Original Article

Efficacy and safety of mesenchymal stem cell therapy for acute respiratory distress syndrome—a systematic review and meta-analysis

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Background: Mesenchymal stem cells (MSC) therapy for acute respiratory distress syndrome (ARDS) represents a burgeoning treatment approach, supported by numerous preclinical studies confirming its efficacy. Our study aims to provide a comprehensive evaluation of both the safety and effectiveness of MSC.

Methods: We conducted searches across three databases (PubMed, Embase, Cochrane) for randomized controlled studies up to June 23, 2024. A meta-analysis was performed on variables including adverse events, mortality, changes in the PaO_2/FiO_2 ratio, intensive care unit (ICU), length of stay, ventilation-free days, and changes in pro-inflammatory and anti-inflammatory cytokines. Relative risk (RR) values were employed for dichotomous variables, while mean difference (MD) and standard mean difference (SMD) were used for continuous variables. Risk bias was assessed using risk of bias 2 (ROB2).

Results: The meta-analysis encompassed 17 experiments involving 796 patients, with 410 undergoing MSC treatment and 386 in the control group. Primary outcomes indicated that MSC treatment did not escalate adverse events [RR =1.04; 95% confidence interval (CI): 0.90, 1.19; P=0.59; I^2=0%]. On the contrary, it significantly diminishes the mortality (RR =0.79; 95% CI: 0.64, 0.97; P=0.02; I^2=0%). Regarding secondary outcomes, MSCs led to a significant improvement in the PaO_2/FiO_2 ratio for ARDS patients (SMD =0.53; 95% CI: 0.15, 0.92; P=0.007; I^2=0%). However, there were no significant differences in ICU length of stay (MD =−1.77; 95% CI: −6.97, 3.43; P=0.50; I^2=63%) and ventilation-free days (MD =−1.29; 95% CI: −4.09, 1.51; P=0.37; I^2=0%). MSCs significantly lowered C-reactive protein (CRP) (SMD =−0.65; 95% CI: −1.18, −0.13; P=0.01; I^2=56%) and interleukin-6 (IL-6) levels compared to the control group (SMD =−0.76; 95% CI: −1.34, −0.17; P=0.01; I^2=74%). However, changes in interleukin-10 (AIL-10) (SMD =−0.46; 95% CI: −1.51, 0.58; P=0.38; I^2=77%), and changes in tumor necrosis factor-alpha (ATNF-α) (SMD =−1.5; 95% CI: −3.39, 0.40; P=0.12; I^2=92%) levels showed no significant changes.

Conclusions: MSC therapy demonstrates reliable safety, with a significant impact on reducing mortality and improving certain clinical symptoms. Moreover, in certain aspects, it may alleviate the inflammatory response in ARDS. Nonetheless, these findings necessitate validation through additional high-quality randomized controlled trials.

Keywords: Acute respiratory distress syndrome (ARDS); mesenchymal stem cells (MSCs); mortality; adverse events; meta-analysis

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Introduction

Acute respiratory distress syndrome (ARDS) is a prevalent clinical syndrome characterized by diffuse pulmonary inflammation and edema, leading to acute respiratory failure. A primary cause of ARDS is the systemic inflammatory response triggered by endotoxins or injurious factors (1-3). This response increases endothelial and epithelial permeability, resulting in alveolar edema and worsening respiratory failure, ultimately leading to ARDS (4). The LUNG-SAFE study indicates that ARDS patients constitute 10.4% of intensive care unit (ICU) admissions in 50 countries, with a high mortality rate ranging from 34.9% to 46.1% (5). Current conventional treatments for ARDS primarily focus on respiratory support, including lung-protective ventilation strategies, prone positioning, extracorporeal membrane oxygenation (ECMO), and others (6). Therefore, there is an urgent need for research into new therapeutic approaches targeting the pathogenesis of ARDS.

As a result of the coronavirus disease 2019 (COVID-19) outbreak, the uncontrolled inflammatory response in ARDS is being increasingly scrutinized. Regulating the pro-inflammatory and anti-inflammatory balance in ARDS has become crucial. Mesenchymal stem cells (MSCs) are proposed as a potential therapeutic modality for ARDS due to their ability to modulate this balance.

MSCs possess characteristics of plastic adhesion and multipotent differentiation potential, making them advanced cell therapy products. MSCs can be isolated from various sources, including bone marrow, adipose tissue, perinatal tissues, dermal tissues, dental tissues, and peripheral blood (7). The potential of MSCs as a treatment for ARDS has been demonstrated in numerous animal experiments.

Firstly, MSCs can modulate the balance of the inflammatory environment by directly secreting soluble factors that regulate immune cells, suppressing pro-inflammatory cytokines, and upregulating anti-inflammatory cytokines (8,9). Secondly, in a mouse lipopolysaccharide (LPS) model, MSCs can reduce tissue damage in the ARDS model, mitigating alveolar hemorrhage, edema, membrane formation, and collagen deposition while restoring the function of endothelial and epithelial cells (10,11). Lastly, MSCs can secrete antimicrobial peptides (AMPs) with direct antibacterial effects to enhance bacterial clearance (9,10,12).

Despite some clinical trials assessing the safety and efficacy of MSC therapy for ARDS, uncertainties persist due to generally small sample sizes and many are associated with COVID-19 (13-29). Therefore, we conducted a comprehensive meta-analysis of clinical trials involving MSC treatment for ARDS patients up to June 23, 2024. We evaluated adverse events, mortality, PaO_2/FiO_2 ratio, ICU length of stay, ventilation-free days, and changes in pro-inflammatory and anti-inflammatory cytokines to thoroughly assess the safety and effectiveness of MSC therapy for ARDS. We present this article in accordance with PRISMA reporting checklist (30) (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-281/rc).

Highlight box

Key findings
- Mesenchymal stem cells (MSCs) do not elevate the risk of adverse reactions in acute respiratory distress syndrome (ARDS) patients.
- Significant reductions in mortality of ARDS can be seen during MSC treatments.
- MSCs can also improve patients' clinical symptoms to a certain extent.
- MSC therapy effectively regulates the uncontrolled inflammatory response.

What is known and what is new?
- MSC therapy for ARDS represents a burgeoning treatment approach, supported by numerous preclinical studies confirming its efficacy.
- Our study comprehensively analyzed the safety and effectiveness of MSC treatment from the clinical trial. We found that MSCs are reliably safe and can significantly improve certain clinical manifestations, reduce inflammatory reactions, and lower mortality rates. Notably, the improvement in clinical symptoms and anti-inflammatory effect has never been reported in previous similar studies.

What is the implication, and what should change now?
- It suggested that MSCs is an effective method to treat ARDS. However, these findings necessitate further validation through high-quality randomized controlled trials.

Methods

Protocol and registration

The study protocol was registered at the International Prospective Register of Systematic Reviews (CRD42023427079).

Eligibility criteria

Our inclusion criteria were as follows: (I) study type: all published randomized controlled trials (RCTs) that evaluated the safety and/or efficacy of MSCs. (II) Study subjects: individuals aged 18 years and above, conclusively diagnosed with ARDS based on the Berlin definition. (III) Intervention measures: the intervention involved the application of MSCs. (IV) Outcome measures: the included outcome measures comprised adverse events, mortality, ICU length of stay, ventilation-free days, and changes in pro-inflammatory and anti-inflammatory cytokines.

The exclusion criteria were as follows: (I) conference records and abstracts; (II) case series studies; (III) animal experiments; (IV) clinical protocols; (V) data that could not be extracted.

Data collection

Between January 23, 2024 and June 23, 2024, we systematically searched for relevant studies in three databases: PubMed, Embase, and Cochrane, encompassing publications up to June 23, 2024.

Search strategy

The search keywords included ‘ARDS’, ‘ALI’, ‘Acute Respiratory Distress Syndrome’, ’shock Lung’, ‘acute lung injury’, ‘Respiratory Distress Syndromes’, ‘MSCs’, ‘Mesenchymal Stem Cell’, ‘Mesenchymal Stromal Cell’, and ‘Mesenchymal Progenitor Cell’. The detailed search strategies for the three English databases can be found in the Appendix 1.

Study selection

Two researchers independently conducted title and abstract screening in the databases to identify literature for full-text assessment. If the information in the titles and abstracts met the inclusion criteria, both researchers retrieved the full text for independent screening. In cases of disagreement, consensus was reached through discussion, or a third party was consulted for resolution.

Data extraction

Two independent data extractors collected pertinent information according to our predefined data extraction table. In instances of discordance, the two extractors engaged in discussion to achieve consensus. The extracted data encompassed: (I) first author, publication year; (II) study type; (III) number of included patients; (IV) details regarding MSC and control group sources, doses, administration routes, and timing; (V) adverse events, mortality, ICU length of stay, ventilation-free days, and changes in pro-inflammatory and anti-inflammatory cytokines.

Analysis of results

The primary outcomes of the study focused on adverse events and all-cause mortality. Secondary outcomes included the changes in the PaO_2/FiO_2 ratio, ICU length of stay, ventilation-free days, as well as changes of levels of pro-inflammatory and anti-inflammatory cytokines.

Risk of bias assessment

For RCTs, we employed the Cochrane Risk of Bias tool for evaluation. This tool assesses six key aspects: (I) sequence generation, (II) allocation concealment, (III) blinding of participants and outcome assessors, (IV) incomplete outcome data, (V) selective outcome reporting, and (VI) other sources of bias. We utilized the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to ascertain the certainty of the impact of MSCs on adverse event rates and mortality.

Statistical analysis

We conducted a meta-analysis of the safety and efficacy of MSCs in treating ARDS using RevMan 5.4 and Stata 15.0 software. For dichotomous variables, we calculated the relative risk (RR) for each relevant outcome between the experimental and control groups. For continuous variables, we computed the mean difference (MD) or standardized mean difference (SMD) between the experimental and control groups. Heterogeneity among studies was assessed using the I^2 test. The random-effects model was utilized in

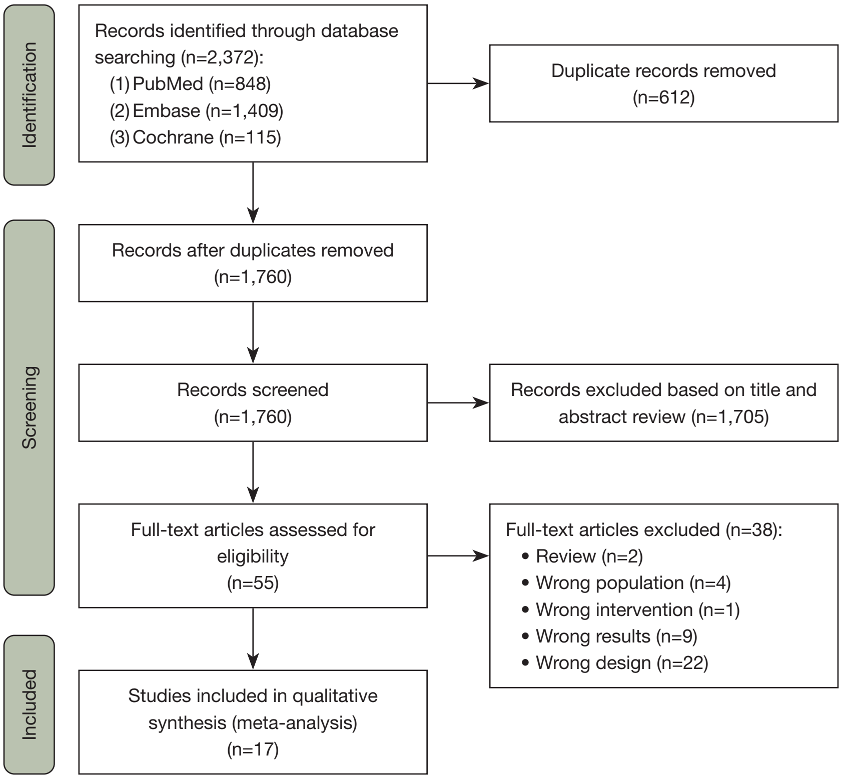

Figure 1 Flowchart of the preferred reporting item search strategy for systematic evaluation and meta-analysis and inclusion of studies.

all our analyses. Funnel plots and the trim-and-fill method were employed for publication bias analysis. Sensitivity analysis was performed to assess the stability of the results. Additionally, subgroup analysis was conducted based on different sources of MSCs. All statistical tests were two-tailed, and a P value less than 0.05 was considered statistically significant.

Results

Literature screening process

Following the designated search strategy, we identified 2,372 records in the databases. After eliminating 612 duplicates, 1,760 remaining records underwent title and abstract screening. During this initial screening, 1,705 records were preliminarily excluded. Subsequently, full-text screening was conducted, resulting in the exclusion of thirty-eight articles for the following reasons: (I) 2 articles were reviews; (II) 4 articles had subjects that did not meet the inclusion criteria; (III) 1 article had inappropriate intervention measures; (IV) 9 articles reported outcomes that did not meet the requirements; (V) 22 articles had flawed experimental designs. Ultimately, 17 articles met the criteria and were included in the meta-analysis (*Figure 1*).

Characteristics of included studies

Tables 1,2 provide a comprehensive overview of the primary features of the 17 included studies and the demographic details of the patients. A total of 796 patients were enrolled in these studies, with 410 in the MSC group and 386 in the control group; of these, males comprised 62.75%. Regarding the severity of ARDS, two studies delineated the distribution among mild, moderate, and severe ARDS patients, while five studies included individuals with PaO_2/FiO_2 <200 mmHg. Concerning the etiology of ARDS, 15 studies reported COVID-19 as the inducing factor, while the remaining two did not specify the cause. Characteristics of MSCs in all studies matched the International Society for Cell & Gene Therapy (ISCT) criteria. The MSC products employed for treatment originated from diverse sources, including adipose tissue, bone marrow, umbilical cord, and placenta. Dosages ranged from 1×10^6/kg to 10×10^6/kg, with intravenous injection as the common administration

Table 1 Characteristics of the included studies

References	Year	Design	Sample size (MSC/COT)	Age (MSC/COT), years	Gender (male ratio)	Group (dose, treatment duration)		Outcomes
						MSC	COT	
Monsel *et al.* (23)	2022	RCT	45 (21/24)	64.00±10.40/63.20±11.40	17 /21 *vs.* 20/24	UC-MSCs, 3×10^6 cells/kg body weight, IV	150 mL NS	PaO_2/FiO_2, biomarkers of endothelial, alveolar epithelial injury and inflammatory response, SARS-CoV-2 N-antigenemia and viral RNA levels, HLA and DSAs directed against UC-MSCs
Bowdish *et al.* (15)	2023	RCT	222 (112/110)	61.80±13.00/59.60±13.80	79/112 *vs.* 75/110	BM-MSCs, 2×10^6 MSC/kg of body weight, IV	Placebo	All-cause mortality, days alive off mechanical ventilation within 60 days, resolution and/or improvement of ARDS, and clinical improvement, total and ICU LOS, the total number of days in hospital, adverse events
Rebelatto *et al.* (25)	2022	RCT	17 (11/6)	53±15.3/61.7±9.7	8/ 11 *vs.* 4/6	UC-MSCs, 5×10^6 cells/kg body weight, IV	Placebo	Adverse events, patient recovery demonstrated through viral load, blood tests and plasma levels of inflammatory cytokines, PBMC assessment of T cell populations, PASC reduction, CT scan
Lanzoni *et al.* (20)	2021	RCT	24 (12/12)	58.58±15.93/58.83±11.61	5/12 *vs.* 8/12	UC-MSCs, $100\pm20\times10^6$ UC-MSCs 2 IV dose	50 mL vehicle solution	Adverse events, survival at day 28, time to recovery, viral load, inflammatory cytokines, chemokines, growth factors
Zheng *et al.* (29)	2014	RCT	12 (6/6)	66.7±20.4/69.8±9.1	6/6 *vs.* 5/6	AD-MSCs, 1×10^6 cells/kg of body weight, one IV dose COT:NS	NS	Adverse events, oxygenation index, length of hospital stay, ventilator-free days, ICU-free days at day 28, SP-D, IL-6 or IL-8 levels in serum
Aghayan *et al.* (14)	2022	RCT	20 (10/10)	62.30/58.40	6/10 *vs.* 8/10	PL-MSCs, 1×10^6 cells/kg body weight, IV	Placebo	Adverse events, vital signs, mortality, the duration of hospitalization, biochemistry, hematology parameters, $CD4^+$ and $CD8^+$ T-cells
Dilogo *et al.* (16)	2021	RCT	40 (20/20)	NR	15/20 *vs.* 15/20	UC-MSCs, 1×10^6 cells/kg body weight, one IV dose	100 mL NS	Mortality rate, length of ventilator usage, length of stay in the ICU, improvement in the routine laboratory value, improvement in biomarker laboratory value of cytokines and lymphocyte subpopulation, adverse events and serious adverse events
Matthay *et al.* (22)	2019	RCT	60 (40/20)	55.00±17.00/55.00±20.00	23 /40 *vs.* 10/20	BM-MSCs, 10×10^6 cells/kg body weight, one IV dose	Placebo	Adverse events, all-cause mortality, ventilator-free days to day 28, duration of ventilation in patients alive, intensive-care-free days, days free from organ failure, SOFA score, oxygenation index, the lung injury score, angiopoietin 2, IL-6 and IL-8, RAGE
Kaffash Farkhad *et al.* (19)	2022	RCT	20 (10/10)	62.00±2.42/61.30±5.34	7/10 *vs.* 6/10	UC-MSCs, 1×10^6 cells/kg body weight, IV	Placebo	Mortality, PaO_2/FiO_2, lung imaging, infammatory biomarkers such as IL-1 beta, IL-6, TNF-α
Gorman *et al.* (18)	2023	RCT	59 (30/29)	58.40±9.20/58.40±12.5	24/30 *vs.* 20/29	UC-MSCs, 400×10^6 cells/person, IV	Placebo	Adverse events, oxygenation index, indices of pulmonary and nonpulmonary organ dysfunction, PaO_2/FiO_2 ratio, SOFA, extubation, reintubation, ventilator-free days, lengths of ICU, hospital stays, mortality, RNA sequencing
Pochon *et al.* (24)	2023	RCT	30 (15/15)	58.45±13.90/65.64±7.36	13/15 *vs.* 7/15	UC-MSCs, 1×10^6 cells/kg, IV	Placebo	The percentage of patients with a PaO_2/FiO_2 >200 mmHg, PaO_2/FiO_2, ventilator free days, SOFA, ICU length of stay, respiratory morbidity, RT-PCR SARS-CoV-2 positivity, adverse events
Zarrabi *et al.* (28)	2023	RCT	35 (11/24)	50.00±12.48/47.75±12.72	10/11 *vs.* 16/24	MSCs derived from perinatal tissue, 100×10^6 cells/person, IV	Placebo	Adverse events, CBC, ABG, biochemistry analysis, inflammatory parameters
Adas *et al.* (13)	2021	RCT	20 (10/10)	NR	NR	WJ-MSCs, 3×10^6 cells/kg body weight, IV	Placebo	Adverse events, mortality, inflammatory parameters
Shi *et al.* (26)	2021	RCT	100 (65/35)	60.72±9.14/59.94±7.79	37/65 *vs.* 19/35	UC-MSC, 4.0×10^7 cells/person, IV	Placebo	Adverse event, chest CT, lung volume
Shu *et al.* (27)	2020	RCT	41 (12/29)	61.00±17.87/57.86±15.79	8/12 *vs.* 16/29	UC-MSCs, 2×10^6 cells/kg, IV	Placebo	The incidence of progression, the time to a clinical improvement, seven-category ordinal scale, hospital stay, oxygenation index, hematological inflammatory factors, imaging
Martínez-Muñoz *et al.* (21)	2024	RCT	20 (10/10)	61.34±25.80/61.81±24.94	5/10 *vs.* 8/10	BM-MSCs, 1×10^6 MSC/kg, IV	Placebo	PaO_2/FiO_2, mortality, clinical status, adverse events, inflammatory parameters
Fathi-Kazerooni *et al.* (17)	2022	RCT	30 (15/15)	46.43±11.91/53.67±10.30	9/15 *vs.* 10/15	MSCs derived from the menstrual blood, 5 mL, IV	Placebo	Adverse events, mortality, chest CT, time to recovery, inflammatory parameters

Data types: sample size/gender: number; age: mean, mean ± standard deviation. MSC, mesenchymal stem cell; COT, control group; RCT, randomized controlled trial; UC-MSC, umbilical cord mesenchymal stem cell; IV, intravenous infusion; NS, normal saline; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; N-antigenemia, nucleocapsid antigenemia; HLA, human leukocyte antigen; DSA, donor-specific antibodies; BM-MSC, bone-marrow-derived mesenchymal stem cell; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LOS, length of stay; PBMC, peripheral blood mononuclear cell; PASC, post-acute sequelae of SARS-CoV-2 infection; CT, computed tomography; AD-MSC, adipose-derived mesenchymal stem cell; SP-D, surfactant protein D; IL, interleukin; PL-MSC, placental mesenchymal stem cells; SOFA, sequential organ failure assessment; RAGE, receptor for advanced glycation end-products; TNF, tumor necrosis factor; RT-PCR, reverse transcription polymerase chain reaction; CBC, complete blood count; ABG, arterial blood gas; NR, not reported.

Table 2 Characteristics of the included studies

References	BMI [MSC/COT], kg/m^2	SOFA [MSC/COT]	Comorbidities (MSC/COT)	Severity of ARDS	PaO_2/FiO_2 [MSC/COT]
Monsel *et al.* (23)	28.6 [3.5]/28 [5.5]	5.5 [2.7]/5.9 [2.7]	HT: 11/10, DM: NR	NR	156.2 [68.2]/171.2 [72.9]
Bowdish *et al.* (15)	NR	6.6 [2.1]/6.7[1.9]	HT: 65/63, DM: 46/42	Moderate 79/76, severe 33/34	NR
Rebelatto *et al.* (25)	NR	NR	HT: 6/3, DM: 4/3	Mild 4/5, moderate 6/0, severe 1/1	NR
Lanzoni *et al.* (20)	34.5 [4.5]/29.6 [3.5]	NR	HT: 7/9, DM: 5/6	Mild-to-moderate 3/3, moderate-to-severe 9/9	118.1 [80.5]/114.7 [81.3]
Zheng *et al.* (29)	NR	NR	HT: 3/3, DM: 2/1	NR	122.4 [42.0]/103.5 [32.2]
Aghayan *et al.* (14)	NR	NR	HT: 4/4, DM: 3/4	NR	NR
Dilogo *et al.* (16)	NR	NR	HT: 6/10, DM: 8/12	NR	NR
Matthay *et al.* (22)	NR	8.1 [3.3]/6.9 [2.7]	NR	NR	135.8 [32.3]/143.3 [39]
Kaffash Farkhad *et al.* (19)	NR	NR	HT: 1/3, DM: 2/1	NR	NR
Gorman *et al.* (18)	NR	7.7 [3.4]/7.9 [3.1]	NR	NR	15.2 [4.2]/16.1 [5.4]
Pochon *et al.* (24)	30.7 [6.5]/34.0 [3.3]	4.4 [2.5]/5.4 [4.1]	HT: 5/10, DM: 3/4	Moderate-to-severe 15/15	138 [49]/137 [36]
Zarrabi *et al.* (28)	NR	NR	NR	NR	NR
Adas *et al.* (13)	NR	NR	NR	NR	NR
Shi *et al.* (26)	24.71 [3.19]/25.01 [3.02]	NR	HT: 17/10, DM: 12/5	NR	NR
Shu *et al.* (27)	NR	NR	HT: 3/6, DM: 3/5	NR	NR
Martínez-Muñoz *et al.* (21)	29.0 [3.1]/32.0 [4.5]	NR	HT: NR, DM: 4/2	NR	99.5 [42.1]/91.0 [37.6]
Fathi-Kazerooni *et al.* (17)	NR	NR	HT: 4/5, DM: 3/4	NR	NR

Data types: BMI, SOFA, PaO_2/FiO_2: mean [standard deviation]; comorbidities, severity of ARDS: number. BMI, body mass index; MSC, mesenchymal stem cell; COT, control group; SOFA, sequential organ failure assessment; ARDS, acute respiratory distress syndrome; HT, hypertension; DM, diabetes mellitus; NR, not reported.

route. Meanwhile, concomitant treatments of the included studies were reported in the Table S1.

Primary results

The primary outcome for assessing the safety of MSC therapy is the number of adverse events. Among the 17 included studies, 12 reported adverse event numbers. Of these, 5 studies documented adverse events related to MSC infusion, all of which were mild and self-limiting (16,18,22,24,29). Additionally, 9 studies reported severe adverse events, but these were deemed unrelated to MSC infusion (13,15,16,18,20,22,24,26,29). The consolidated findings revealed no significant difference in adverse event numbers between the MSC and control groups, suggesting that MSC infusion does not lead to an increase in adverse events [RR =1.04; 95% confidence interval (CI): 0.90, 1.19; P=0.59; I^2=0%] (*Figure 2*). The evidence quality was considered good, with no evident heterogeneity observed and no notable publication bias detected (Figure S1).

For all-cause mortality, data from all 16 studies were available. Combining the results across all studies, it indicates that MSCs can significantly reduce mortality (RR =0.79; 95% CI: 0.64, 0.97; P=0.02; I^2=0%) (*Figure 3*). The evidence exhibits low heterogeneity, and no evident publication bias was observed (Figure S2).

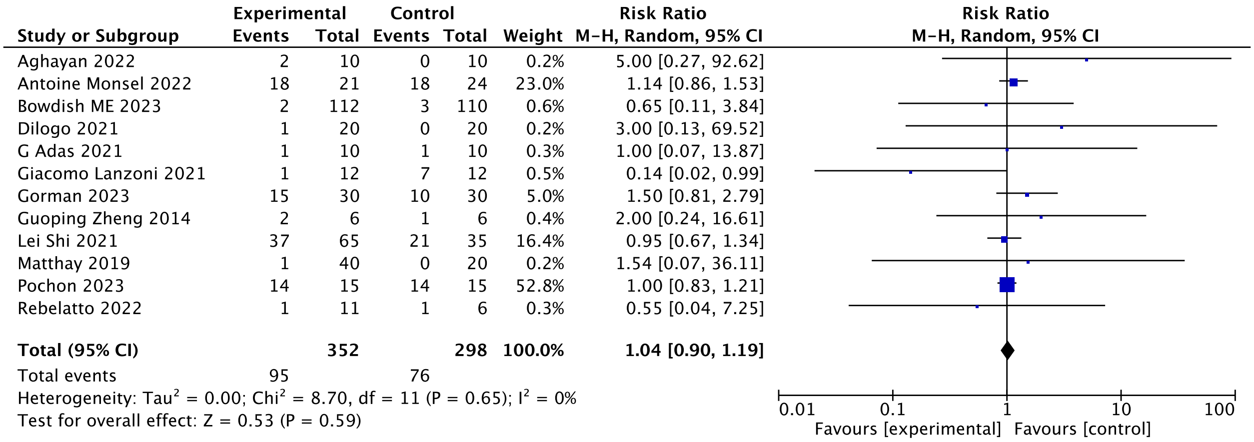

Figure 2 Forest plot of adverse event counts. M-H, Mantel-Haenszel test; CI, confidence interval.

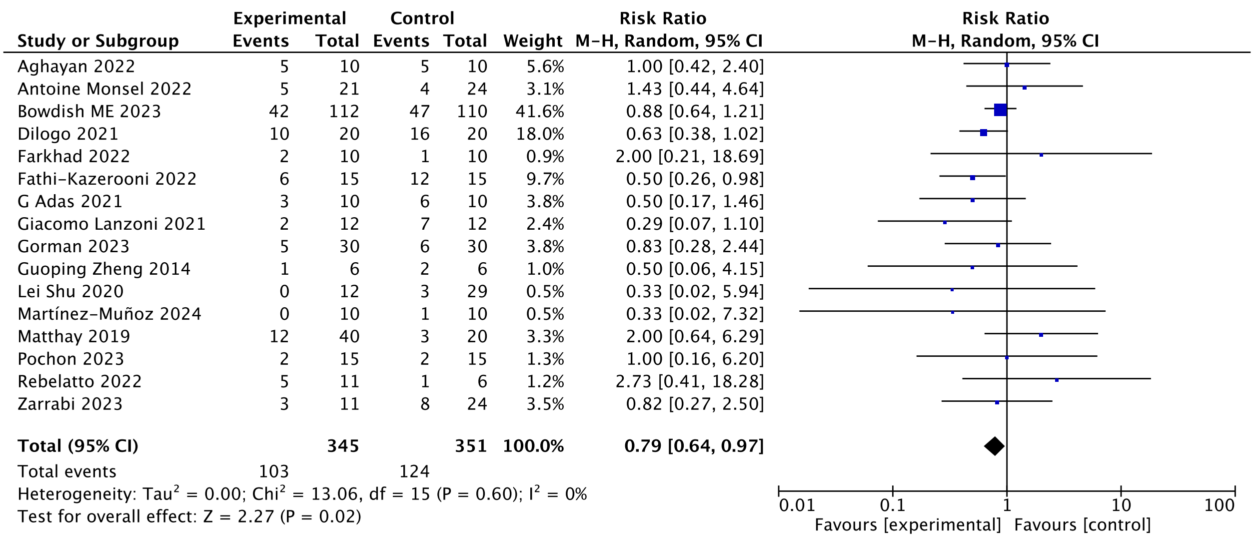

Figure 3 Forest plot of all-cause mortality. M-H, Mantel-Haenszel test; CI, confidence interval.

Sensitivity analysis indicated a robust stability of the results (Figures S3,S4).

Secondary outcomes

Change in the PaO_2/FiO_2 ratio

Five studies examined changes in the PaO_2/FiO_2 ratio, and our analysis identified significant heterogeneity in one of these studies (19,21,23,24,29). Upon exclusion of this outlier, it was revealed that MSC treatment had an obvious positive effect on improving the PaO_2/FiO_2 ratio (SMD =0.53; 95% CI: 0.15, 0.92; P=0.007; I^2=0%) (*Figure 4*, Figure S5). This suggests that MSCs may enhance clinical outcomes to some extent. Additionally, no significant publication bias was detected, and the quality of the data remained stable (Figures S6,S7).

ICU length of stay

Five studies provided data on the ICU length of stay (15,16,18,21,24). The results of the analysis indicate that, in comparison to the control group, the MSC group shows a trend towards a shorter ICU stay, although it

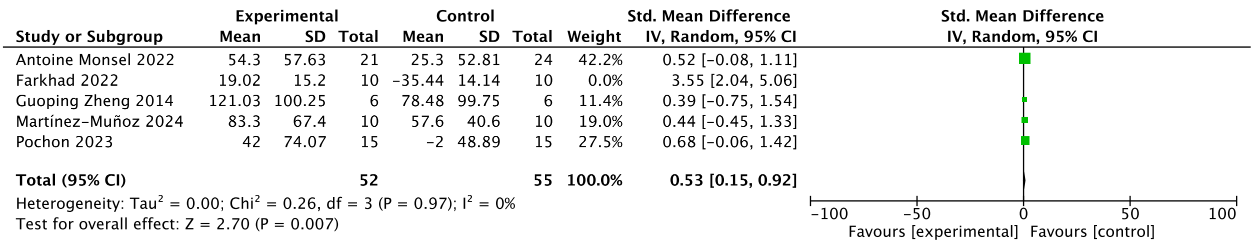

Figure 4 Forest plot of changes in PaO_2/FiO_2 ratio. IV, inverse variance; SD, standard deviation; CI, confidence interval.

lacked statistical significance (MD =−1.77; 95% CI: −6.97, 3.43; P=0.50; I^2=63%) (Figure S8). This observation may be influenced by the small sample size in the included experiments and baseline imbalances. The data did not reveal any significant bias (Figure S9).

Ventilation-free days

The duration without mechanical ventilation supporting to some extent reflected the extent of respiratory function recovery in ARDS patients. Six studies analyzed the days without mechanical ventilation support (15,18,22-24,29). Unfortunately, similar to the ICU length of stay, MSC treatment had the potential to increase ventilation-free days, but the change was not statistically significant (MD =−1.29; 95% CI: −4.09, 1.51; P=0.37; I^2=0%) (Figure S10). The data quality was high, and there is low heterogeneity (Figure S11).

Analysis of pro-inflammatory and anti-inflammatory cytokines

All 17 studies reported data on pro-inflammatory and anti-inflammatory cytokines. Among them, seven studies provided values for C-reactive protein (CRP) (13,17,19,22,25,27,28). The analysis of ΔCRP (the difference in CRP levels between baseline and the endpoint) revealed a significant difference in CRP levels between the MSC and control groups whether or not heterogeneity is excluded (SMD =−0.65; 95% CI: −1.18, −0.13; P=0.01; I^2=56%) (*Figure 5A*, Figure S12). Eight studies reported changes in interleukin-6 (IL-6) levels (13,19,20,22,25,27-29), and pooled analysis of ΔIL-6 showed a significant reduction in IL-6 levels in the MSC group (SMD =−0.76; 95% CI: −1.34, −0.17; P=0.01; I^2=74%) (*Figure 5B*). Other pro-inflammatory factors such as tumor necrosis factor alpha (TNF-α) (SMD =−1.5; 95% CI: −3.39, 0.40; P=0.12; I^2=92%) showed no significant differences between the MSC and control groups (Figure S13).

Concerning anti-inflammatory factors, we performed a statistical analysis of ΔIL-10 levels. After excluding an article with significant heterogeneity, the results revealed no statistically significant difference in IL-10 levels between the MSC group and the control group (SMD =−0.46; 95% CI: −1.51, 0.58; P=0.38; I^2=77%) (Figure S14).

The results presented above exhibit significant heterogeneity. Galbraith plot for heterogeneity in ΔIL-6 (Figure S15) revealed that 3 articles exhibited high heterogeneity in ΔIL-6, collectively representing 37.5% of the total studies included in the meta-analysis. Simple exclusion of these studies was deemed inappropriate. Subsequently, we conducted a trim-and-fill analysis, which did not alter the results. Moreover, sensitivity analyses for it affirmed the stability and reliability of the findings (Figures S16,S17). Correlation analysis of CRP level also showed similar results (Figures S18,S19). The limited number of studies and inconsistency in endpoint times may contribute to the observed heterogeneity.

Subgroup analysis results

We performed subgroup analyses for all-cause mortality rates and the number of adverse events based on the different sources of MSCs. The studies included 3 using MSCs from bone marrow (15,21,22), 1 from placental origin (14), 1 from adipose tissue (29), 10 from umbilical cord (13,16,18-20,23-27), 1 from human menstrual blood (17), and 1 from perinatal tissue (without clarification if it was from placenta or umbilical cord) (28).

Mortality was statistically significant for UC-MSCs but not for bone marrow origin MSCs, likely due to the small number of studies (Figure S20). No significant difference was observed between subgroups in the number of adverse events (Figure S21).

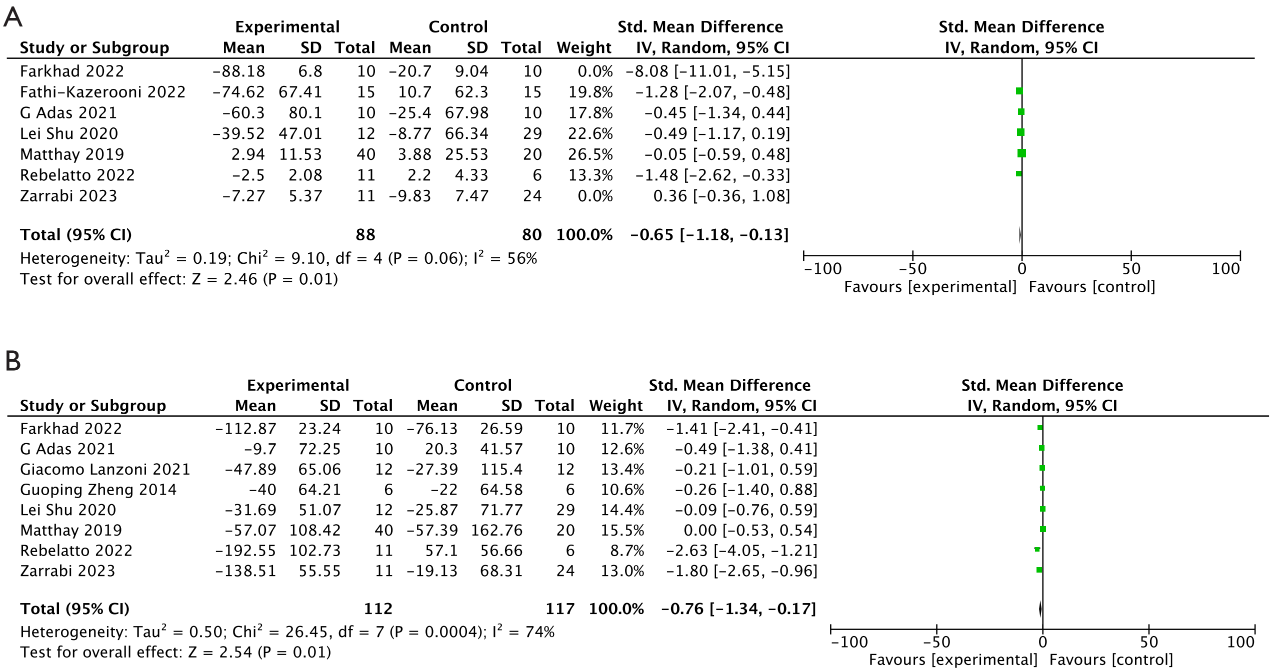

Figure 5 Forest plot of ΔCRP and ΔIL-6. (A) The forest plot of ΔCRP. (B) The forest plot of ΔIL-6. IV, inverse variance; SD, standard deviation; CI, confidence interval; CRP, C-reactive protein; IL, interleukin.

Risk of bias assessment

We employed the ROB2 tool to evaluate the risk of bias in RCTs. Most domains received a low-risk rating, with some uncertainties primarily arising from unspecified randomization methods (Figure S22).

Discussion

Our study reveals that, firstly, in terms of safety, MSCs exhibit similarity to the standard treatment group, suggesting that the use of MSCs does not elevate the risk of adverse reactions. Secondly, significant reductions in mortality can be seen during MSC treatments. Lastly, MSC therapy not only effectively regulates the uncontrolled inflammatory response but also improves patients' clinical symptoms to a certain extent.

Among the 17 included studies, the analysis of adverse reactions indicates the reliability of MSC treatment's safety. Adverse reactions induced by MSCs were mostly non-severe, such as diarrhea and rash, with the majority of patients recovering within 1–2 days, as reported in most studies. Such results are consistent with the findings of Wilson *et al.* (31).

According to previous studies, the over-activated immune state in ARDS patients, characterized by a severe imbalance between anti-inflammatory and pro-inflammatory factors, is a significant cause of their mortality (3). In contrast, MSCs have been shown to inhibit pro-inflammatory factors and increase the capacity of anti-inflammatory factors (32,33). Based on this mechanism, MSC treatment has the potential to reduce mortality in ARDS patients. A meta-analysis of animal experiments on MSC treatment of ARDS by McIntyre *et al.* found that MSC substantially reduced mortality in animal models of ARDS (34). This finding is consistent with the results of our meta-analysis of clinical studies. Furthermore, Chen's cohort study also supports our conclusion (35). Our study, which used mortality as the primary measure of the effectiveness of MSC treatment, found that MSC significantly reduced mortality in ARDS patients. Only the studies by Matthay and Rebelatto showed opposite results (22,25), which were related to the imbalance of clinical baseline characteristics between the experimental and control groups.

Alveolar injury caused by a storm of inflammatory factors is a significant determinant of respiratory function and prognosis in patients with ARDS. Improvement in clinical symptoms in ARDS depends on the recovery of alveolar epithelial function. Animal experiments have demonstrated that MSC reduces inflammatory lung injury and promotes the recovery of alveolar epithelial function (36). In the case report series by Atluri *et al.*, MSC effectively relieved patients' clinical symptoms and improved their oxygenation index, consistent with our findings (37). However, these results still need to be supported by more large-scale clinical trials.

In our statistical analysis of anti-inflammatory and pro-inflammatory cytokines, MSCs were found to significantly reduce CRP and IL-6 levels, especially the IL-6 levels, aligning with the findings of Jackson *et al.* Their study demonstrated that in an ARDS model, MSC administration led to a substantial reduction in IL-6 levels (38-43). IL-6 plays a pivotal role in the inflammatory response to ARDS. A marked increase in IL-6 can trigger various immune cells to migrate from the circulation to specific organs, resulting in immune hyperactivity and invasion of lung tissue (44). Evidence suggests that ARDS patient survival rates are lower when the baseline level of IL-6 is higher, and the substantial reduction in IL-6 levels induced by MSCs partially reflects the potency of the anti-inflammatory impact of MSCs (45). While a trend of reduction in pro-inflammatory factors such as TNF-α was observed, significance was not evident.

In terms of anti-inflammatory factors, Rebelatto's study shows that the ΔIL-10 levels can also be substantially reduced (25). However, in our study, we found that the MSC group did not show a significant increase in the levels of IL-10. Therefore, more experiments are needed to prove that MSC can promote the production of anti-inflammatory factors.

We observed significant heterogeneity in the statistical results of these biomarkers. After analyzing the sources of heterogeneity, we found that half of the studies contributed to the observed heterogeneity, suggesting the need for more large-scale RCTs to systematically investigate changes in the levels of inflammatory factors and standardize endpoint time points to reduce heterogeneity. However, through the application of trim-and-fill analysis and sensitivity analysis, we bolstered the stability of the results, indicating that the findings are robust and reliable. Thus, to some extent, it can be inferred that MSCs may mitigate inflammatory responses and modulate the inflammatory storm in ARDS.

Although MSC therapy is a promising treatment, it is crucial to use it wisely. We analyzed different sources of MSC as one of the factors that may affect its effectiveness (46-48). In our subgroup analysis of different MSC sources, we found that only the umbilical cord source demonstrated a statistically significant reduction in mortality. This may also be related to the lack of experimental data for the bone marrow source. Additionally, varying MSC doses and the microenvironment of ARDS patients may influence the efficacy of MSC, which warrants further investigation in future studies.

There are some limitations in this study. Firstly, the absence of large-scale RCTs and the relatively small sample size may introduce selection bias. Secondly, the measurement of mortality and laboratory indicators at non-uniform time points introduces variability. Thirdly, there is an imbalance in the male-to-female ratio, with a higher proportion of males. Lastly, the majority of experiments focused on ARDS caused by COVID-19, and there is a lack of data from studies on ARDS unrelated to COVID-19.

Conclusions

In summary, the safety of MSC therapy is deemed reliable. MSCs have the ability to reduce mortality and improve clinical symptoms to some extent. Furthermore, MSCs may offer certain benefits in alleviating the inflammatory response in ARDS. However, these findings necessitate further validation through high-quality RCTs.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-281/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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