Article

Discovery Medicine 2023; 35(175): 201–207
https://doi.org/10.24976/Discov.Med.202335175.21

Efficacy and Safety of Mesenchymal Stem Cells for COVID-19 Infection: A Meta-Analysis and Systematic Review

Li Chen[1], Qinfei Xu[2], Fen Sheng[3], Beibei Wang[4,5,*]

[1]Department of Respiratory and Critical Care Medicine, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 318050 Taizhou, Zhejiang, China
[2]Endoscopy Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 318050 Taizhou, Zhejiang, China
[3]Department of Respiratory and Critical Care Medicine, Taizhou First People's Hospital, 318050 Taizhou, Zhejiang, China
[4]Department of Infectious Diseases, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 318050 Taizhou, Zhejiang, China
[5]Department of Infectious Diseases, Enze Hospital, Taizhou Enze Medical Center (Group), 318050 Taizhou, Zhejiang, China
*Correspondence: wbb4119236@163.com (Beibei Wang)
Published: 1 April 2023

Background: COVID-19 (coronavirus disease 2019) is a pandemic around the world, and its treatment options often fail to achieve ideal results. There is a lot of controversy in the treatment of COVID-19 with mesenchymal stem cells (MSCs). The study aims to assess the safety and efficacy of mesenchymal treatment of new coronary pneumonia.
Methods: We manually searched electronic databases including PubMed, Embase, Cochrane Library, and Web of Science until 25th July 2022, and Stata 15.0 (StataCorpLLC: College Station, TX, USA) was used to analyze the data.
Results: A total of 8 randomized controlled trials were included, involving a total of 345 people, of which 180 were in the MSCs group and 165 were in the placebo group. The analysis results showed that MSCs can reduce mortality in COVID-19 patients compared to placebo [RR (Risk Ratio) = 0.56, 95% CI (Confidence Interval) (0.36, 0.89); p = 0.003]. There was no significant difference between the mesenchymal stem cell group and the placebo group in the incidence of adverse reactions [RR = 0.64, 95% CI (0.34, 1.18); p = 0.281]; In the SpO_2/FiO_2 (Oxygen Saturation/Fraction of Inspiration O_2) [WMD (Weighted Mean Difference) = 9.07, 95% CI (–38.01, 56.15); p = 0.080]; In ICU (Intensive Care Unit) stay [WMD = –1.66, 95% CI (–7.23, 3.91); p = 0.131].
Conclusions: Mesenchymal stem cells can reduce the mortality of COVID-19 patients.

Keywords: mesenchymal stem cells; COVID-19; systematic review; adverse events

Introduction

Coronavirus disease 2019 (COVID-19) is pneumonia caused by the 2019 novel coronavirus [1,2]. It causes fever and fatigue [3]. Most of the severe patients aggravate and develop dyspnea after a week of onset [4–6]. Although the global new crown vaccine vaccination rate has reached 11.2 billion doses [7]. With the progression of the disease, it will appear a systemic inflammatory response and immune system dysfunction, and multiple organs such as the heart, lungs and kidneys will be involved, and myocardial damage, dyspnea and hypoxemia may occur [8]. Severe metabolic acidosis and multiple organ failure may also occur [9]. Therefore, the diagnosis and treatment plan advocates staging (observation period, clinical treatment period, recovery period) and classification (light, common, severe, critical) for treatment [10–12]. At present, the treatment of new coronary pneumonia mainly includes general treatment such as supportive care or symptomatic treatment, as well as antiviral, antibacterial and traditional Chinese medicine, but there is no specific drug to treat COVID-19 [13–15].

Stem cells are a kind of special cells with immune regulation, regeneration ability and differentiation characteristics [16,17]. The differentiated progeny cells maintain local tissue homeostasis and also have the same functions as non-differentiated cells. Among them, mesenchymal stem cells (MSCs) come from fat, placenta, amniotic fluid, umbilical cord blood, dental pulp, hair follicles and skin [18]. MSCs' plasticity, can differentiate into multiple lineages. MSCs in immune regulation and anti-inflammatory signal transduction are particularly suitable for the treatment of severe COVID-19, mainly by activating immune responses through immune cells, and participating in non-specific immune regulation and specific immune regulation [18]. Due to the rapid transformation of immune overactivation and immunosuppression in critically ill patients, mesenchymal stem cells can suppress excessive immune responses, protect alveolar function, and reduce lung and systemic organs in patients with new coronary pneumonia when they regulate immune cells through direct contact or paracrine various cytokines [19,20]. There is a lot of controversy about

the treatment of new coronary pneumonia with mesenchymal stem cells in clinical practice [21]. Therefore, we hope to evaluate the efficacy and safety of MSCs in the treatment of COVID-19 through this study and provide new options for COVID-19.

Materials and Methods

Retrieval Strategy

Search in PubMed, Embase, Cochrane Library, and Web of Science was conducted for articles published by 25th July 2022 on mesenchymal stem cells for coronavirus disease 2019. The search terms used were "mesenchymal stem cells" and "COVID-19" in PubMed and Embase (**Supplementary Table 1**).

Inclusion and Exclusion Criteria

The inclusion criteria were the population that was affected by COVID-19 and received mesenchymal stem cells. Randomized controlled studies (RCT) including mortality rate, stay in the ICU (Intensive Care Unit), and adverse events were included. Duplicate publications, animal experiments, case reports and conference abstracts were excluded.

Data Extraction

The data extracted from the articles were: Investigator's name, publication year, country, number of included cases, gender, age, stem cell type, number of stem cells, follow-up, and outcome. The information from the studies was extracted by two people.

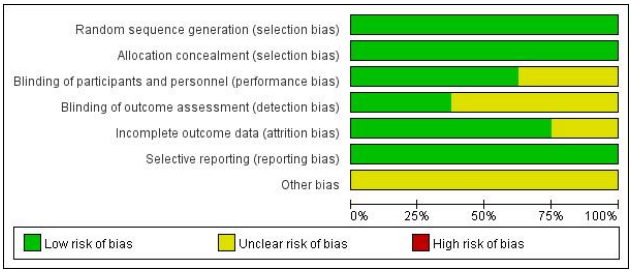

Fig. 1. Graphical representation of the risk of bias. N.B.: Author's assessment per risk of bias domain by percentage across all included studies. Green: Low risk of bias; Yellow: Unclear risk of bias; Red: High risk of bias.

Risk of Bias Evaluate

Randomized, cross-over trials (RoB2.0) was used to assess the risk of bias [22]. RoB2.0 was also paired by two independent investigators. If two investigators disagreed on the risk of bias analyzed, a consensus was performed by a third investigator. The evaluators examined the randomization process, deviations from expected interventions, missing outcome data, choice of outcome measures, and reported outcomes (Figs. 1,2).

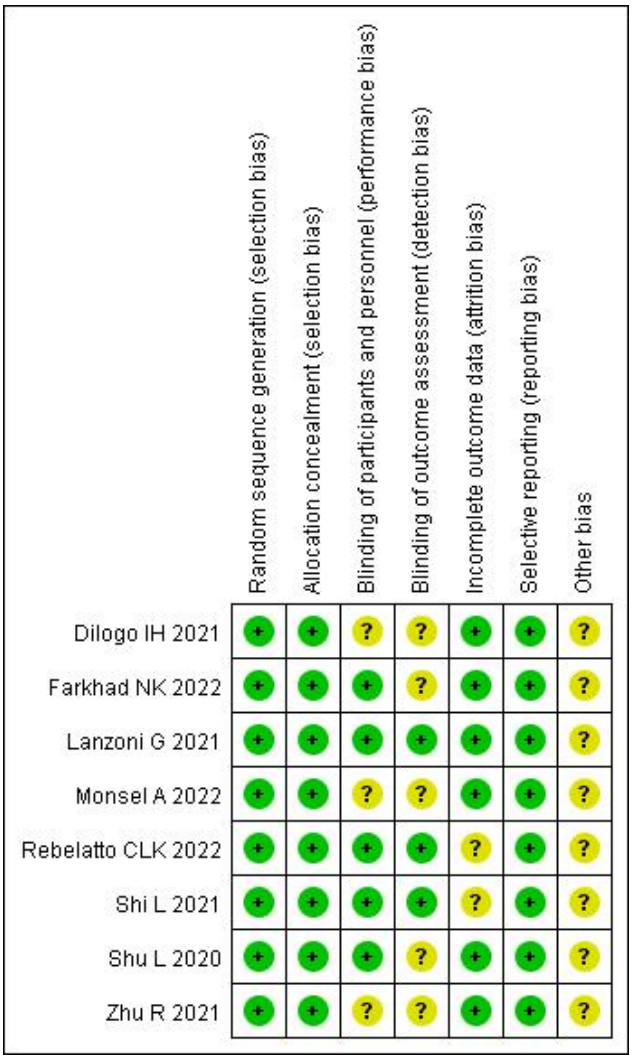

Fig. 2. Summary of the risk of bias. N.B.: Author's assessment per risk of bias domain for each included study. Green: Low risk of bias; Yellow: Unclear risk of bias.

Data Analysis

The extracted data were entered into Stata 15.0 software (StataCorp, College Station, TX, USA) and it was used for statistical analysis. Heterogeneity was tested by I^2 value or Q statistic. I^2 values of 0%, 25%, 50% and 75% represent no, low, medium and high heterogeneity, respectively. Sensitivity analyses were performed to explore potential sources of heterogeneity when the I^2 value was $\geq$50%.

Results

Literature Screening and Characteristics

Through manual retrieval, a total of 1610 articles were obtained: 1073 articles were obtained after removing dupli-

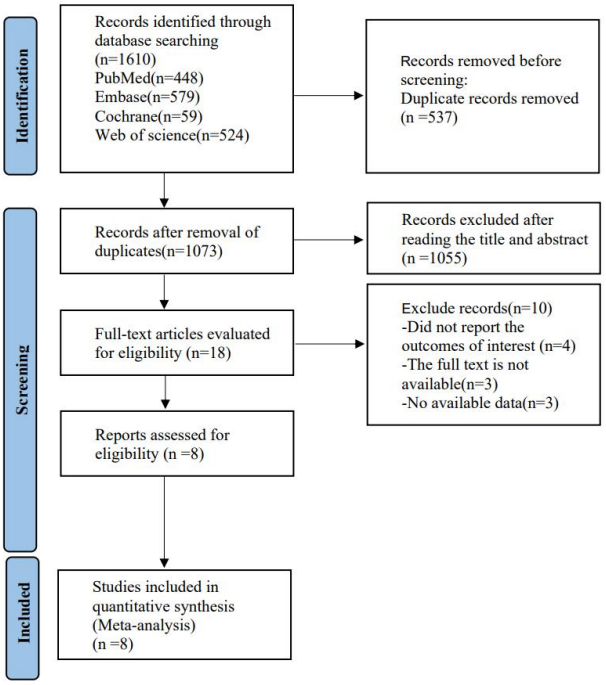

Fig. 3. Literature search chart. N.B.: PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram showing study identification, selection, eligibility, and inclusion [31]. For more information, visit http://www.prisma-statement.org/.

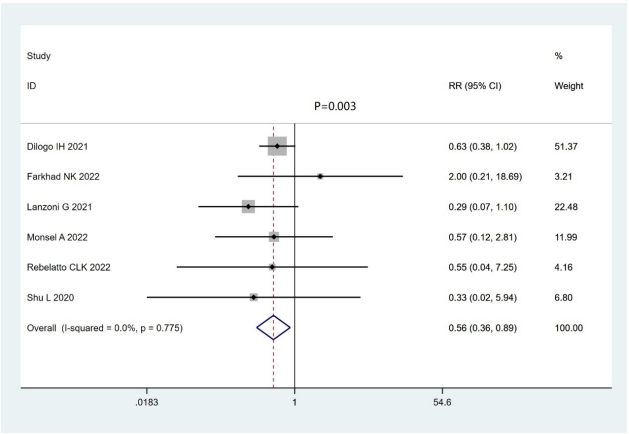

Fig. 4. Forest plot of the impact of MSCs on mortality rate in COVID-19 patients. N.B.: Statistical tests for heterogeneity (Chi^2 and I^2) can be unreliable with small sample sizes—heterogeneity explored using other strategies.

cates, 18 articles were obtained by checking the titles and abstracts of the articles, and 8 articles [23–30] were finally included in the analysis by reading the full text (Fig. 3, Ref. [31]).

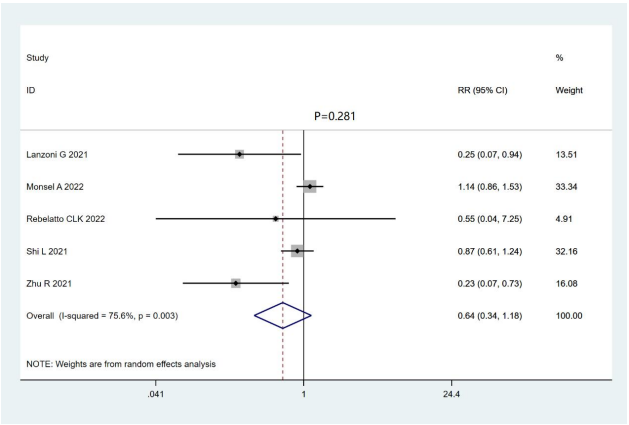

Fig. 5. Forest plot of adverse events of MSCs in COVID-19 patients. N.B.: Statistical tests for heterogeneity (Chi^2 and I^2) can be unreliable with small sample sizes—heterogeneity explored using other strategies.

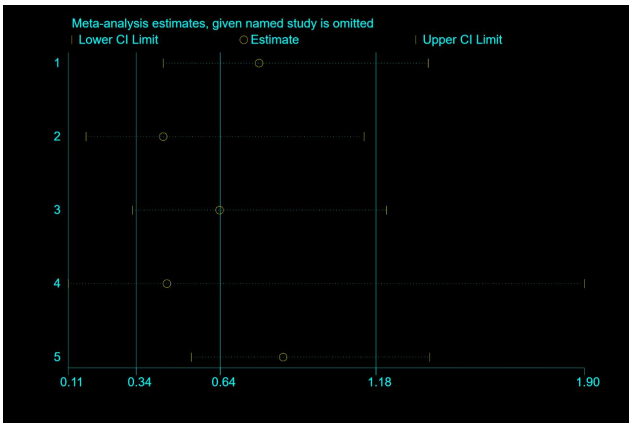

Fig. 6. Adverse events sensitivity analysis.

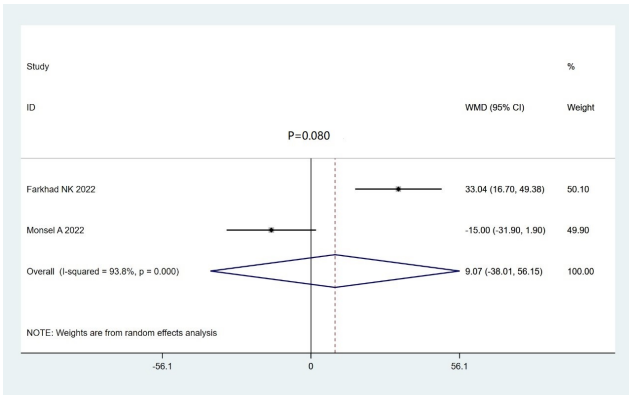

Fig. 7. Forest plot of meta-analysis on the effect of MSCs on SpO_2/FiO_2 in COVID-19.

Characteristics of Literature

A total of 8 randomized controlled trial studies were included. Human umbilical cord mesenchymal stem cells were used in all the included articles and the specific char-

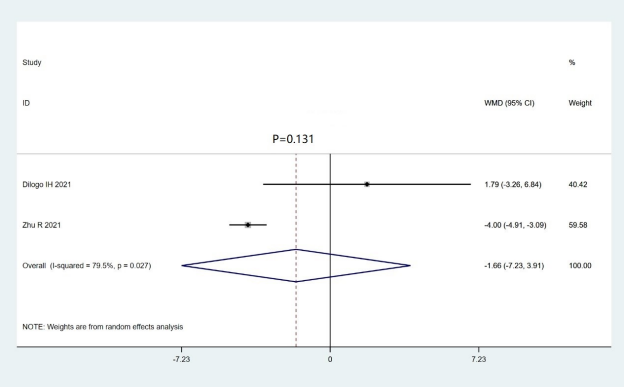

Fig. 8. Forest plot of meta-analysis on the effect of MSCs on ICU stay in COVID-19.

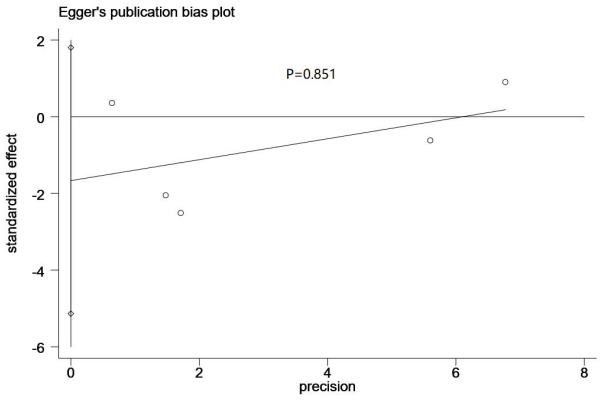

Fig. 9. The impact of MSCs on Adverse events funnel plot.

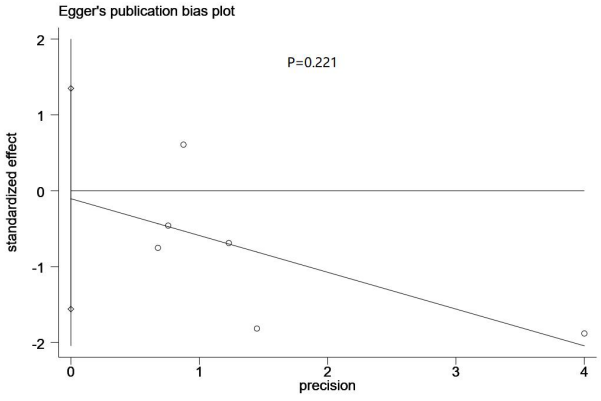

Fig. 10. The impact of MSCs on Mortality rate funnel plot.

acteristics of the studies (Table 1, Ref. [23–30]).

Meta-Analysis

Mortality Rate

A total of 6 studies [23–27,29] involved 187 patients with COVID-19 (I^2 = 0%, p = 0.775) implying there was no heterogeneity. Fig. 4 [RR (Risk Ratio) = 0.56, 95% CI (0.36, 0.89); p = 0.003] suggested that MSCs can reduce mortality in COVID-19 patients compared to placebo.

Adverse Events

A total of 5 studies [25–29] involved 246 patients with COVID-19 (I^2 = 75.6%, p = 0.003) implying great heterogeneity. Fig. 5 [RR: 0.64, 95% CI (Confidence Interval) (0.34, 1.18); p = 0.281] suggested that there was no significant difference in the incidence of adverse reactions between the two groups. Sensitivity analysis was performed on the deleted articles one by one. Fig. 6 indicates whether the sensitivity of the analysis results was small, and the stability of the analysis results.

SpO_2/FiO_2

A total of 2 studies [24,26] involved 65 patients with COVID-19 (I^2 = 93.8%, p = 0.000) implying high heterogeneity. Fig. 7 [WMD (Weighted Mean Difference) = 9.07, 95% CI (–38.01, 56.15); p = 0.080] suggested that there was no significant difference in SpO_2/FiO_2 (Oxygen Saturation/Fraction of Inspiration O_2) between the mesenchymal stem cell group and the placebo group.

ICU Stay

A total of 2 studies [23,30] involved 98 patients with COVID-19 (I^2 = 79.5%, p = 0.027) implying great heterogeneity. Fig. 8 [WMD = –1.66, 95% CI (–7.23, 3.91); p = 0.131] suggested that there was no significant difference in ICU stay between the mesenchymal stem cell group and the placebo group.

Publication Bias

Egger's test was used to evaluate publication bias of highly heterogeneous indicators such as mortality and adverse events, and it showed that the mortality and adverse event were p = 0.851 and p = 0.221. The results suggested that mortality and adverse events were less likely to have publication bias (Figs. 9,10).

Discussion

The autopsy and biopsy of histopathological results of COVID-19 patients showed that the lung tissue of the deceased patient had different degrees of pulmonary edema and lung consolidation [32,33]. At the same time, local lung tissue showed alveolar cell shedding, and intraalveolar fibrous exudate with hyaline membrane formation, consistent with the pathological features of acute respiratory distress syndrome (ARDS) [34]. In response to ARDS caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), MSCs mainly play a role in immune regulation and regeneration and repair and stabilize alveolar epithelial [35]. MSCs are mainly formed by a variety of cytokines, especially keratinocyte growth factor (KGF), which promotes the clearance of alveolar fluid by up-regulating the

Table 1. Characteristics of the studies.

Study	Country	Sample size		Gender (M/F)	Age (year)		Stem cell type	Number of stem cells	Follow-up (D)	Outcome
		T	C		T	C				
Dilogo IH [23] 2021	Indonesia	20	20	45229	18–95		UC-MSCs	1×10^6	50	Q1; Q2; Q3
Farkhad NK [24] 2022	Iran	10	10	45120	50–69		UC-MSCs	1×10^6	17	Q1; Q4; Q5; Q6; Q7
Lanzoni G [25] 2021	USA	12	12	45243	58.58	58.83	UC-MSCs	1×10^8	31	Q1; Q10
Monsel A [26] 2022	France	21	24	13728	64	63.2	UC-MSCs	3×10^6	7	Q1; Q4; Q10
Rebelatto CLK [27] 2022	Brazil	11	6	45265	53	61.7	UC-MSCs	5×10^5	14	Q1; Q8; Q9; Q10
Shi L [28] 2021	China	65	35	56/44	60.72	59.94	UC-MSCs	4×10^7	28	Q10; Q11
Shu L [29] 2020	China	12	29	24/17	61	57.86	UC-MSCs	2×10^6	28	Q1; Q3
Zhu R [30] 2021	China	29	29	22/36	64	66	UC-MSCs	1×10^6	14	Q3; Q10

T, treatment group; C, control group; D, day; UC-MSCs, umbilical cord mesenchymal stromal cells; Q1, mortality rate; Q2, length of ventilator usage; Q3, stay in the ICU; Q4, SpO_2/FiO_2; Q5, CRP; Q6, IL-6; Q7, IFN-g; Q8, IL-10; Q9, TNF-α; Q10, adverse events; Q11, 6-minute walking distance.

α1 subunit of AECII (Alveolar Epithelial Type II) , and relieves acute lung injury induced by endotoxin [36]. At the same time, KGF can up-regulate the activity of alveolar cell sodium-potassium ATPase (Adenosine Triphosphatase), improve alveolar fluid transport, and in bacteria Pneumonitis-induced ARDS and lung injury [37]. This may be an important way for MSCs to act on patients with COVID-19. Flow analysis of peripheral blood from patients with COVID-19 showed that the number of peripheral $CD4^+$ and $CD8^+$ T cells decreased, but their activity increased [38]. Some studies have suggested that SARS-CoV-2 can bind ACE2 (Angiotensin-Conyerting Enzyme 2) receptors to invade cells. Viral binding to ACE2 also depletes ACE2, leading to multisystem inflammation [39]. Under inflammatory conditions, MSCs can increase the level of angiopoietin 1 (Ang-1) in the above pathways. At the same time, single-cell analysis of transplanted MSCs showed that MSCs were ACE2-negative suggesting that MSCs may be helpful to maintain the balance of the RAS (Renin-Angiotensin System) system affected by SARS-CoV-2 [40,41]. These mechanisms further confirmed the feasibility and scientific nature of MSCs in the treatment of COVID-19.

The results of this study concluded that after MSCs treatment, the fatality rate of COVID-19 patients was greatly reduced. Meng *et al*. [42] found that after UC-MSCs (Umbilical Cord Mesenchymal Stromal Cells) treatment in moderate to severe COVID-19 patients, the number of cases requiring mechanical ventilation and dyspnea decreased, and the serum levels of IL-6 (Interleukin 6) decreased. Among the 4 severe patients, the highest levels of IL-6 decreased the most, and the oxygenation index improved the most. It is suggested that patients with high inflammatory cytokines are more likely to benefit from UC-MSCs treatment. Feng *et al*. [43] conducted a prospective cohort follow-up study. After three months of follow-up, the blood routine, C-reactive protein and calcitonin, tumor markers and visual acuity of the two groups were almost within the normal range [43]. Moreover, the average FEV1 (Forced Expiratory Volume in 1 second) and FEV1/FVC (Forced Vital Capacity) of the HUC-MSC (Human Umbilical Cord Mesenchymal Stem Cell) group were higher, and the St. George's score was lower. Studies have shown that venous transplantation of HUC-MSC can partially promote the recovery of lung function. In the clinical trials of Shu *et al*. [29], the levels of CRP (C-Reactive Protein) and IL-6 in the treatment group were significantly reduced, and the absorption of lung inflammation by CT (Computed Tomography) imaging was significantly shorter than that in the control group. The study also unexpectedly found that COVID-19 patients with diabetes had reduced use of insulin after UC-MCS transplantation [29]. UC-MCS transplantation may be the most appropriate treatment for such patients, the above studies suggest that MSCs have a broad prospect in the treatment of COVID-19. There is no significant difference between the MSCs group and the placebo group in the side effects of COVID-19 treatment. Although no serious adverse events related to MSCs have occurred so far, some scholars still believe that intravenous MSCs may damage microcirculation and have the risk of mutagenicity and carcinogenicity. Aerosol inhalation of MSC-derived exosomes can avoid such risks [44–46].

Although this study has confirmed the efficacy of MSCs in the treatment of COVID-19, it still has the following limitations. First, the number of included articles is small, which may lead to potential deviation. Second, although human umbilical cord mesenchymal stem cells were used in all the papers, the number of stem cells was inconsistent, which may lead to great heterogeneity in the studies. Third, the follow-up time of the included articles was inconsistent, which is also a potential source of heterogeneity.

Conclusions

This study demonstrates that mesenchymal stem cells can reduce the mortality of COVID-19 patients.

Availability of Data and Materials

Not applicable.

Author Contributions

LC and BBW—were responsible for the concept and study design; QFX and FS—were responsible for data collection, data analysis and interpretation; LC, QFX and FS—was responsible for drafting the manuscript; BBW—provided critical review of the manuscript. All authors have read and approved the final article and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335175.21.

References

[1] Mina MJ, Peto TE, García-Fiñana M, Semple MG, Buchan IE. Clarifying the evidence on SARS-CoV-2 antigen rapid tests in public health responses to COVID-19. *Lancet.* 2021;397(10283):1425–1427. doi: 10.1016/S0140-6736(21)00425-6

[2] Young BC, Eyre DW, Kendrick S, *et al*. Daily testing for contacts of individuals with SARS-CoV-2 infection and attendance and SARS-CoV-2 transmission in English secondary schools and colleges: an open-label, cluster-randomised trial. *Lancet.* 2021;398(10307):1217–1229. doi: 10.1016/S0140-6736(21)01908-5

[3] Eyre DW, Taylor D, Purver M, *et al*. Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. *N Engl J Med.* 2022;386(8):744–756. doi: 10.1056/NEJMoa2116597

[4] Edara VV, Hudson WH, Xie X, Ahmed R, Suthar MS. Neutralizing Antibodies Against SARS-CoV-2 Variants After Infection and Vaccination. *JAMA.* 2021;325(18):1896–1898. doi: 10.1001/jama.2021.4388

[5] Gans JS, Goldfarb A, Agrawal AK, Sennik S, Stein J, Rosella L. False-Positive Results in Rapid Antigen Tests for SARS-CoV-2. *JAMA.* 2022;327(5):485–486. doi: 10.1001/jama.2021.24355

[6] Rubin R. COVID-19 Testing Moves Out of the Clinic and Into the Home. *JAMA.* 2021;326(14):1362–1364. doi: 10.1001/jama.2021.15679

[7] Peeling RW, Heymann DL, Teo YY, Garcia PJ. Diagnostics for COVID-19: moving from pandemic response to control. *Lancet.* 2022;399(10326):757–768. doi: 10.1016/S0140-6736(21)02346-1

[8] Bergwerk M, Gonen T, Lustig Y, *et al*. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *N Engl J Med.* 2021;385(16):1474–1484. doi: 10.1056/NEJMoa2109072

[9] Thompson MG, Burgess JL, Naleway AL, *et al*. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. *N Engl J Med.* 2021;385(4):320–329. doi: 10.1056/NEJMoa2107058

[10] Mussini C, Cozzi-Lepri A. Another piece in the COVID-19 treatment puzzle. *Lancet.* 2022;399(10325):609–610. doi: 10.1016/S0140-6736(22)00154-4

[11] Tang C, Wang Y, Lv H, Guan Z, Gu J. Caution against corticosteroid-based COVID-19 treatment. *Lancet.* 2020;395(10239):1759–1760. doi: 10.1016/S0140-6736(20)30749-2

[12] Usher AD. The global COVID-19 treatment divide. *Lancet.* 2022;399(10327):779–782. doi: 10.1016/S0140-6736(22)00372-5

[13] Chinnery PF, Bonnet M, Cave A, *et al*. Choosing drugs for UK COVID-19 treatment trials. *Nat Rev Drug Discov.* 2022;21(2):81–82. doi: 10.1038/d41573-021-00203-7

[14] Kuriakose S, Singh K, Pau AK, *et al*. Developing Treatment Guidelines During a Pandemic Health Crisis: Lessons Learned From COVID-19. *Ann Intern Med*. 2021;174(8):1151–1158. doi: 10.7326/M21-1647

[15] Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for Drug Interactions on QTc in Exploratory COVID-19 Treatment. *Circulation.* 2020;141(24):e906–e907. doi: 10.1161/CIRCULATIONAHA.120.047521

[16] Harschnitz O, Studer L. Human stem cell models to study host-virus interactions in the central nervous system. *Nat Rev Immunol.* 2021;21(7):441–453. doi: 10.1038/s41577-020-00474-y

[17] Lee ARYB, Wong SY, Chai LYA, *et al*. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ.* 2022;376:e068632. doi: 10.1136/bmj-2021-068632

[18] Chen X, Shan Y, Wen Y, Sun J, Du H. Mesenchymal stem cell therapy in severe COVID-19: A retrospective study of short-term treatment efficacy and side effects. *J Infect.* 2020;81(4):647–679. doi: 10.1016/j.jinf.2020.05.020

[19] Barros I, Silva A, de Almeida LP, Miranda CO. Mesenchymal stromal cells to fight SARS-CoV-2: Taking advantage of a pleiotropic therapy. *Cytokine Growth Factor Rev.* 2021;58:114–133. doi: 10.1016/j.cytogfr.2020.12.002

[20] Monguió-Tortajada M, Bayes-Genis A, Rosell A, Roura S. Are mesenchymal stem cells and derived extracellular vesicles valuable to halt the COVID-19 inflammatory cascade? Current evidence and future perspectives. *Thorax*. 2021;76(2):196–200. doi: 10.1136/thoraxjnl-2020-215717

[21] Kakabadze Z, Kipshidze N, Paresishvili T, Kipshidze N, Vadachkoria Z, Chakhunashvili D. Human Placental Mesenchymal Stem Cells for the Treatment of ARDS in Rat. *Stem Cells Int.* 2022;2022:8418509. doi: 10.1155/2022/8418509

[22] Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. doi: 10.1136/bmj.l4898

[23] Dilogo IH, Aditianingsih D, Sugiarto A, *et al*. Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: A randomized controlled trial. *Stem Cells Transl Med.* 2021;10(9):1279–1287. doi: 10.1002/sctm.21-0046

[24] Kaffash Farkhad N, Sedaghat A, Reihani H, *et al*. Mesenchymal stromal cell therapy for COVID-19-induced ARDS pa-

tients: a successful phase 1, control-placebo group, clinical trial. *Stem Cell Res Ther.* 2022;13(1):283. doi: 10.1186/s13287-022-02920-1

[25] Lanzoni G, Linetsky E, Correa D, *et al*. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. *Stem Cells Transl Med.* 2021;10(5):660–673. doi: 10.1002/sctm.20-0472

[26] Monsel A, Hauw-Berlemont C, Mebarki M, *et al*. Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: a multicenter randomized double-blind trial. *Crit Care.* 2022;26(1):48. doi: 10.1186/s13054-022-03930-4

[27] Rebelatto CLK, Senegaglia AC, Franck CL, *et al*. Safety and long-term improvement of mesenchymal stromal cell infusion in critically COVID-19 patients: a randomized clinical trial. *Stem Cell Res Ther.* 2022;13(1):122. doi: 10.1186/s13287-022-02796-1

[28] Shi L, Huang H, Lu X, *et al*. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. *Signal Transduct Target Ther.* 2021;6(1):58. doi: 10.1038/s41392-021-00488-5

[29] Shu L, Niu C, Li R, *et al*. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther.* 2020;11(1):361. doi: 10.1186/s13287-020-01875-5

[30] Zhu R, Yan T, Feng Y, *et al*. Mesenchymal stem cell treatment improves outcome of COVID-19 patients via multiple immunomodulatory mechanisms. *Cell Res.* 2021;31(12):1244–1262. doi: 10.1038/s41422-021-00573-y

[31] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097

[32] de Beer PAM, Van den Abbeele K. Inviting adolescents aged 12-17 for covid-19 vaccination: the need for patience. *BMJ.* 2021;374:n2172. doi: 10.1136/bmj.n2172

[33] Eleftheriou I, Dasoula F, Dimopoulou D, *et al*. Real-life evaluation of a COVID-19 rapid antigen detection test in hospitalized children. *J Med Virol.* 2021;93(10):6040–6044. doi: 10.1002/jmv.27149

[34] Elliott P, Haw D, Wang H, *et al*. Exponential growth, high prevalence of SARS-CoV-2, and vaccine effectiveness associated with the Delta variant. *Science.* 2021;374(6574):eabl9551. doi: 10.1126/science.abl9551

[35] Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. *Lancet.* 2021;398(10317):2126–2128. doi: 10.1016/S0140-6736(21)02758-6

[36] Laine C, Moyer DV, Cotton D. COVID-19: Challenging Clinical Questions. *Ann Intern Med.* 2022;175(2):276–277. doi: 10.7326/M21-4611

[37] Lavine JS, Bjornstad O, Antia R. Vaccinating children against SARS-CoV-2. *BMJ.* 2021;373:n1197. doi: 10.1136/bmj.n1197

[38] Li Z, Liu F, Cui J, *et al*. Comprehensive large-scale nucleic acid-testing strategies support China's sustained containment of COVID-19. *Nat Med.* 2021;27(5):740–742. doi: 10.1038/s41591-021-01308-7

[39] Lopez Bernal J, Andrews N, Gower C, *et al*. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ.* 2021;373:n1088. doi: 10.1136/bmj.n1088

[40] Mwenda M, Saasa N, Sinyange N, *et al*. Detection of B.*1*.351 SARS-CoV-2 Variant Strain - Zambia, December 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(8):280–282. doi: 10.15585/mmwr.mm7008e2

[41] Son HA, Hang DTT, Thuan ND, *et al*. A simple method for detection of a novel coronavirus (SARS-CoV-2) using one-step RT-PCR followed by restriction fragment length polymorphism. *J Med Virol.* 2020;92(11):2839–2846. doi: 10.1002/jmv.26171

[42] Meng F, Xu R, Wang S, *et al*. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. *Signal Transduct Target Ther.* 2020;5(1):172. doi: 10.1038/s41392-020-00286-5

[43] Feng G, Shi L, Huang T, *et al*. Human Umbilical Cord Mesenchymal Stromal Cell Treatment of Severe COVID-19 Patients: A 3-Month Follow-Up Study Following Hospital Discharge. *Stem Cells Dev.* 2021;30(15):773–781. doi: 10.1089/scd.2021.0015

[44] Hammerman A, Sergienko R, Friger M, *et al*. Effectiveness of the BNT162b2 Vaccine after Recovery from Covid-19. *N Engl J Med.* 2022;386(13):1221–1229. doi: 10.1056/NEJMoa2119497

[45] Pilishvili T, Gierke R, Fleming-Dutra KE, *et al*. Effectiveness of mRNA Covid-19 Vaccine among U.*S*. Health Care Personnel. *N Engl J Med*. 2021;385(25):e90. doi: 10.1056/NEJMoa2106599

[46] Wolter N, Jassat W, Walaza S, *et al*. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet.* 2022;399(10323):437–446. doi: 10.1016/S0140-6736(22)00017-4