Cellular therapy for traumatic brain injury in adults: a meta-analysis of controlled clinical trials

Keywords
transplantation, traumatic brain injury, stem cells, clinical trial, progenitor cells

Abstract
Objective: Traumatic brain injury (TBI) has got no effective treatment. Cellular therapy is the transfer of autologous or allogeneic cells or cellular material into patient(s) for treatment, showed better outcomes in TBI in several clinical and preclinical studies. We performed a meta-analysis to accumulate and analyze the current evidence related to cellular therapy for TBI in adult patients.
Methods: We performed a meta-analysis on published articles on the topic of cellular therapy for the treatment of TBI in adult patients.
Results: Five studies that met the selection criteria and considered as high quality, containing 367 participants, with an average follow up time of (7.58±6.93) months, were included in meta-analysis.
Conclusion: This meta-analysis suggests that cellular therapy improves the condition of TBI patients in clinic. Larger, multi-central trials are required to further confirm and detail the use of stem cells in TBI.

Running title: Cellular therapy and TBI patients

Cellular therapy for traumatic brain injury in adults: a meta-analysis of controlled clinical trials

Abstract

Objective: Traumatic brain injury (TBI) has got no effective treatment in the clinic. Cellular therapy, which is the transfer of autologous or allogeneic cells or cellular material into patient(s) for treatment or prevention of disease, showed better outcomes in TBI in several clinical and preclinical studies. We performed a meta-analysis to accumulate and analyze the current evidence related to cellular therapy for TBI in adult patients.

Methods: We performed a meta-analysis on published articles on the topic of cellular therapy for the treatment of TBI in adult patients. The literature search was done via PubMed, China National Knowledge Infrastructure (CNKI), Cochrane Library, Embase, Wan Fang Data and Google Scholar with no restrictions on publication year. Studies were included based on selection criteria and quality assessment. The following data were extracted from included articles; author names, publication year and place, type of study, (number, sex and age) of participants, type of cells used, and post-treatment follow up. The required data related to Fugl-Meyer Motor Scale (FMMS), Disability Rating Scale (DRS) and patients Overall improvement were pooled and analyzed using RevMan (Ver.5.4.1).

Results: Five studies that met the selection criteria and considered as high quality, containing 367 participants, with an average follow up time of (7.58±6.93) months, were included in meta-

analysis. The results showed that cellular therapy significantly improves (OR=0.26; 95% CI= 0.15 to 0.48; P=0.0001) the overall performance of the patients. Moreover, the improvements in FMMS (MD=3.79; 95% CI= -2.53 to 10.10; P=0.24) and DRS (MD= -0.16; 95% CI= -1.51 to 1.19; P=0.82) were not statically significant, but they are obviously clinically significant.

Conclusion: This meta-analysis suggests that cellular therapy improves the condition of TBI patients in clinic. Larger, multi-central clinical trials are required to further confirm and detail the use of stem cells in TBI.

Key words: traumatic brain injury; stem cells; progenitor cells; transplantation; clinical trial

Introduction

TBI is mainly caused by external physical insults to the brain, which may lead to alterations in consciousness, mental or physical state of the patient [1]. TBI remains one of the principal causes of deaths and disabilities with almost ten million victims worldwide each year [2, 3]**.** Nearly two and half million Americans suffer from the tragic consequences of TBI. These patients live with impairment in sensory, motor, behavioral, or cognitive functions. The incidence rate for moderate and severe TBI in children has not improved in the last ten years with a disappointing outcome for severely injured candidates [4-6]**.**

World health organization warns that along with the human loss, TBI is one of the top financial burdens on health providing platforms [2, 7]**.** The damage that occurs during the primary impact is referred as “primary injury”, whereas the damage secondary to the initial insult via cellular, physiological and biochemical events is referred to as “secondary injury” [8]**.** Brain edema followed by increased intracranial pressure (ICP) is the characteristic of many neurosurgical

diseases. An extreme ICP is believed to be the main cause of death in such patients. The drug of choice to decrease an acute ICP is mannitol or hypertonic saline [9, 10].

The current treatment options for TBI, such as hyperbaric oxygenation, rehabilitation and brain stimulation are only of supportive nature, therefore it is a need to seek an absolute therapeutic option [11, 12]. Looking at the complexity of pathomechanism of TBI, a treatment that could maintain or restore the function of injured neurons would be the best approach. Progenitor cells are of great importance in this regard due to their plasticity, migration and self-renewal capacity [13, 14]. Recently cellular therapy has gained a particular interest in various disease such as, cerebral palsy, TBI, stroke, spinal cord injury and autism [15-17].

Several types of cells, such as bone marrow derived stem cells, neural stem cells, embryonic cells, pluripotent cells and umbilical cord blood cells have improved TBI in different animal models [18-21]. The way transplanted cells help to repair TBI might be via replacing the damaged cells through proliferation and differentiation, or by secreting trophic factors to cause endogenous repair [22]. As cell transplantation for TBI is not only studied in preclinical models, but also tried in various clinical trials, therefore we aim to perform a meta-analysis on the effects of cellular therapy for TBI in adult patients.

Methods

This meta-analysis is compliant with PRISMA 2020, and follows preciously described protocol [23].

Search strategy

A systemic search was conducted on PubMed, China National Knowledge Infrastructure (CNKI), Cochrane Library, Embase, Wan Fang Data and Google Scholar using search terms;

"traumatic brain injury", "cellular therapy" and "clinical trial" for articles published in English language prior to May 2024. Two researchers independently examined the titles and abstracts of all searched records, and excluded those that were not meeting eligibility criteria.

Inclusion criteria

The studies were included if they met the following criteria: (1) the main focus of the study was on cellular therapy for TBI; (2) original, controlled clinical trial research article; (3) adult patients of 18 years or over; (4) full text article available.

Exclusion criteria

The studies were excluded if they met one of the following criteria: (1) patients of less than 18 years old; (2) no full text accessible; (3) no control available; (4) case report; (5) letter to editor; (6) preclinical study; (7) review article; (8) study with no quantitative data; (9) meeting abstract; (10) book chapter; (11) low-quality study.

Quality assessment

In order to assess the quality of a study, Newcastle–Ottawa Scale (NOS) was utilized. In case-control trials, NOS covers three areas namely, selection, exposure and comparability, while in a cohort study it covers, selection, outcome and comparability [24]. A numbered item in exposure, outcome or selection categories can be maximally awarded with one star, whereas two stars at max can be given to a numbered item in comparability category [25]. A study can maximally get 9 stars, and a study was considered as high quality with 6+ stars, moderate quality with 4-5 stars, and low quality with less than 4 stars [26].

Data extraction

The following data were extracted from all included articles: First authors' names, publication year, country of research, type of study, (number, sex and age) of participants, type of cells used, and post-treatment follow up. The extracted data were entered into a predesigned data collecting sheet, and then tabulated onto a spreadsheet (Table-1). Moreover, outcomes such as, Fugl-Meyer Motor Scale (FMMS), Disability Rating Scale (DRS) and overall improvement of the patients were extracted and analyzed using RevMan (Ver.5.4.1). FMMS is a broadly accepted scale in clinical practice to measure motor deficit of affected limb(s) in conditions such as stroke or TBI. It has got 100 scores in total, with zero score indicating hemiplegia and 100 scores representing a normal individual[27, 28]. DRS measures general functional changes in TBI patients. Its scores range from zero to 29, with zero representing no disability and 29 designating profound vegetative state[27, 29].

Table 1. Summarized characteristics of the studies included in meta-analysis.

Study	Country	Type of study	Treatment (n)	Control (n)	Sex (M/F)	Age (y)	Type of cells used	Follow up	Ref.
Masahito Kawabori 2021	Japan	Double-blind, randomized, controlled, phase 2 clinical trial	46	15	43/18	34.4 ±11.8	Allogeneic modified bone marrow–derived MSCs (SB623 cells).	6 m	
Charles S Cox Jr 2017	USA	Open label, non-randomized, controlled, phase I/IIa clinical trial	15	9	18/6	32 ± 3	Autologous bone marrow mononuclear cells (BMMNCs).	6 m	
Sen Wang 2013	China	Randomized, single-blind, controlled clinical trial	20	20	32/8	28.07 ± 9.78	Umbilical cord mesenchymal stem cell (UCMSCs).	6 m	
Chunlei Tian 2013	China	Nonrandom, open-labeled, controlled clinical trial	97	69	NA	29.5 ± 7.91	Autologous Bone Marrow Mesenchymal Stem Cells (BMMSCs).	14 d	
Victor I. Seledtsov 2005	Russia	Randomized, controlled, clinical trial	38	38	56/20	37.70 ±11.51	Fetal brain neural & hematopoietic liver cells.	(18-24) m	
Total			216	151					

Abbreviations: NA= not available; y= year; m=month; d d=day; M=male; F=female.

Statistical analysis

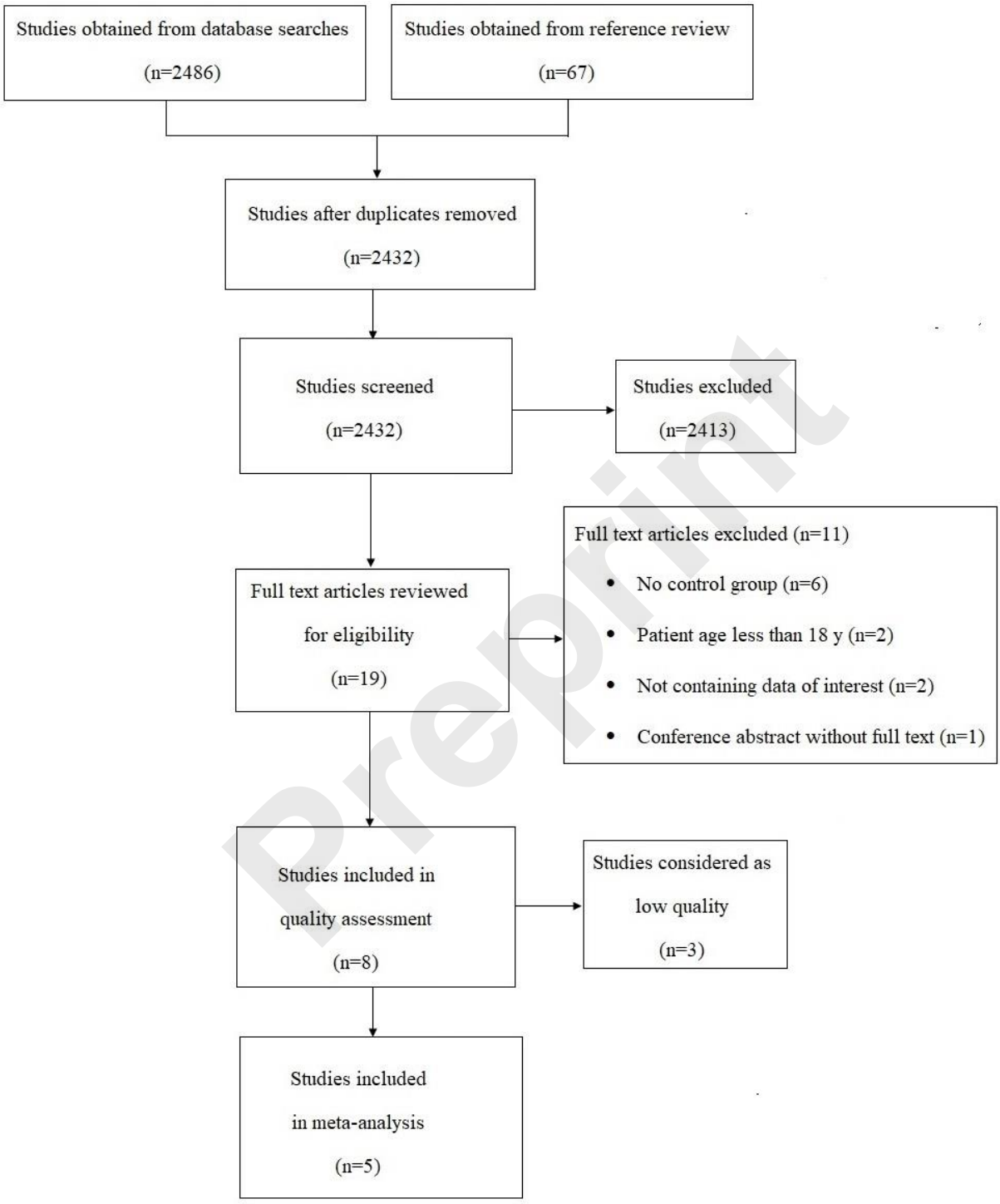
The data were analyzed using RevMan (Ver.5.4.1) software. Heterogeneity was tested among the studies, and a p-value<0.5 or I^2>50% was considered to demonstrate significant heterogeneity [10]. Dichotomous data such as in "overall improvement" were expressed as odds ratio (OR) with 95% confidence interval (CI). Continuous data such as in FMMS and DRS were expressed as mean difference (MD) with 95% CI. A P-value less than 0.05 was considered to be statistically significant.

Results

Characteristics and selection of individual studies

Initially 2553 articles were identified through database searches and reference review. The records were checked for duplicates, and 2432 articles were left after repetitive articles were removed. Screening the titles and abstracts of remaining articles, 2413 articles were removed, 19 articles were selected to be relevant and their full texts were accessed. The 19 full text articles were evaluated for eligibility; 6 articles had no control group, the participants of 2 articles were less than 18 years old, 2 articles contained no extractable data, 1 article was a conference abstract, and 3 articles were of low literature quality. After applying the eligibility criteria, 5 controlled clinical trials (Table-2) were finally included in meta-analysis (**Fig-1**). The included articles contained 367 patients, with a sample size at the range of 24 to 166.

Figure 1. Flow chart showing studies identification and selection strategy.



Overall improvement of the patients

Two studies [30, 31] provided data on overall improvement of the patients after cellular therapy comparing treatment and control groups. Fixed effect model was chosen based on statistically significant heterogeneity (I^2= 75%, p=0.04) among the studies. The pooled mean difference (MD) of overall improvement in treatment groups versus control groups was 0.26 (95% CI: 0.15 to 0.48, p=0.0001) which indicates that the treatment significantly improves overall condition of the patients **(Fig-2A)**.

Table 2. Quality assessment of the trials included in meta-analysis using Newcastle–Ottawa Scale.

Study	Selection	Comparability	Outcome	Total score
Masahito Kawabori 2021	****	**	***	9/9
Charles S Cox Jr 2017	***	**	***	8/9
Sen Wang 2013	***	**	**	7/9
Chunlei Tian 2013	***	**	***	8/9
Victor I. Seledtsov 2005	***	**	**	7/9

Fugl-Meyer Motor Scale

FMMS related information was obtained from two studies [27, 32], comparing treatment and control groups. Heterogeneity (I^2= 0%, p=0.55) across the studies was not significant based on fixed effect model. The pooled MD of FMMS in the two groups was 3.79 (95% CI: -2.53 to 10.10, p=0.24). Even though, the data shows that the treatment in improving motor activity is not statistically significant, but its clinical significance is still of value **(Fig-2B)**.

Disability Rating Scale

DRS was reported by two studies [27, 33]**,** comparing treatment and control groups. There was no heterogeneity among the studies (I^2= 0%, p=0.90) with fixed effect model. The pooled MD was -0.16 (95% CI: -1.51 to 1.19, p=0.82) showing that cellular therapy does not significantly improve disability in TBI patients **(Fig-2C)**.

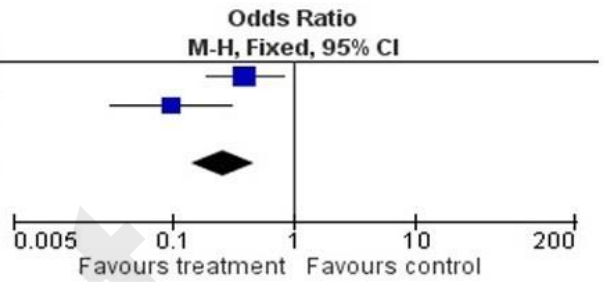
Risk of bias

To estimate the risk of publication bias, funnel plots were obtained and visually assessed for all studies included in meta-analysis. Based on the symmetric distribution of the studies effect sizes in the funnel plots, it was concluded that no publication bias was present **(Fig-2(D-F)).**

(A) Overall Improvement:

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chunlei Tian 2013	59	97	55	69	55.8%	0.40 [0.19, 0.81]
Victor I. Seledtsov 2005	5	38	23	38	44.2%	0.10 [0.03, 0.31]
Total (95% CI)		**135**		**107**	**100.0%**	**0.26 [0.15, 0.48]**
Total events	64		78			

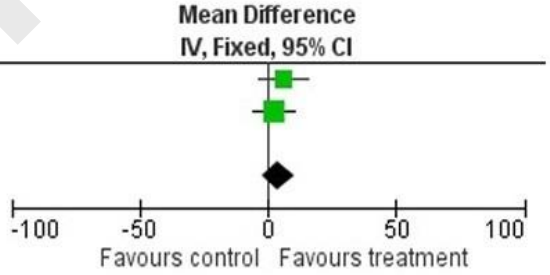
Heterogeneity: Chi² = 4.06, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 4.39 (P < 0.0001)



(B) Fugl-Meyer Motor Scale (FMMS):

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Masahito Kawabori 2021	60.6	20.8	46	54.6	15	15	42.5%	6.00 [-3.68, 15.68]
Sen Wang 2013	33.05	14.03	20	30.9	12.81	20	57.5%	2.15 [-6.18, 10.48]
Total (95% CI)			**66**			**35**	**100.0%**	**3.79 [-2.53, 10.10]**

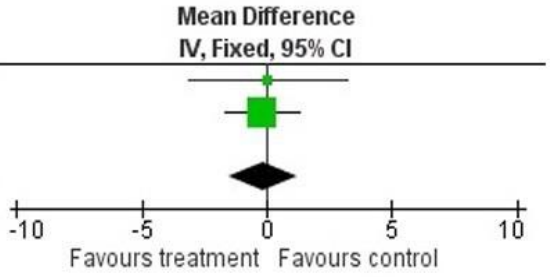
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)



(C) Disability Rating Scale (DRS):

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Charles S Cox Jr 2017	4.923	2.783	13	4.889	4.285	9	17.9%	0.03 [-3.15, 3.22]
Masahito Kawabori 2021	4.1	2.4	46	4.3	2.6	15	82.1%	-0.20 [-1.69, 1.29]
Total (95% CI)			**59**			**24**	**100.0%**	**-0.16 [-1.51, 1.19]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



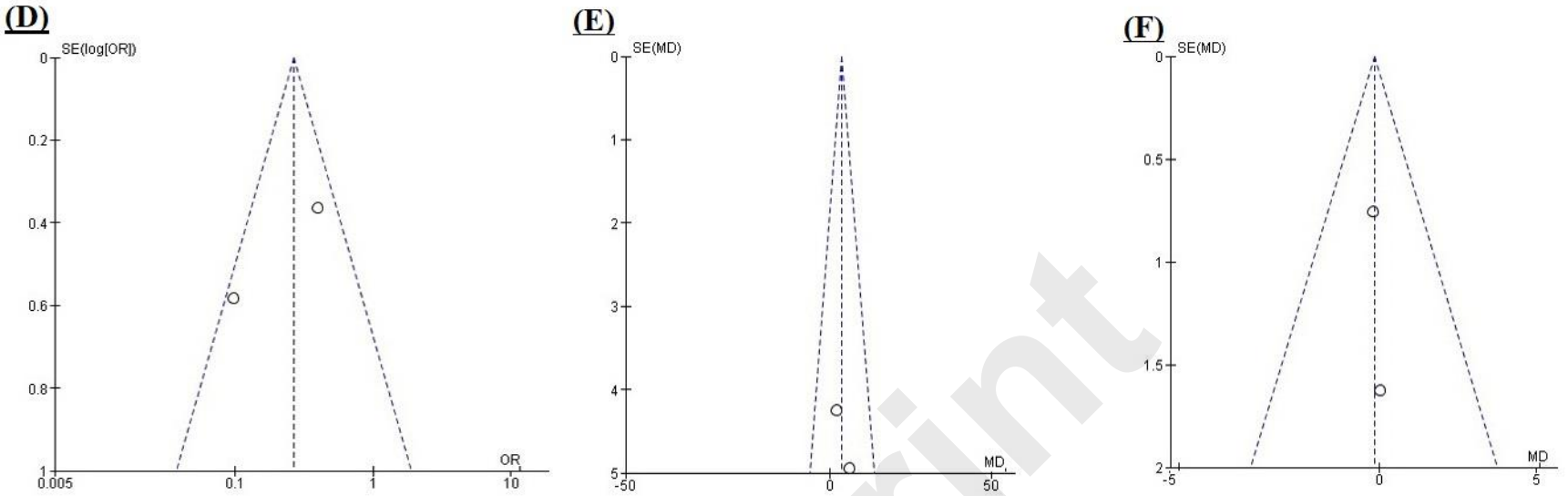


Figure 2. Forest and funnel plots of all included studies in meta-analysis. Forest plots of, overall improvement (A), Fugl-Meyer Motor Scale (B), and Disability Rating Scale (C) comparing treatment versus control groups. Funnel plots for observing any possible publication bias in, overall improvement (D), Fugl-Meyer Motor Scale *(*E), and Disability Rating Scale (F).

Discussion

Our meta-analysis includes five clinical trials covering overall outcome, motor activity and disability improvement of adult TBI patients after cell therapy. Pathophysiological events during TBI fall into two categories, primary and secondary. The biomechanical or physical insults that lead to the immediate events are followed by a flow of events such as, production of free radicals, excitotoxicity, hypoperfusion, ischemia, disturbance to cerebrovascular autoregulation, intracranial hypertension and metabolic dysfunction [34]. The flow of events that release various biological factors causes cellular death which results in local or global cerebral atrophy [35]. Thyroid cancer stem cells (TCSCs) are interesting biomarkers and possible targets for clinical intervention since they are essential to the pathophysiology, metastasis, and therapeutic response of thyroid cancer. Numerous research conducted in the last few years have shown a strong correlation between cancer stem cells (CSCs) and the development and progression of tumors[36]. Research findings suggest that global injury occurs more common which is mainly evidenced in frontal lobe, hypothalamus, temporal lobe, basal ganglia, corpus callosum, fornices, hippocampus and superior cerebral peduncles[37, 38]. Salidroside can decrease both the neurological impairment score and the infarct volume of the rat brain in the focal cerebral ischemia/reperfusion injury model in rats[39]. Injury to these structures initially causes mood disorders, psychiatric deficits, depression and neurobehavioral alterations[40].

Various preclinical studies have shown the regenerative ability of stem cells in animal TBI models [41-45]. Several preclinical TBI models have demonstrated improvement in motor, behavioral and cognitive functions after neural, mesenchymal or progenitor stem cells therapy. These effects are most likely caused by production of neurotrophic factors, improvement of

angiogenesis and down regulating of astrogliosis[18, 46, 47]. Treating unilateral limbal stem cells deficits has shown promise with autologous limbal epithelium transplantation[48]. When existing treatment options and accepted medical standards are inadequate, transplantology is a branch of medicine that saves lives[49]. Ma and teammates indicated that transplanted cells significantly decrease at the early stage of transplantation. The possible reason could be the post-traumatic inflammatory cascade in the recipient brain that affects the survival of the cells [50, 51]**.** Zhang et al. tried bone marrow derived autologous mesenchymal stem cells in seven TBI patients via intracranial and intravenous route, their findings showed that it was safe and the patients got significant improvement in neurological functions[52]. Moreover, Cox et al. and Liao et al. also transplanted bone marrow mononuclear cells to severe TBI patients through intravenous route, and they too reported the treatment to be safe and clinically significant [53, 54]. Histopathological damage and the CNS inflammatory response progressively resolve and return. Consequently, microglia may be one of the key targets of thermal stimulation-mediated central nervous system injury, and controlling their polarization by restricting M1 or encouraging M2 activation may develop into a viable therapeutic approach for disorders that produce heat-induced brain damage[55]. The administration of autologous bone marrow mononuclear cells to chronic TBI patients by Sharma and colleagues too improved the condition of the patients with no any major side effect[1].

Studies have shown that NSCs therapy have bettered the neurological functions in preclinical models of TBI [56-58]**.** Several potential mechanisms have been proposed for gaining these effects such as; immunomodulation and restoring neuronal circuits[59], production of neurotrophic factors[60], secretion of specific neurotransmitters[61], and neuronal cell replacement[62]. Research on spinal cord injury (SCI) in animals has demonstrated that SCI

causes two types of damage: first, mechanical damage, and second, secondary injury caused by neuronal apoptosis in the central nervous system (CNS), which causes the damage to spread. According to our research, the rs531564 polymorphism may cause down-regulation of miR-124, which in turn may enhance the production of BIM. This could lead to death in cells and extend the amount of time that patients recover following SCI[63]. Together necrosis and apoptosis result in death of neurons and glia during TBI. Some preclinical studies show that, NSCs transplantation reduces apoptosis around the ischemic spots resulting in functional improvement [64]. Osteoblast progenitors found in bone marrow stem cells (MSCs) in blood clots can result in the production of bone on scaffolds in the presence of growth stimuli[65].

It is also possible that these transplanted cells enhance endogenous repairing response such as improving synaptogenesis, neurogenesis and angiogenesis [66-69]. Some researchers also propose that, the secretion of specific trophins such as BDNF, NGF, GDNF and VEGF by transplanted cells could be a possible mechanism for neuronal regeneration and repair [70, 71]. As the capacity of the brain is very limited to regenerate neurons, therefore it is challenging to repair a damaged structure in the brain. At the present, no treatment exists to treat diffuse axonal injury and to divert the cascade of pathological events that leads to cellular death [1]**.** Even in preclinical TBI models, transplantation of NSCs remains with several questions yet to be answered such as, ideal time of therapy, effective route of administration and optimal does for the cells [72].Cellular therapy demonstrated potential to repair cerebral damage via neuroprotective and neurorestorative mechanisms. It is believed that stem cells use their neurogenic ability to repair injured brain [41]**.** After all, stem cell therapy remains the only hope for the future of TBI patients.

Conclusion

In summary, this meta-analysis suggests that cellular therapy significantly improves (p=0.0001) the overall condition of adult TBI patients. Moreover, the pooled data for Fugl-Meyer motor scale (p=0.24) and disability rating scale (p=0.82) shows a non-statistically significant improvement which is still of great importance in clinic.

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Disclosure

The authors have no conflict of interest to report.

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No Graphical abstract is available.

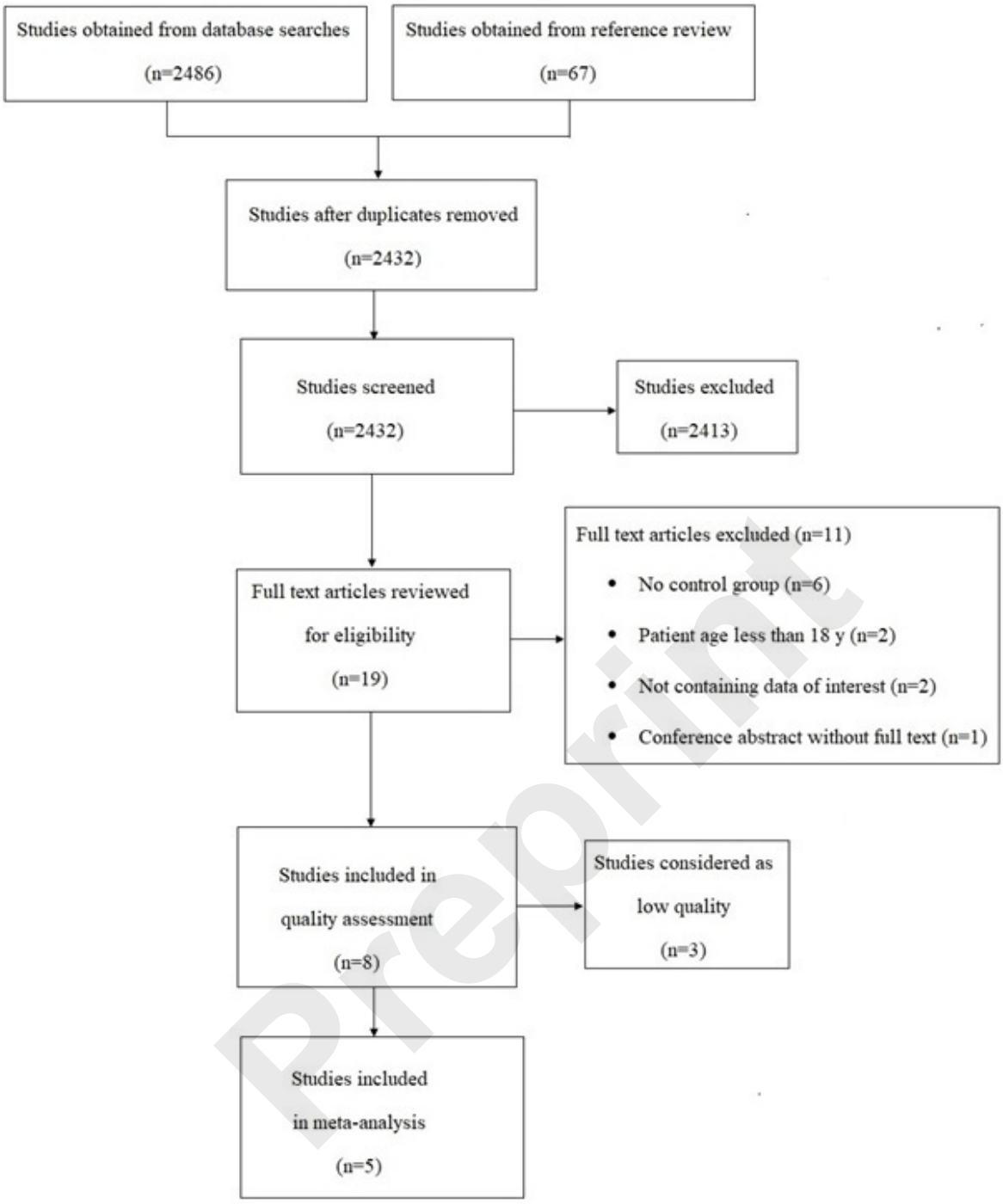
Table 1. Summarized characteristics of the studies included in meta-analysis.

Study	Country	Type of study	Treatment (n)	Control (n)	Sex (M/F)	Age (y)	Type of cells used	Follow up	Ref.
Masahito Kawabori 2021	Japan	Double-blind, randomized, controlled, phase 2 clinical trial	46	15	43/18	34.4 ±11.8	Allogeneic modified bone marrow–derived MSCs (SB623 cells).	6 m	
Charles S Cox Jr 2017	USA	Open label, non-randomized, controlled, phase I/IIa clinical trial	15	9	18/6	32 ± 3	Autologous bone marrow mononuclear cells (BMMNCs).	6 m	
Sen Wang 2013	China	Randomized, single-blind, controlled clinical trial	20	20	32/8	28.07 ± 9.78	Umbilical cord mesenchymal stem cell (UCMSCs).	6 m	
Chunlei Tian 2013	China	Nonrandom, open-labeled, controlled clinical trial	97	69	NA	29.5 ± 7.91	Autologous Bone Marrow Mesenchymal Stem Cells (BMMSCs).	14 d	
Victor I. Seledtsov 2005	Russia	Randomized, controlled, clinical trial	38	38	56/20	37.70 ±11.51	Fetal brain neural & hematopoietic liver cells.	(18-24) m	
Total			216	151					

Abbreviations: NA= not available; y= year; m=month; d d=day; M=male; F=female.

Table 1. Quality assessment of the trials included in meta-analysis using Newcastle–Ottawa Scale.

Study	Selection	Comparability	Outcome	Total score
Masahito Kawabori 2021	****	**	***	9/9
Charles S Cox Jr 2017	***	**	***	8/9
Sen Wang 2013	***	**	**	7/9
Chunlei Tian 2013	***	**	***	8/9
Victor I. Seledtsov 2005	***	**	**	7/9



Flow chart showing studies identification and selection strategy.

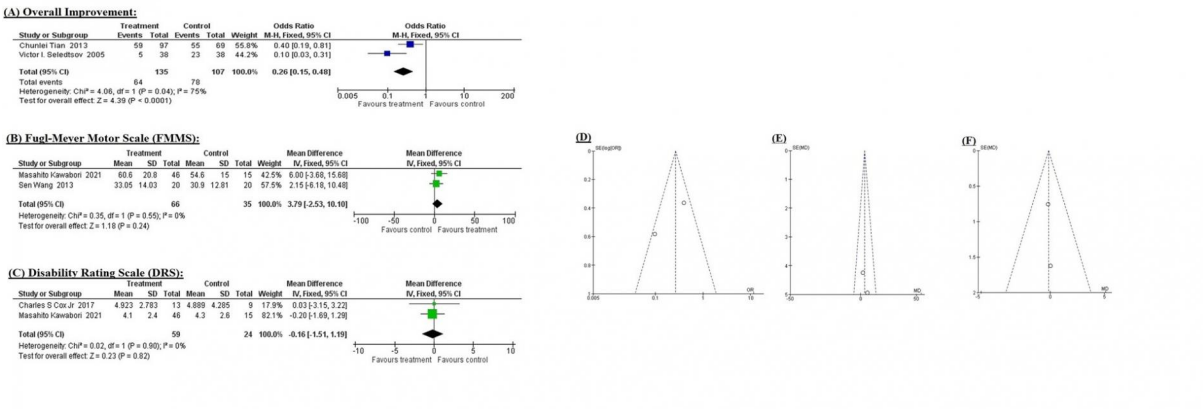


Figure 2. Forest and funnel plots of all included studies in meta-analysis. Forest plots of, overall improvement (A), Fugl-Meyer Motor Scale (B), and Disability Rating Scale (C) comparing treatment versus control groups. Funnel plots for observing any possible publication bias in, overall improvement (D), Fugl-Meyer Motor Scale (E), and Disability Rating Scale (F).