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Original article

The clinical efficacy and safety of mesenchymal stromal cells for patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials

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Objectives: This meta-analysis of randomized controlled trials (RCTs) investigated the usefulness of mesenchymal stromal cells (MSCs) to treat patients with COVID-19. Methods: PubMed, Embase, Ovid MEDLINE, the Cochrane Library, and Clinicaltrials.gov were searched for RCTs published before November 7, 2021. Only RCTs that compared the clinical efficacy and safety of MSCs with other alternative treatments or placebos in the treatment of patients with COVID-19 were included.

Results: Six RCTs were included, in which the MSC and control groups consisted of 158 and 135 patients, respectively. The patients who received MSCs had a significantly lower 28-day mortality rate (7.6% vs 21.5%; OR, 0.18; 95% CI, 0.06–0.52; \(I^2 = 0\)%) and significantly higher clinical improvement rate (OR, 6.05; 95% CI, 2.31–15.83; \(I^2 = 0\%\)) than the controls. The patients who received MSCs were associated with a similar risk of adverse events (AEs) and serious AEs to the control group (AEs: OR, 33; 95% CI, 0.09–1.18; \(I^2 = 59\%\); serious AEs: OR, 0.30; 95% CI, 0.02–4.41; \(I^2 = 53\%\)).

Conclusions: MSC treatment may help to improve the clinical outcomes of patients with COVID-19. In addition, MSC treatment appears to be a safe therapeutic option for patients with COVID-19.

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Introduction

The COVID-19 pandemic has spread around the world since its first appearance at the end of 2019 [1], with more than 535 million cumulative cases and 6 million deaths globally [2]. The clinical manifestations of SARS-CoV-2 infection range from asymptomatic, acute respiratory disease, pneumonia, and acute respiratory distress syndrome (ARDS) [3–5]. Severe or critical COVID-19 can be associated with cytokine storm and cause a high morbidity and mortality [4]. Therefore, anti-inflammatory agents are an important treatment modality in addition to initial anti-viral agents [6–8]. At present, only corticosteroids and anti-interleukin-6 (IL-6) agents have demonstrated clinical efficacy in reducing the mortality of patients with COVID-19 [9,10]. Mesenchymal stromal cells (MSCs), which can be collected from a variety of adult and neonatal tissues and mediated partly by conditioned media or through secreted extracellular vesicles, have been shown to exhibit significant immunomodulatory and tissue repair capabilities [11–14]. SARS-CoV-2 infection can cause life-threatening illness due to an activated immune response. Due to the potent anti-inflammatory activity of MSCs and their

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MSC, mesenchymal stem cell; MV, mechanical ventilation; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
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secretomes, MSCs have been repurposed to treat COVID-19. Many clinical studies of MSCs have demonstrated their potential efficacy and safety in the treatment of SARS-CoV-2 infection during this global pandemic, however, only a small number of studies with limited information have been completed [15–21]. A systematic search and meta-analysis is therefore urgently needed to comprehensively review the results of these studies and provide solid evidence on the potential benefit of MSCs. Therefore, we conducted this systematic review and meta-analysis using updated data to provide robust and timely evidence.

Methods

Study search and selection

We searched PubMed, Embase, Ovid MEDLINE, the Cochrane Library, and Clinicaltrials.gov were searched for RCTs published before November 7, 2021. The following search terms were used: “mesenchymal stromal cells,” “mesenchymal stem cells,” “MSCs,” “mesenchymal stromal cell conditioned medium,” “exosomes,” “mesenchymal stromal cell extracellular vesicles,” “microvesicles,” “Covid-19,” “SARS-CoV-2,” “coronavirus,” “2019-nCoV,” and “coronavirus.” Only RCTs that compared the clinical efficacy and safety of MSCs with other alternative agents or placebos in the treatment of patients with COVID-19 were included. The inclusion criteria were: (1) studies with a RCT design; (2) study subjects were patients with COVID-19; (3) intervention was MSCs or their secretomes derived from any tissue source (e.g., bone marrow, adipose, umbilical cord, dental pulp, placenta, etc.), which could be syngeneic, allogeneic, or xenogeneic; and (4) comparator was a conventional therapy for COVID-19 (e.g., antivirals, immunomodulatory drugs, anticytokine drugs, combination therapies, etc.) or placebo. The exclusion criteria were: (1) not a RCT design (case reports, case series, observational studies, and retrospective cohort studies); (2) in vitro studies; (3) pharmacodynamic or pharmacokinetic studies; and (4) no available data regarding the outcome of interest. Two authors (CYC and WCC) independently reviewed the identified abstracts and selected articles for full review. Disagreements were resolved by the third author (CKH). For each included study, we extracted the following data: year of publication, study design, interventions, patient populations, methods of MSC isolation and characterization, primary and secondary clinical outcomes, and adverse event (AEs). This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22] and the study protocol is registered in PROSPERO (CRD42021288552).

Outcome measurements

The primary outcome of this meta-analysis was 28-day overall mortality, and the secondary outcomes were the rate of clinical improvement, time to recovery, length of hospital stay, the need for mechanical ventilation (MV), and the risk of AEs.

Data analysis

The Cochrane risk of bias tool [23] was used by two authors (CYC and WCC) to assess the quality of the included RCTs and their associated risk of bias. Any discrepancies between these two authors were resolved by a third author (CCL). All statistical analyses were performed using Review Manager (version 5.3; Nordic Cochrane Center, Copenhagen, Denmark). Heterogeneity was evaluated using Q statistics generated by the $\chi^2$ test, and the $I^2$ statistic was used to
assess statistical heterogeneity. Heterogeneity was significant when the $P$ value was $< 0.10$ or $I^2 > 50\%$. We used a fixed-effects model when the data were homogeneous and a random-effects model when the data were heterogeneous. We calculated pooled odds ratios (ORs) and mean differences (MDs) along with 95% confidence intervals (CIs) for outcome analyses.

## Results

### Study selection

The search results yielded a total of 441 studies ($n = 358$ from PubMed; $n = 35$ from Embase; $n = 38$ from Ovid MEDLINE; $n = 24$ from the Cochrane Library; and $n = 7$ from Clinicaltrials.gov), of which 21 were excluded as duplicates. In addition, we determined that 247 studies were not relevant to this review after screening their titles and abstracts. Finally, we included 6 RCTs [15,16,18,20,21,24] in this meta-analysis (Fig. 1).

### Study characteristics

Of the six RCTs, four were single center studies [16,20,21,24] (Table 1). Three RCTs were conducted in China [18,20,21], and one each in the US, [16] Indonesia [15], and Russia [24]. The inclusion criteria varied; three included patients with severe COVID-19 [18,21,24] and two included critical patients with ARDS. [15,16] The regimens of MSCs also varied. Overall, the number of the patients in study group treated with MSCs in addition to standard of care was 158, and the control group consisted of 135 patients (Table 2). The risk of bias in each study is shown in Fig. 2. Two studies [20,21] had high risk of performance bias. Unknown risk of detection and selection bias was found for three [16,20,21] and two studies [18,21], respectively.

### Primary outcome

Pooled analysis of the six RCTs [15,16,18,20,21,24] showed that the 28-day mortality rates were 7.6% (12/158) and 21.5% (29/135) in the study and control groups, respectively. Overall, the patients who received MSCs had a significantly lower 28-day mortality rate than the controls (OR, 0.18; 95% CI, 0.06–0.52; $I^2 = 0\%$, Fig. 3). The results remained unchanged when the random-effects model was used (OR, 0.18; 95% CI, 0.06–0.50; $I^2 = 0\%$). The results also remained consistent in the leave-one-out sensitivity test by excluding one study from each analysis. Furthermore, the MSC group was associated with a lower mortality rate than the control group in the subgroup analysis of patients with critical COVID-19 (OR, 0.16; 95% CI, 0.05–0.53; $I^2 = 0\%$). The subgroup analysis of patients with severe COVID-19 also showed that the study group had a lower mortality rate than the control group, however the difference did not reach statistical significance (OR, 0.24; 95% CI, 0.03–2.09; $I^2 = 0\%$). In pooled analysis of five RCTs [15,16,18,21,24] that reported 14-day mortality, the study group had a lower 14-day mortality rate than the control group (8.5% [11/129] vs 21.7% [23/106]; OR, 0.24; 95% CI, 0.08–0.74; $I^2 = 0\%$).

### Secondary outcomes

In analysis of the five RCTs [15,16,20,21,24] that reported clinical improvement, the study group was associated with a significantly higher clinical improvement rate than the control group (OR, 2.72; 95% CI, 2.31–8.32; $I^2 = 0\%$), Fig. 4). In pooled analysis of the two RCTs [20,21] that had available data on the time to clinical improvement, the study group was associated with a faster time to recovery than the control group (MD, −4.02 days; 95% CI, −6.42 to −1.63; $I^2 = 0\%$). In addition, the study group was associated with a shorter length of hospital stay than the control
In this meta-analysis, we reviewed six RCTs [15,16,18-21] that had available data on the need for MV. None of the three RCTs [18,21] that had available data on the need for MV, none of the 96 patients in the control group needed MV. However, the difference did not reach statistical significance (OR: 0.21; 95% CI: 0.12–1.79; p = 0.6). Finally, the statistical significance (OR: 0.21; 95% CI: 0.09–0.18; p = 0.59) was associated with a similar risk of AEs and serious AEs to the control group (AEs: OR, 0.33; 95% CI: 0.03–0.89; p = 0.32; serious AEs: OR, 0.30; 95% CI: 0.02–4.41; p = 0.53; Fig. 5).

### Table 2

| Study                  | Inclusion criteria                                                                 | No of patients | Mean or median age of patients | Male (%) |
|------------------------|-------------------------------------------------------------------------------------|----------------|-------------------------------|---------|
| Dileo et al., 2021 [15]| Respiratory failure with ARDS, shock, multiorgan failure and monitored in ICU        | 20             | NA                            | 75      |
| Lanzoni et al., 2021 [16]| Peripheral oxygen saturation ≤ 94% on room air or requiring supplemental oxygen; PaO2/FiO2 ratio ≤ 300 mg; bilateral infiltrations on chest radiograph or bilateral ground glass opacities on CT | 12             | 58.6                          | 41.7    |
| Shi et al., 2021 [18]  | CT confirmed pneumonia combined with lung damage and any of the following: (1) respiratory rate ≥ 30; (2) oxygen saturation ≤ 93%; PaO2/FiO2 ratio ≤ 300 mg; (3) bilateral infiltrations on chest radiograph; (4) bilateral ground glass opacities on CT | 65             | 60.7                          | 56.9    |
| Shu et al., 2020 [21]  | CT indicated pneumonia and any of the following: (1) respiratory rate ≥ 30; (2) oxygen saturation ≤ 93%; PaO2/FiO2 ratio ≤ 300 mg | 12             | 61.0                          | 58.5    |
| Zhu et al., 2021 [20]  | Severe or critically severe COVID-19                                                | 29             | 64                            | 41.4    |
| NCT0491240, 2020 [24] | Pneumonia requiring hospitalization, oxygen saturation of < 94% indoors or a need for auxiliary oxygen, the confirmed volume of lung damage of 30–80% by CT | 20             | 50.2                          | 30      |

ARDS, acute respiratory distress syndrome; CT, computed tomography; ICU, intensive care unit; PaO2, arterial oxygen partial pressure; FiO2, fraction of inspired oxygen.
groups. These findings regarding the benefits of MSC treatment for patients with COVID-19 are consistent with those of recent observational studies [25,26]. One small series of five patients showed that MSC infusion could help improve the pulmonary function and overall outcome of patients with COVID-19 and ARDS [25]. In addition, another series of seven patients with COVID-19 pneumonia showed that MSC treatment could cure or significantly improve lung function without observed AEs [26]. Moreover, our findings were consistent with previous meta-analyses, which based on the analyses of RCT and non-RCTs [27–29]. In contrast, our findings were based on the analyses of only RCTs, and could provide more solid evidence than previous meta-analyses [27–29]. Finally, we found that MSCs was associated with the similar risk of any AE or serious AE to the comparator, and these findings were consistent with previous studies [25–29]. Thus, MSC treatment is a safe therapeutic option for patients with COVID-19. Taken together, these findings indicate that MSC treatment may positively impact the clinical outcomes of patients with COVID-19, and suggest a potential clinical role for MSC treatment.

Although this study cannot provide plausible mechanisms, several studies have demonstrated the anti-inflammatory activity of MSCs when treating patients with COVID-19 [15,16,20,21]. Shu et al. showed that C-reactive protein (CRP) and IL-6 levels were significantly lower after infusion of MSCs, and that the time for the lymphocyte count to return to normal range was significantly faster in the MSC group than in the control group [21]. Zhu et al. also demonstrated that MSC infusion could reduce the levels of CRP, proinflammatory cytokines, and neutrophil extracellular traps, and promote the maintenance of SARS-CoV-2-specific antibodies [20]. Moreover, Lanzoni et al. observed significant differences between MSC and control groups in the concentrations of GM-CSF, IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF-β, PDGF-BB, and RANTES after treatment [16]. Taken together, these anti-inflammatory activities of MSCs may explain the improved clinical outcomes of patients with COVID-19.

This study has several limitations. First, the number of study patients was small; hence, some differences between the study group and control group did not reach statistical significance. Additional large-scale RCTs are required to validate our findings.
Second, we observed some differences in the study subjects and MSC regimens among the included RCTs. However, most of the outcome analyses in this study demonstrated low heterogeneity, which may minimize the confounding effect of heterogeneity. Finally, two [20,21] of included five RCTs carried the high risk of performance bias, so our findings should be interpreted with caution.

Conclusions

This meta-analysis found that MSCs may help improve the clinical outcomes of patients with COVID-19, and suggest its potential clinical role. However, further large-scale research is required to validate our findings.

Ethical approval

Not required.

CRediT authorship contribution statement

Ching-Yi Chen, Chih-Cheng Lai: Conception, Drafting and writing. Ching-Yi Chen, Wang-Chun Chen, Chih-Cheng Lai: Study design. Ching-Yi Chen, Wang-Chun Chen, Chi-Kuei Hsu, Chih-Cheng Lai: Analysis and interpretation. Chih-Cheng Lai: Substantially revised and critically reviewed.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

This paper did not receive any funding. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

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Consent for publication

Not Applicable.

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