Safety and efficacy of mesenchymal stem cells in severe/critical patients with COVID-19: A systematic review and meta-analysis

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Summary

Background The present study aims to better understand the efficacy and safety of mesenchymal stromal cells (MSCs) in treating severe/critical patients with COVID-19.

Methods PubMed, the Cochrane Library, and the Chinese electronic database CNKI were searched from inception up to Dec 19, 2021. Original comparative studies for MSC treatment + standard treatment for severe/critical patients with COVID-19, with placebo or standard treatment as the control group, were included. The primary outcomes were in-hospital mortality and adverse events (AEs). A meta-analysis was performed to compare the mortality rates between the two groups. Then, a subgroup analysis was performed according to the category of the disease (severe or critical) and MSC dose. Afterwards, a descriptive analysis was performed for AEs and secondary outcomes. The funnel plot and Egger's test were used for the publication bias assessment.

Findings Compared to placebo or standard care, MSCs provide significant benefit in the treatment of patients with severe/critical COVID-19, in terms of in-hospital mortality rate (odds ratio: 0.52, 95% CI 0.32-0.84), with very low heterogeneity (P=0.998 [Q test], I^2=0.0%) and less AEs. No significant difference was found in mortality rate due to the different disease categories or MSC doses. Furthermore, no publication bias was found.

Interpretation The present study demonstrates that MSCs are highly likely to reduce mortality and are safe to use for patients with severe or critical COVID-19, regardless of whether 1-3 doses are applied. However, due to the small sample size of the included studies, further high-quality, large-scale trials are needed to confirm this statement in the future.

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Keywords: Coronavirus disease-19 (COVID-19); Cellular therapy; Mesenchymal stem cells; Systematic review; Meta-analysis

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Research in context

Evidence before this study

We searched the Cochrane Library, Medline, and Embase databases up until Dec 19, 2021. The search identified 3638 references (Medline: 1213, Embase: 2337, and Cochrane Library: 88). After duplicate checking, approximately 2630 records were collected and stored in the Endnote library. Approximately 150 reviews related to the topic were found. However, there was no systematic review and meta-analysis on mesenchymal stromal cells (MSCs) for severe COVID-19. A systematic review in treating COVID-19 patients was published (2021) but not severe/critical COVID-19. According to the systematic review (2021), stem cell therapy has a remarkable effect in reducing the mortality and morbidity of patients with COVID-19.

Added value of this study

This study summarised the presently available evidence on the efficacy and safety of MSCs for severe COVID-19. To our knowledge, this is the first systematic review and meta-analysis conducted on this topic. The present study revealed that the mortality in the experimental group significantly decreased (OR: 0.52, 95% CI: 0.32-0.84), with fewer AEs. Furthermore, an apparent improvement in pulmonary function and imaging appearance in patients with severe/critical COVID-19 was determined after the use of MSCs. In addition, it was found that the cytokines decreased or tended to decrease in the experimental group, further proving the pulmonary repair function of MSCs in severe/critical patients with COVID-19. In terms of resource use, it was found that the length of hospitalisation and ICU stays were shorter in the experimental group, when compared to the control group.

Implications of all the available evidence

The present study demonstrated that MSCs can significantly reduce mortality, and are safe to use for patients with severe or critical COVID-19, regardless of whether 1-3 doses are used. In addition, MSCs have a high potential to improve pulmonary function, save resource use, and decrease inflammatory cytokines in these patients. However, due to the small sample size of the included studies, high-quality, large-scale trials are needed to confirm this statement in the future.

Introduction

Approximately 270 million COVID-19 cases and more than five million related deaths have been confirmed worldwide.[1] The most common symptoms of COVID-19 include cough, fever, myalgias, fatigue, headache and diarrhoea.[2] Severe or critical COVID-19 usually begins at approximately one week after disease onset.[3] Dyspnea and hypoxemia, followed by progressive respiratory failure, are the most common severe disease symptoms.[4] Most severe or critical patients can progress to acute respiratory distress syndrome (ARDS).[3] It has been reported that the mortality can reach up to 49% for critically ill patients.[5]

Scientists are presently working on developing effective drugs for COVID-19. Remdesivir is the only antiviral drug approved by the Food and Drug Administration (FDA) in the United States of America (USA) to treat COVID-19 in adults, and children of 12 years old and older.[6] Respiratory support and dexamethasone remains as the main therapy for most hospitalised patients with COVID-19.[7,8] Hence, there is an urgent need for novel therapies that can help in the recovery of respiratory function and decrease the mortality of patients with severe COVID-19.

Mesenchymal stem cells, also known as mesenchymal stromal cells (MSCs), are a subset of heterogeneous cells that can differentiate into cells of multiple lineages.[9] The biomolecular basis of adipose-derived MSCs was found to be correlated to the activity of receptor tyrosine kinases (RTKs).[10,11] MSCs have been shown to have an antimicrobial function, enhance tissue repair, and balance hyperinflammatory processes and overactive immune systems.[9]

Severe patients with COVID-19 often present with noticeable inflammatory cell infiltration following rapid viral replication.[12] Furthermore, several studies have identified the presence of the "cytokine storm" (excessive inflammation) and ARDS in patients with COVID-19 due to the dysregulated immune response.[13–15] Moreover, several observational studies have reported the efficacy and safety of MSCs in COVID-19 disease treatment.[16–19] Therefore, MSCs appear to be a suitable cell-based therapy due to their function in reducing lung injury by modulating the immune response.[20] A recent living systematic review conducted by Kirkham *et al.* stated that treating COVID-19 using MSCs appear promising.[21] However, there is a lack of systematic evidence on the efficacy and safety of MSCs in treating severe/critical patients with COVID-19. The present study aims to systematically review the literature to better understand the efficacy and safety of MSCs in treating severe/critical patients with COVID-19.

Methods

Study design

The present study was reported following the PRISMA guidelines for reporting systematic reviews.[22] Due to the retrospective and anonymous characteristics of the study, the informed consent from patients and ethics approval were waived.

Search strategy and selection criteria

English electronic databases (PubMed and Cochrane Library) and the Chinese electronic database CNKI were

searched. The search terms used were, as follows: "COVID", "SARS-CoV-2", "coronavirus disease", "novel coronavirus", "novel coronaviral", "mesenchymal stem cell", "mesenchymal stromal cell", "MSC*", "stem cell", and "stromal cell". Additional references were searched by cross-checking the bibliographies of the retrieved studies or relevant reviews. The final search date for the literature search was December 19, 2021. The search strategy is presented in the Appendix.

Inclusion criteria: (a) original comparative studies that included randomised controlled trials (RCTs), retrospective or prospective cohort studies, and case-control studies; (b) patients with severe and/or critical COVID-19 disease, without age restriction, or studies with subgroup information on severe and/or critical COVID-19 disease patients; (c) MSCs with standard treatment as the experiment group; (d) standard treatment or placebo combined with standard treatment as the control treatment group; (e) studies with information on the outcomes of survival rate or adverse effects. Exclusion criteria: (a) other study designs, including case reports, clinical research protocols, and non-controlled trials; (b) studies not written in the English language; (c) abstracts without full-text reports.

Study selection

Two independent authors (WY and HD) with more than three years of research experience performed the study selection. After deleting the duplicate studies, title and abstract screening were performed according to the eligibility criteria, using the Endnote (X_9 version) software. Then, the full-text reports of potentially eligible studies were retrieved for further screening. Studies that may not have information on the target outcomes were excluded during the data analysis process. During the full-text screening process, Excel spreadsheets were used to record the reasons for each excluded study. Any disagreements between the two reviewers were resolved by discussion or referring to a third authority (JQ).

Data extraction

Two independent authors (WY and HD) used an Excel data collection form to collect the data for each included study. Missing or unclear information was requested from the corresponding author of the study through E-mail.

The primary outcome included short-term mortality and adverse events (AEs), including any AEs and MSC-related AEs. The secondary outcomes were, as follows: (a) pulmonary function and imaging changes, (b) the resource use was measured according to the length of hospitalisation or ICU stay, and (c) the change in inflammatory cytokines.

The following data were collected: (a) study characteristics (study design, first author, year of publication, country, and sample size for each group); (b) patient characteristics (age, gender and comorbidities); (c) information and characteristics of the MSC treatment and control treatment; (d) information on other treatments; (e) information on the co-therapy.

Quality assessment and certainty of the evidence

Two independent reviewers (WY and HD) performed the risk of bias assessment for each included study. Any disagreements were resolved by discussion or referred to a third authority (JQ). The revised Cochrane risk-of-bias tool for randomised trials was applied to assess the risk of bias for each RCT study. The risk of bias assessment was performed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool for observational studies.[23] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[24] was applied to assess the outcome results with the meta-analysis result.

Data analysis

For the primary outcome, the mortality was measured using odds ratio (OR) with 95% confidence interval (CI). Since there was not enough data to perform a meta-analysis, descriptive analysis was performed for the AEs and all secondary outcomes. Two independent reviewers together performed the meta-analysis using the STATA software, version 16.0 (Stata Corp., College Station, TX, USA). $P<0.05$ was considered statistically significant.

For the mortality rate, merely studies that used the outcome data to compare the two interventions were included in the meta-analysis. Data conversions were required when there was no appropriate direct number for the meta-analysis. If there was any missing data or unclear data, an e-mail was sent to the corresponding author of the study to request information. The pooled event rates were calculated using a double arcsine transformation to stabilise the variances of the original proportions. Each pooled rate was presented in proportion, with 95% CI. Based on the information obtained from the domain and research question, a meta-analysis was performed for outcome measures when there were at least two clinically homogenous studies (studies with similar participants, interventions, and outcomes), and a forest plot was generated for each meta-analysis. Due to the potential high heterogeneity of the included studies, the random-effects model was initially chosen for all analyses. The heterogeneity was estimated using the Q-test and I^2 score. If the P-value was ≥ 0.1 (for Q-test) and I^2 was $\leq 50\%$, the result was considered not heterogeneous. Subsequently, a fixed-effects model was applied for the analysis as the final result.[25–27] The subgroup analysis was performed

according to the number of MSC doses and COVID-19 category (severe or critical). The sensitivity analysis was conducted by deleting the data of each included study, one by one, in order to assess the robustness of the synthesised results.

Reporting for bias assessment

Publication bias analysis by Egger's test was performed for all response rates when the results were obtained from at least 10 studies. $P<0.05$ suggests the presence of publication bias. This was dealt with using the trim-and-fill method.[28]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had the final responsibility for the decision to submit the study for publication.

Results

Study selection

A total of 3644 articles were extracted from the literature search. After omitting duplicate studies, 2632 articles underwent title and abstract screening. Among these articles, 24 articles were selected for the full-text review. Finally, 13 studies reported in 14 articles were included for the study quality assessment and data analysis.[5,29–41] The study selection process and reasons for excluding studies are presented in Figure 1.

Study characteristics

A total of 557 patients were involved in the included 13 studies, with a sample size range of 8-210 patients. The number of RCTs, prospective cohort studies, and retrospective cohort studies was 7, 5 and 1, respectively. All articles were published in 2020 or 2021. Diabetes and hypertension were the most common reported comorbidities. The details of the participants, including the age, male rate, treatments, follow-up and primary outcomes, in the included 13 studies reported in 14 articles are listed in Table 1.

Among the 13 included studies, eight studies used umbilical cord-derived derived MSCs,[5,29,32,33,36,38–41] two studies used healthy bone-marrow-derived MSCs,[34,35] one study used menstrual blood-derived MSCs,[30] and one study used non-hematopoietic enriched stem cells.[37] For the dose, seven studies administered 1-3 $\times$ 10^6 cells per kg of body weight,[5,32,35,36,38,39,41] four studies administered 3-12 $\times$ 10^7 cells per infusion,[29,30,33,40] and two studies did not report the stem cell dose.[34,37] Among the 210 patients in the experimental group, 59 patients received a single dose,[5,32,36,39,41] 35 patients received two doses,[35,37,40] and 116 patients received three doses of therapy.[29,30,33–35,38] All included studies applied intravenous (IV) as the route of delivery. However, not all studies reported the details of standard care. Among the reported treatments,[5,32,38,39] the most common standard treatments included antipyretic, antiviral, glucocorticoid, and supportive therapy. There was diversity on the details of the standard treatment between different hospitals and countries.

Risk of bias in the studies

The risk of bias in seven RCTs is summarised in Table 2.[5,29,36–38,40,41] Three studies had bias concerns in randomisation,[36–38] and one study had a high risk of bias due to randomisation.[5] Furthermore, two studies had concerns in selection reporting,[40,41] and one study had concerns about the deviation of the intervention.[36] For the overall assessment, one study was defined as having a high risk of bias,[5] five studies were defined as having some concerns,[36–38,40,41] and one study was defined as having a low risk of bias.[29,31]

For the six cohort studies, the risk of bias assessment results is listed in Table 3. All six studies had a risk of bias in the selection of the reported result since none of these studies published a priori protocol. Furthermore, there was no evidence that these had problems in the domains with bias in the measurement of outcomes into the study, or bias in the classification of interventions. However, all studies had problems in risk of bias due to confounding. Therefore, the overall risk of bias was defined as moderate and serious risk of bias in four (66.7%)[32–35] and two (33.3%) studies,[30,39] respectively.

Short-term mortality

Among the 13 included studies, three studies reported that all patients who participated survived.[31–33] The detailed number of deaths reported in each included article is presented in Table 4. The mortality for all other remaining studies indicated that patients in the stem cell group had a lower mortality rate (0.08; 95% CI: 0.01, 0.20), when compared to those in the control group (0.28; 95% CI: 0.12, 0.48). The present meta-analysis revealed that compared to standard treatment, MSC therapy can significantly decrease the mortality rate of patients with severe/critical COVID-19 (OR: 0.52, 95% CI: 0.32-0.84), with very low heterogeneity (P=0.998 [Q-test], I^2=0.0%) (Figure 2 & Appendix).

According to the subgroup analysis, no statistical significance was found between severe cases (OR: 0.59; 95% CI: 0.29, 1.18) and critical cases (OR: 0.56; 95% CI: 0.26, 1.19). In addition, no statistical significance was found among the one-dose MSC therapy (OR: 0.55;

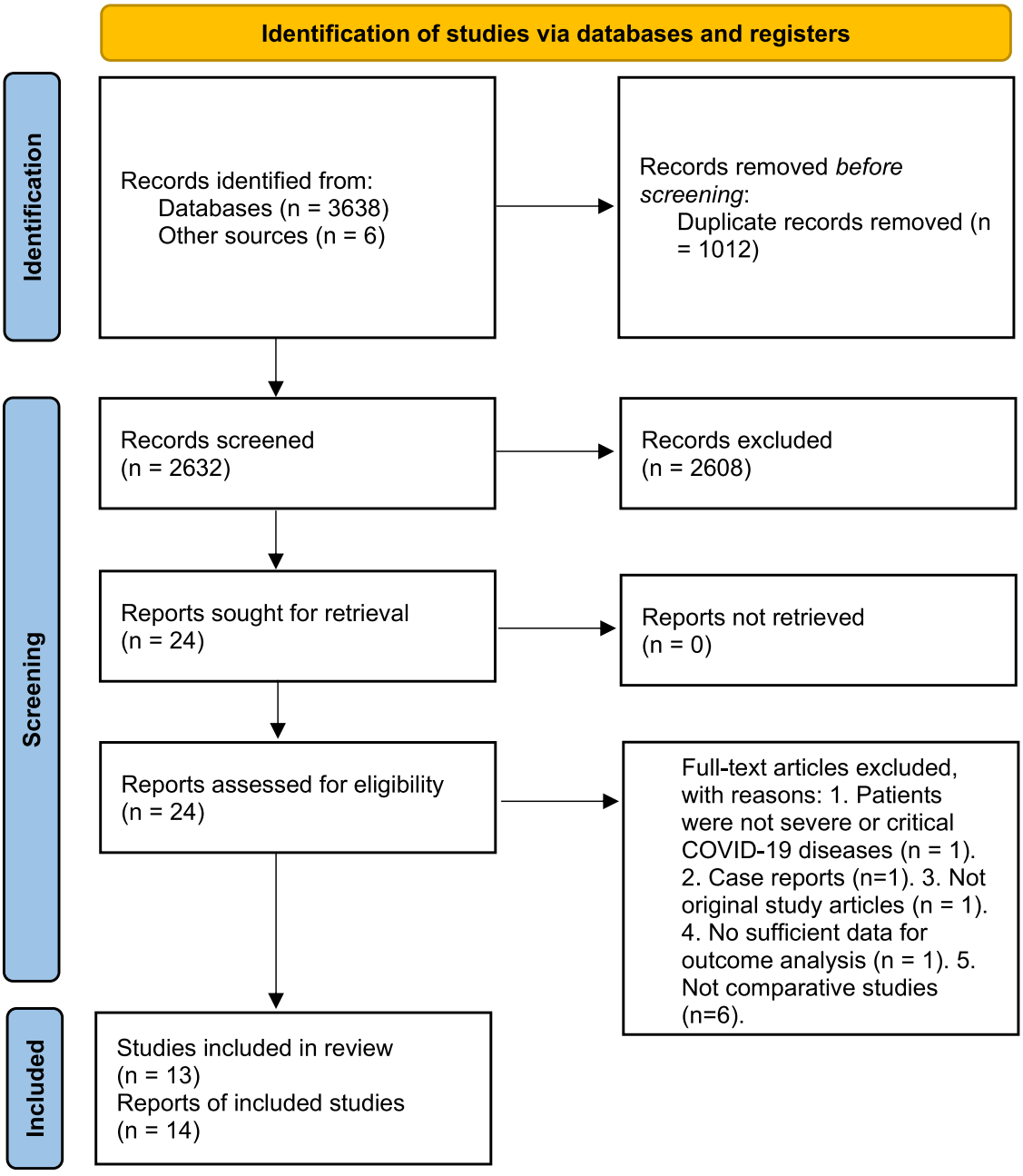

Figure 1. PRISMA flow diagram for article selection.

95% CI: 0.25, 1.24), two-dose MSC therapy (OR: 0.47; 95% CI: 0.18, 1.24), and three-dose MSC therapy (OR: 0.52; 95% CI: 0.24, 1.15).

After deleting the data obtained from observational studies, the OR for the mortality rates between the two groups was 0.54 (95% CI: 0.29-1.00), which was similar to the total results. In addition, after excluding the data obtained from serious risk of bias studies, the OR for the mortality rates between the two groups was 0.57 (95% CI: 0.34-0.95), which was similar to the total results.

The *P*-value in Egger's test for the comparison of mortality rates was 0.07. Combined with the funnel plots (Figure 3), it was found that there was no publication bias in the included studies for the OR of mortality rates between the two groups.

First author (publication year), country	Study Design	Included patients	Total sample size (experimental arm/control arm), *n*	Total sample age (experimental arm/control arm), mean ± SD or specified	Experimental arm male /control arm male, n (%)	Comorbidities (*n*, experimental arm/control arm)	Experimental treatment	Control treatment	Follow up days	Primary outcome(s)
Kaushal et al. (2020), USA	Retrospective cohort study	Critically ill ECMO patients with COVID-19	40 (9/31)	Median: Not specified (38/ 42)	4 (44.44%)/29 (93.55%)	Asthma (4/1); Diabetes (3/8); Chronic Renal insufficiency (1/16)	MSC infusion + ECMO treatment	ECMO treatment	Not specified	Safety
Leng et al. (2020), China	Prospective cohort study	Patients with COVID-19 Pneumonia (severe or critical)	8 (5/3)	60.75 ± 11.62 (58.20 ± 8.90 / 65.00 ± 16.46)	3 (60.00%)/ 0 (0)	Not specified	MSC transplant	Placebo	Not specified	Primary safety data (infusional and allergic reactions, secondary infection, and life-threatening adverse events) and the primary efficacy data (the level of cytokine variation, the level of C-reactive protein in plasma, and the oxygen saturation)
Meng et al. (2020), China	Prospective cohort study	Patients with severe COVID-19	8 (4/4)	45.00 ±10.86 (42.25 ± 11.44/ 47.75 ± 11.15)	4 (100%)/ 2 (50.00%)	Asthma (0/1), Hypertension (2/1), Diabetes (1/0), Fatty liver disease (1/0),	Standard treatment plus hUC-MSC infusion	Standard treatment	28 days	Safety
Shu et al. (2020), China	Open-label RCT	Patients with severe COVID-19 disease	41 (12/29)	58.78 ± 16.26 (61.00 ± 17.87/ 57.86 ± 15.79)	8 (66.67%)/ 16 (55.17%)	Diabetes (3/5), Hypertension (3/6)	Standard treatment plus hUC-MSC infusion	Standard treatment	28 days	The incidence of progression from severe to critical illness and the 28-day mortality rate
Adas et al. (2021), Turkey	RCT	Patients with critical COVID-19	20 (10/10)	Mean: 56 (not specified)	Not specified	Not specified	Conventional treatment plus MSC transplantation	Conventional treatment	Not specified	Markers of the cytokine storm and mortality
Dilogo et al. (2021), Indonesia	RCT	Patients with critical COVID-19	40 (20/20)	Not specified	15 (75.00%)/15 (75.00%)	No difference in the number of comorbidities (*P*=0.112)	Standard care plus MSC infusion	Standard care	Not specified	Mortality rate and length of ventilator use.
Feng et al. (2021), China	Prospective cohort study	Patients with severe COVID-19 disease	28 (8/20)	Median (IQR): 51.00 (43.25, 64.00) [50.50 (39.00, 72.75)/ 51 (43.25, 63.5)]	4 (50.00%)/9 (45.00%)	Diabetes and/or hypertension (4/7)	Standard treatment plus hUC-MSC infusion	Standard treatment	3 months	Adverse events
Haberle et al. (2021), Germany	Prospective cohort study	Patients with severe COVID-19 ARDS	23 (5/18)	Median (IQR): not specified [39 (32 to 50)/ 59 (54 to 79)]	3 (60.00%)/ 13 (72.22%)	Diabetes (0/2), arterial hypertension (1/13), chronic heart failure (0/2), coronary heart disease (0/2), pulmonary diseases (0/1)	Standard treatment plus MSC infusion	Standard treatment	Experiment group: 49 days. Control group: 15 days.	ICU stay
Lanzoni et al. (2021), USA	RCT	Patients with severe COVID-19 ARDS	24 (12/12)	Not specified (58.58 ± 15.93/ 58.83 ± 11.61)	5 (41.70)/ 8 (66.70)	Diabetes (5/6), Hypertension (7/9), Cancer (0/1), heart disease (1/3)	Standard treatment plus UC-MSC infusion	Standard treatment	1 month	Safety and cardiac arrest or death within 24 hours post-infusion,

Table 1 (Continued)

First author (publication year), country	Study Design	Included patients	Total sample size (experimental arm/control arm), *n*	Total sample age (experimental arm/control arm), mean ± SD or specified	Experimental arm male /control arm male, n (%)	Comorbidities (*n*, experimental arm/control arm)	Experimental treatment	Control treatment	Follow up days	Primary outcome(s)
Shi et al. (2021), China	RCT	Severe patients with COVID-19	100 (65/35)	Not specified (60.72 ± 9.14/ 59.94 ± 7.79)	37 (56.92%)/ 19 (54.29%)	Any comorbidities (34/18)	UC-MSCs	Placebo	1 year	Imaging and clinical outcomes
Ventura-Carmenate et al. (2021), United Arab Emirates	Open-label RCT	Severe patients with COVID-19	44 (20/24)	Not specified	Not specified	Not specified	Standard care plus PB-NHESC-C	Standard care	28 days	Hospital discharge and mortality
Xu et al. (2021), China	Prospective cohort study	Severe and critically ill patients with COVID-19	44 (26/18)	Not specified (58.31 ± 12.49/ 61.11 ± 11.03)	17 (65.38%)/ 13 (72.22%)	Not specified	MSC infusion plus concomitant medication	Concomitant medication	1 month	Survival rate
Zhu et al. (2021), China	RCT	Severe and critically ill patients with COVID-19	27 (14/13)	Not specified	Not specified	Diabetes (4/4), hypertension (11/11), cerebrovascular disease (3/2), coronary heart disease (3/3), Chronic respiratory diseases (1/0)	Standard treatment plus MSC infusion	Standard treatment plus placebo	Not specified	Hospital stays

***Table 1*: Characteristics of the 13 included studies in 14 articles.**

Abbreviation: RCT, randomised controlled trial; SD, standard deviation; hUC-MSC, human umbilical cord mesenchymal stem cell; USA, United states of America; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PB-NHESC-C, peripheral blood non-hematopoietic enriched stem cell cocktail.

Author (publication year)	Randomisation	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Shu et al. (2020), China	−	+	+	+	+	−
Adas et al. (2021), Turkey	+/−	+	+	+	+	+/−
Dilogo et al. (2021), Indonesia	+	+	+	+	+/−	+/−
Lanzoni et al. (2021), USA	+	+	+	+	+/−	+/−
Shi et al. (2021), China	+	+	+	+	+	+
Ventura-Carmenate et al. (2021), United Arab Emirates	+/−	+	+	+	+	+/−
Zhu et al. (2021), China	+/−	+/−	+	+	+	+/−

Notes: + Low risk of bias, − High risk of bias, +/− Some concerns.

***Table 2*: Summary assessment of risk of bias for the included studies using the revised Cochrane risk-of-bias tool for randomised trials (RoB2).**

Author publication year	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Overall risk of bias
Kaushal et al. (2020), USA	×	+	+	+	⊕	+	⊕	Serious risk of bias
Leng et al. (2020), China	⊕	+	+	⊕	+	+	⊕	Moderate risk of bias
Meng et al. (2020), China	−	+	+	⊕	+	+	⊕	Serious risk of bias
Feng et al. (2021), China	−	⊕	+	+	+	+	⊕	Serious risk of bias
Haberle et al. (2021), Germany	⊕	⊕	+	+	+	+	⊕	Serious risk of bias
Xu et al. (2021), China	⊕	+	+	+	+	+	⊕	Moderate risk of bias

Notes: + for low risk of bias, ⊕ for moderate risk of bias, − for serious risk of bias, × for critical risk of bias, +/− for no information.

***Table 3*: Summary assessment of the risk-of-bias for the five included studies using the ROBIN-I tool.**

First author (publication year), country	Mortality rate (MSC group vs. Control group)	AEs	Pulmonary function	Pulmonary imaging changes	Length of hospitalisation (MSC group *vs.* Control group)	Inflammatory cytokines
Kaushal et al. (2020), USA	(2/9) *vs.* (15/31)	No patients were lost to follow-up for the primary outcome of safety with MSC infusion, and there were no reported side effects.	Not specified.	Not specified.	Not specified.	Isolated plasma exosomes containing the SARS-COV-2 spike protein decreased after MSC infusions between day 14 or 21 after administration ($P = 0.003$ and $P = 0.005$, respectively), and this was associated with the decrease in COVID-19 IgG spike protein titer at the same time points ($P = 0.006$ and $P = 0.007$, respectively). Control ECMO patients who received convalescent plasma did not clear the COVID-19 IgG during the same time frame.
Leng et al. (2020), China	(0/5) *vs.* (1/3)	No acute infusion-related or allergic reactions were observed within two hours after transplantation. Similarly, no delayed hypersensitivity or secondary infections were detected after treatment.	For all the experimental patients, the oxygen saturations rose to ≥95% at rest, with or without oxygen uptake (5 liters per minute).	Not specified.	Not specified.	After the intravenous injection of MSCs, the decrease ratio of serum pro-inflammatory cytokine TNF-α before and after MSC treatment was significant ($P<0.05$). Meanwhile, the increase ratio of anti-inflammatory IL-10 ($P<0.05$) was remarkable in the MSC treatment group.
Meng et al. (2020), China	(0/4) *vs.* (0/4)	There were no serious adverse events associated with the UC-MSC infusion. Two patients who received UC-MSCs developed transient facial flushing and fever immediately on infusion, and this was spontaneously resolved within four hours.	In most experimental severe patients, the partial pressure of arterial oxygen: percentage of inspired oxygen (PaO^2/FiO^2) ratio improved after UC-MSC treatment.	The CT scans indicated that patients in the MSC group presented with absorption of pulmonary pathological changes.	Hospital stay: 20.00 *vs.* 23.00 days, $P = 0.306$	There was a decreasing trend in the levels of all these cytokines in UC-MSC-treated patients within 14 days.
Shu et al. (2020), China	(0/12) *vs.* (4/29)	All patients who received UC-MSC treatment had no adverse reactions (such as rash, allergic reactions and febrile reactions, after infusion).	The arterial blood gas analysis revealed that the time for the oxygenation index to return to the normal range was faster in the UC-MSC treatment group, when compared to the control group.	The chest CT scans indicated that the CT scores, number of lobes involved, GGO, and consolidation, which reflects the decrease in lung inflammation in the stem cell treatment group, were significantly better, when compared to those in the control group.	Not specified.	Compared with those of the control group, the C-reactive protein and IL-6 levels significantly decreased from day dat of the stem cell infusion in the UC-MSC group.

Table 4 *(Continued)*

First author (publication year), country	Mortality rate (MSC group vs. Control group)	AEs	Pulmonary function	Pulmonary imaging changes	Length of hospitalisation (MSC group *vs.* Control group)	Inflammatory cytokines
Adas et al. (2021), Turkey	(3/10) *vs.* (6/10)	No adverse or serious adverse events related to the MSC therapy occurred.	Not specified.	Not specified.	Not specified.	When the MSC group and control group were compared, the serum ferritin, fibrinogen and CRP levels in the MSC group significantly decreased.
Dilogo et al. (2021), Indonesia	(10/20) *vs.* (16/20)	The intravenous infusion of MSCs was found to be safe and well-tolerated, with no life-threatening complications or acute allergic reactions during the administration. The critically ill patients with severe COVID-19 presented no immediate death or acute anaphylactic shock after MSC application.	Not specified.	Not specified.	The difference in length of stay in the intensive care unit and ventilator usage were not statistically significant.	Inflammatory markers, namely, procalcitonin, and CRP, were not significantly different between the MSC group and control group.
Feng et al. (2021), China	(0/8) *vs.* (0/20)	In the UC-MSC group, none of the patients experienced any adverse reactions, such as skin itchiness, dizziness, loss of appetite, or foggy vision, after discharge. Two patients had slightly increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and one patient had mildly elevated levels of CA12-5.	Compared to the control group (59.45%−27.45%), the UC-MSC group (71.88%− 8.46%) had a higher mean FEV1 (P<0.01). The mean FEV1/FVC ratio was significantly higher in the UC-MSC group, when compared to that in the control group (79.95%-8.00% *vs.* 58.97%-19.16%, P<0.05).	There were no significant differences in CT scores between the two groups (0.60-0.88 *vs.* 1.00-1.31, P = 0.917).	Not specified.	There were no significant differences in CPR (P = 0.111), but there were significant differences in procalcitonin (P = 0.002) between the two groups at follow-up after three months
Haberle et al. (2021), Germany	(1/5) *vs.* (10/18)	Not specified.	At discharge, the MSC-treated patients had a significantly lower Murray score of 0.3+0.1, when compared to control patients, who presented an average score of 1.3+1.1.	Not specified.	Patients in the control group had a shorter length of stay in the intensive care unit, when compared to the MSC group, but the difference was not significant (P = 0.07).	The values for CRP and IL-6 did not significantly differ between the groups during ICU treatment.
Lanzoni et al. (2021), USA	(2/12) *vs.* (7/12)	Two serious adverse events (SAEs) were observed in the UC-MSC group, and 16 SAEs were observed in the control group, affecting 2 of 12 and 8 of 12 subjects, respectively (P = 0.04, Fisher's exact test). Significantly more subjects experienced SAEs in the control group, when compared to the UC-MSC treatment group. Merely one AE was possibly related to the treatment in the UC-MSC group.	Not specified.	Not specified.	Not specified.	Inflammatory cytokines significantly decreased in UC-MSC-treated subjects at day six.

Table 4 *(Continued)*

First author (publication year), country	Mortality rate (MSC group vs. Control group)	AEs	Pulmonary function	Pulmonary imaging changes	Length of hospitalisation (MSC group *vs.* Control group)	Inflammatory cytokines
Shi et al. (2021), China	(0/65) *vs.* (0/35)	The incidence of AEs reported during the study was similar in the MSC group (55.38%) and placebo group (60%) All AEs were unrelated to the UC-MSC intervention. No deaths were observed in this trial. There was no difference in adverse events at the 1-year follow-up.	The 6-minute walk test revealed an increase in distance in patients treated with UC-MSCs (difference: 27.00 m; 95% CI: 0.00, 57.00; $P = 0.057$).	UC-MSCs significantly reduced the proportions of solid component lesion volume, when compared to the placebo (median difference: -15.45%; 95% CI: -30.82%, -0.39%; $P = 0.043$). More interestingly, 17.9% (10/56) of patients in the MSC group had normal CT images at month 12, but there was none in the placebo group ($P = 0.013$).	Not specified.	There was no significant difference in the subsets of peripheral lymphocyte counts (CD4+ T cells, CD8+ T cells, B cells, NK cells) and plasma markers between the two groups.
Ventura-Carmenate et al. (2021), United Arab Emirates	(4/20) *vs.* (7/24)	In total, adverse events were reported in 50 (72.46%) patients who received stem cell treatment, when compared to the 51 (72.85%) patients in the control group ($P = 0.9419$). A total of 240 adverse events were reported during the 28-day follow-up for all enrolled patients.	Not specified.	Not specified.	After nine days of follow-up (evaluating the first tertial after cell therapy), 63.3% of patients in the experimental group recovered, and were discharged from the hospital. In the control group, this percentage was only 57.1%, and a non-significant difference was found.	The IL-6 and C-reactive protein levels also significantly decreased in the treated group during the follow-up. In the control group, only statistically significant changes were observed in the reduction of C-reactive protein levels.
Xu et al. (2021), China	(2/26) *vs.* (6/18)	The frequency of each AE was statistically similar between the two groups, except for the AE related to high blood pressure, which was more common in the control group. Furthermore, the experimental group had a lower incidence of AEs (76.92%), when compared to the experimental group (100.00%), but the difference was not statistically significant.	SpO_2 significantly improved following MSC infusion, from 94.72± 3.4% before treatment to 96.04± 5.93% after treatment ($P<0.001$).	The chest CT results suggest that the relative improvement rate was higher in the experimental group at one month after MSC infusion, when compared to the control group.	Length of stay in the ICU (mean±SD, days), experimental group: 24.00±12.67; control group: 22.17±20.66.	For inflammatory indices, there were no significant differences in CRP ($P = 0.486$) and IL-6 ($P = 0.375$).
Zhu et al. (2021), China	(0/14) *vs.* (2/13)	More serious adverse events were recorded in the placebo group, when compared to the MSC group, but the difference was not statistically significant.	Not specified.	The CT and X-ray significantly improved in the experimental group ($P = 0.008$).	Median time of hospitalization stay (days): 11 (8, 14) *vs.* 15 (11, 19) with $P = 0.0198$.	The MSC infusion reduced the levels of C-reactive protein, proinflammatory cytokines, and neutrophil extracellular traps (NETs).

***Table 4*: Outcomes for the 13 studies in the 14 articles for efficacy and safety.**
Abbreviations: UC-MSC, umbilical cord mesenchymal stem cell; AEs, adverse events; *vs.*, versus; CRP, C-reactive protein; CT, computed tomography.

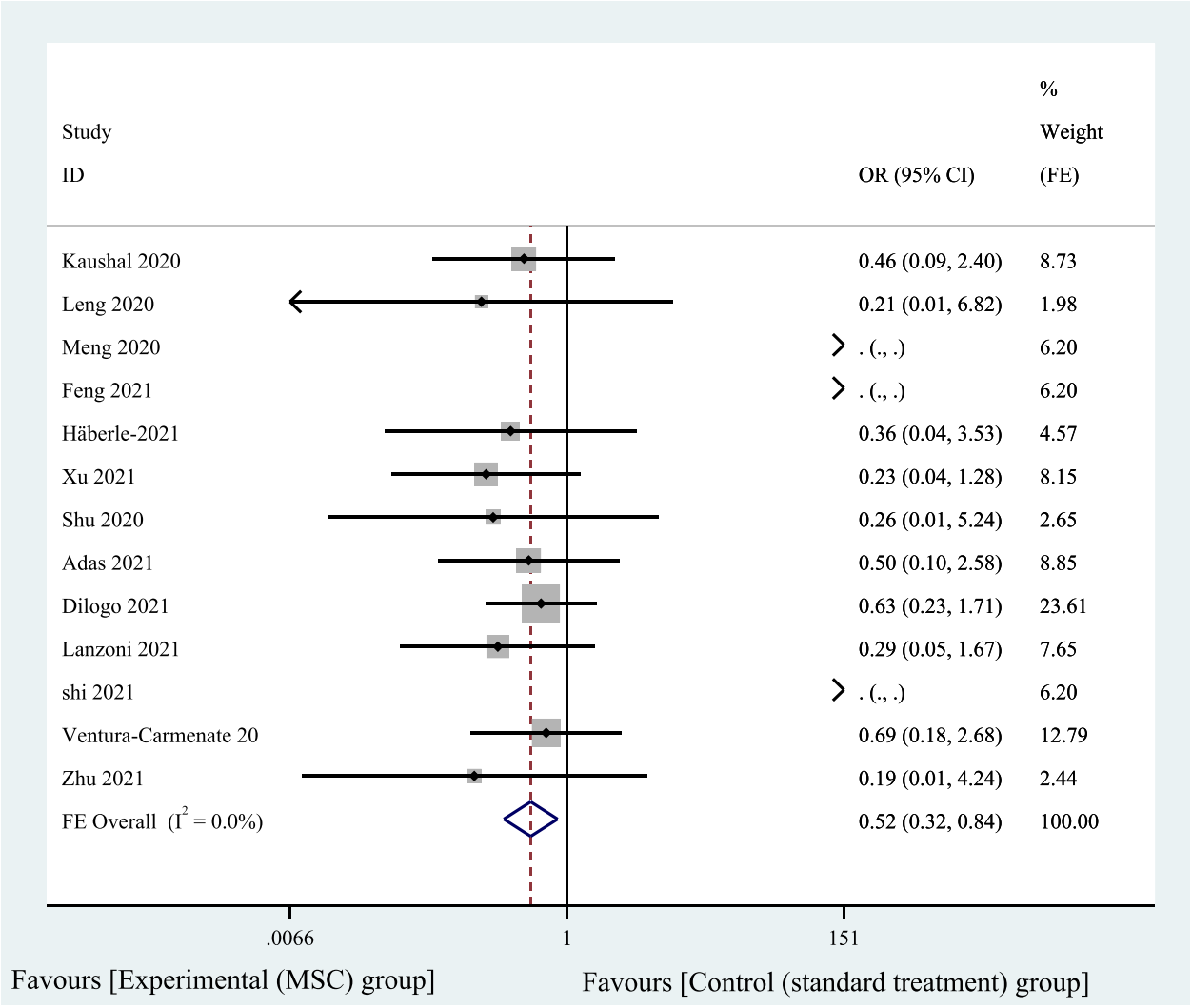

Figure 2. Forest plot for the comparison of mortality rates between the experimental group (stem cell therapy + standard treatment) and control group (standard treatment).

Adverse events

All included articles, except for the article published by Haberle *et al.*,[35] reported safety outcomes. None of the included studies reported any treatment-related serious AEs or death related to cell infusion (Table 4). Merely one study reported a subject with bradycardia with possible infusion-related AE. This patient experienced worsening of the bradycardia, and required transient vasopressor treatment.[40] Furthermore, none of the studies, except for the study published by Meng *et al.*,[33] reported infusion-related AEs. Meng *et al.* reported one case of transient facial flushing and fever that immediately occurred upon infusion, and another case of transient fever, which was resolved without treatment.[33] Five studies compared non-treatment-related AEs during the trials between the two groups.[29,30,36,37,40] In all five studies, the incidence of AEs in the experimental group was similar to or less than that in the control group.

Pulmonary function and imaging changes

Eight included studies reported the pulmonary function and/or imaging changes between the two groups.[5,29,30,32,33,35,36,39] Compared to the control group, the experimental group was reported to have better pulmonary function improvement and imaging appearance (Table 4).

Resource use

Resource use was reported in six included studies (Table 4).[5,33,35–37,41] Meng *et al.* and Ventura-Carmenate *et al.* reported shorter length of hospitalisation stays, but the

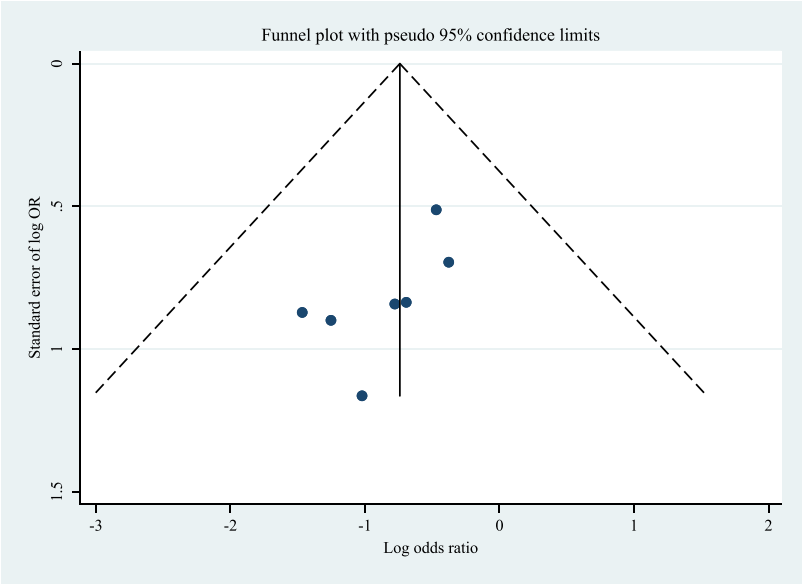

Figure 3. Funnel plot for the odds ratios of mortality rates obtained from the seven included articles.

difference was not statistically significant.[33,37] Furthermore, Zhu *et al.* reported that the experimental group had a significantly shorter length of hospitalisation stay (P=0.0198).[36] Moreover, Dilogo *et al.* and Haberle *et al.* reported shorter length of ICU stays in the experimental group, when compared to the control group, but the difference was not statistically significant.[35,41]

Inflammatory cytokines

All included studies reported the changes in inflammatory cells and cytokines (Table 4). The cytokines were found to be decreasing or tended to decrease in the experimental group. Furthermore, two studies reported that the decease between the two groups was statistically significant.[5,38]

Certainty of the evidence (GRADE)

According to the GRADE assessment, the evidence for primary outcome mortality had low certainty for the total results, but this was moderate in the meta-analysis results obtained from the RCTs, because the observational study design meant that the GRADE rating started as moderate−certainty evidence. Another critical reason for the downgrading of scores is the small sample size, which increased the imprecision of the results.

Discussion

The therapeutic function of MSCs is its anti-inflammatory and immunomodulatory activities. These have been proven for many autoimmune diseases, including multiple sclerosis, inflammatory bowel disease, and type 1 diabetes mellitus.[42] The potential therapeutic effects of MSCs in respiratory viruses (e.g. COVID-19) have also been discussed and summarised.[43] To the best of our knowledge, the present study is the first systematic review and meta-analysis on MSC therapy that focused on patients with severe/critical COVID-19. In the present systematic review, the efficacy and safety of MSCs, as an adjunctive therapy for severe/critical patients with COVID-19, were verified.

In terms of the decrease in short-term mortality, it was found that the mortality in the experimental group significantly decreased (OR: 0.52, 95% CI: 0.32-0.84). This result is similar to a recent systematic review, which reported that for general patients with COVID-19, MSCs can reduce mortality (RR: 0.471, 95% CI: 0.270-0.821).[44] The present findings indicated that even for severe/critical patients with COVID-19, MSCs can achieve efficacy, in terms of mortality. However, according to the present subgroup analysis, the efficacy in mortality reduction was not associated to the dose or category of the disease (critical or severe). In addition, MSCs may be harvested from many tissues, and adipose-derived MSCs are the most popular resources in practice.[45] However, there were not enough data to analyse and determine whether the efficacy of MSCs is associated with the resources. Considering the relatively small sample size of all the included studies, large-scale prospective studies are needed to confirm this statement.

The safety of MSCs for severe/critical patients with COVID-19 was excellent in the present review. Furthermore, none of the included studies reported treatment-related serious AEs or death related to cell infusion. However, it was reported that the intravascular

administration of MSCs can increase fever risk (RR: 2.48, 95% CI: 1.27-4.86).[46] Among the included studies, merely Meng *et al.* reported two cases with infusion-related fever, which was resolved without interventions. Furthermore, in studies that reported general AEs, the incidence of AEs in the experimental group was similar to or less than that in the control group. Therefore, it appears that MSCs are safe for patients with severe/critical COVID-19.

In the present study, an apparent improvement in pulmonary function and imaging appearance in patients with severe/critical COVID-19 were found after using MSCs. The rationale of this therapeutic efficacy is that cytokines were released due to the damage to the organs or tissues, causing the migration of MSCs to the sites of inflammation and injury.[47] In addition, it was found that the cytokines decreased or tended to decrease in the experimental group, further proving the pulmonary repair function of MSCs in severe/critical patients with COVID-19.[48] In terms of resource use, it was found that the length of hospitalisation and ICU stays were shorter in the experimental group, when compared to the control group. However, most of the differences were not statistically significant.

The present systematic review was performed using rigorous search strategies and scientific methodology. The present systematic review and meta-analysis suggest that treatment with MSCs is efficient and safe for severe and critical COVID-19, although the certainty of this effect remains limited. According to the GRADE assessment, the evidence for primary outcome mortality had low certainty for the total results. There were some limitations in the studies. First, the sample size of the included studies was not very large, which decreased the precision of the results. Second, due to the different diagnosis guidelines of different hospitals, the definitions for the included severe/critical patients with COVID-19 were slightly different in the included studies. This may have introduced a selection bias to the present findings. Next, most of the included studies did not provide details for the MSC characteristics, limiting the confidence in the cell product used. Lastly, due to the urgent need for evidence for COVID-19 treatment, the present review was not registered, and the outlined protocol was not published. Therefore, future high-quality, large-scale trials are needed to confirm the present statement, which could provide benefits for the treatment of COVID-19 and other similar diseases at present or in the future.

Given the evolution of COVID-19 variants and widespread vaccination programs, the treatment regimens for COVID-19 should be updated in a timely manner. However, for severe/critical cases, there is still an urgent need for efficient and safe treatments, such as MSCs. Furthermore, according to all included studies in the present study (Table 1), the treatment regimens are diverse. Therefore, treatment guidelines for MSCs are needed, in terms of standard regimens, suitable resources and adjustments, according to the different conditions of patients.

The present study demonstrated that MSCs have a high possibility of significantly reducing mortality and are safe for patients with severe or critical COVID-19, regardless of whether 1-3 doses are used. In addition, MSCs have a high potential to improve pulmonary function, save resource use, and decrease the inflammatory cytokines in these patients. However, due to the small sample size of the included studies, high-quality, large-scale trials are needed to confirm this statement in the future.

Contributors

WY and HD designed the methods. WY, QJ, YZ and LS carried out the acquisition, analysis, and interpretation of data. WY and HD drafted the manuscript. LS and YZ critically revised the manuscript for important intellectual content. LS and YZ performed the statistical analysis and were responsible for the integrity of the data and accuracy of the data analysis. All authors approved the final manuscript. All authors had full access to all data in the study and had the final responsibility for the decision to submit the study for publication.

Data sharing statement

The data are available from the corresponding authors upon reasonable request.

Declaration of interests

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101545.

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