All animal models of SCI were performed using rats. Therefore, large animal models should be required to evaluate the functional recovery efficacy before large-scale clinical trials with humans.

In conclusion, these Bayesian network meta-analysis findings strongly indicated that BMSCs combined with scaffolds is more effective to improve motor functional recovery than BMSCs and scaffolds alone. The fibrin, gelatine, ASC, and collagen may be favourable scaffolds for the injured spinal cord and that scaffolds with BMSCs could be a promising option in regeneration therapy for patients with SCI.

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AUTHOR CONTRIBUTIONS

WL conceived the study and wrote the manuscript, DZ analyzed the data. WL and YS extracted the data. All authors reviewed the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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