

Stem Cell-Based Interventions for COVID-19: A Systematic Evaluation

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Abstract

Introduction: Developing efficient treatment plans is now essential because of the similarly destructive COVID-19 pandemic. Several individuals are interested in the possible immunomodulatory and regeneration properties of mesenchymal stem cell (MSC) therapy to treat COVID-19 patients. This systematic review introduces the key aspects of using MSCs as therapeutic agents and evaluates the safety and efficacy of using MSC for COVID-19 treatment.

Methods: To find pertinent research published between January 2020 and January 2023, a comprehensive search of primary databases, including PubMed and Scopus, was carried out. The methodological quality of prospective trials was thoroughly evaluated, and details on effectiveness outcomes (such as clinical improvement and death rates) and safety results (such as adverse events) were gathered. Moreover, on the clinical trial registration database, we also searched for details on registered stem cell therapies regarding COVID-19 patient treatment.

Results: The preliminary results reveal that MSC treatment shows potential as a therapeutic remedy for severe COVID-19 patients, with great tolerability profiles as well as positive clinical results.

Discussion: Though more efficient randomized controlled clinical studies are required to determine the best guideline for this stem cell therapy, when to administer them, and the long-term consequences of MSC therapy in COVID-19 management, but preliminary results support the beneficial influence of the treatment.

Keywords: Mesenchymal stem cells, COVID-19, Clinical Trials, Stem cell therapy

Introduction

During the month of December 2019, the coronavirus disease 2019 (COVID-19) was reported for the first time in China. Since then, it has quickly spread to other regions of the world, becoming

among the most pressing global public health concerns at the present time (1). The virus causes many infections and the mortality rate due to affecting various aspects of human life (2,3). Coronaviruses are a group of RNA viruses that have

high recombination and mutagenic potential and are highly compatible with their host due to these key features (4). The coronavirus is spherical in shape and has an envelope that is thicker than the membranes of other biological cells (5). Previous evidence suggests that the virus binds to the surface of cells that express the angiotensin-converting enzyme two (ACE-2) receptor through its spike glycoprotein once it passes in the body. A cytokine storm caused by an inflammatory response causes acute respiratory syndrome (6,7). So far, various therapy strategies, such as the use of corticosteroids recommended by the World Health Organization, some antibiotics, as well as widespread vaccination, however, have not shown efficacy in completely governing the disease(8). Due to their capacity to separate from numerous resources, such as bone marrow, adipose tissue, and dental pulp, MSCs are an essential class of multipotent stem cells that, in the past few years, have drawn more and more attention for their ability to differentiate into a variety of tissues and self-renew. One way to characterize mesenchymal stem cells after isolation is to confirm the expression of some CD markers such as CD₄₄ and CD₁₀₅ by immunohistochemistry techniques (9,10). From a clinical point of view, various studies have mentioned the important functions of MSCs, including the fact that these cells are involved in hematopoiesis and can play a role in decreasing inflammation by fast immigration to areas where there is inflammation (10). These cells also have low immunogenicity because some markers, such as CD₈₀, do not express and have high safety (11). MSCs modulate the immune system, which leads to their high application in cell therapy. The immune system is modulated by MSCs in a variety of ways. These processes include the inhibition of natural killer cells through the restriction of interleukin 2, the regulation of B cells via the suppression of cell

proliferation, and the production of regulatory T cells. One of the important factors that can play a role in promoting the modulation of the immune system by MSCs is growth factors such as TGF- β , which causes the production of prostaglandin type E (PGE-2), and also HGF(12,13). The use of MSCs for the management of Covid 19 was recently approved by regulatory organizations because it has helped to renovate the function of the respiratory system through the effect on cells and also has shown more established therapeutic effects in the body, therefore they are one of the important candidates in the treatment of Covid 19 disease (14). This work aimed to assess the security and efficacy of MSCs after first determining how they affected COVID-19 patients' clinical and paraclinical symptoms.

Materials and Methods

Literature Search

The systematic review was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15). The proper registration of the review protocol on PROSPERO was completed with the registration number CRD42021293566. We investigated publications published from January 2020 until January 2023 and indexed in the PubMed and Scopus databases. Following is a list of the search phrases that were employed:

#1 Coronavirus disease, #2 Novel coronavirus, #3 nCoV, #4 Acute respiratory syndrome coronavirus 2, #5 SARS-CoV-2, #6 COVID19, #7 COVID-19, #8 2019-nCoV, #9 Cell therapy, #10 Cell-based therapy, #11 Stem cells, #12 SC, #13 Mesenchymal stem cells, #14 Mesenchymal stromal cells, #15 MSCs, #16 Randomised controlled trial, #17 Controlled clinical trial, #18 Randoed*, #19 Randomly*, #20 Trials, #21 Clinical Trial, #22 Case

series, #23 CCT, #24 RCT, #25 Case report #26 OR/ (OR/#1–#8) AND (OR/#9–#15)–#25, Brief formula of search: (OR / #1– #8) AND # (OR/ #9– #15) AND #OR / (OR/ #1– #8) AND (OR/ #9– #15)– #26.

Eligibility criteria

Randomized controlled trials (RCTs), controlled clinical trials (CCTs), retrospective studies, case reports, letters (with good data), and case series assessing the impact of MSCs in COVID-19 patients made up our collection. All research, notwithstanding the language in which they were published, were included in this review. Examples of studies that did not disclose original data include clinical reviews, editorials, letters, and erratums. These studies were not considered for inclusion.

Study selection process

The two reviewers independently selected the studies and extracted them. Publications not meeting the eligibility requirements were not taken into consideration for inclusion in the study; the screening was done in compliance with the summary and title of the publication.

Following a thorough study of the complete text, the final studies were chosen. It was the responsibility of the corresponding author to get in touch with studies whose complete texts were not accessible. Eventually, a third reviewer looked over the research that had been conducted (Fig. 1).

Data extraction and management

Two experts will independently gather the data required from inclusion criteria employing a predetermined data acquisition form. The information includes reference ID, author details, publication period, research category, sampling methods, type of intervention, source of stem cell participant charac-

teristics (such as age, number of participants, gender, severity of disease, laboratory tests, CT scans, etc.), MSC treatment groups, and control groups (including details of randomization, blinding, allocation, intervention approach, etc.). An additional reviewer will be engaged to resolve any discrepancies among the notes provided by the two initial reviewers. Prior to being transferred to the RevMan software, each piece of data will undergo thorough verification (V.5.1).

Study quality assessment.

Examiners A and B, who are autonomous, carried out the quality assessments. A senior examiner (C) participated in the decision-making process when there were differences in the prejudice evaluation results. The updated Cochrane risk-of-bias (RoB) tool and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) assessment were used in this study to assess the possibility of bias. The quality of randomized interventional studies, including and without blinding, was evaluated using the RoB tool. The ROBINS-I device used the labels "low," "moderate," and "severe" to categorize the risk of the examined research. The Cochrane Risk of Bias Evaluation Instrument will be employed by two reviewers to assess the probability of prejudice in publication in every study included in the review, spanning eight fields: randomization a series generation, randomization allocation concealment, participant blinding, personnel blinding, outcome assessor blinding, unfinished results, selective stating bias, and other bias. Each domain's risk of bias will be evaluated and classified as high, unresolved, or minimal. Reviewers are going to get in touch with the contributing authors of the original work when there are questions about a domain. Discrepancies will be handled by engaging in dialogue with another re-

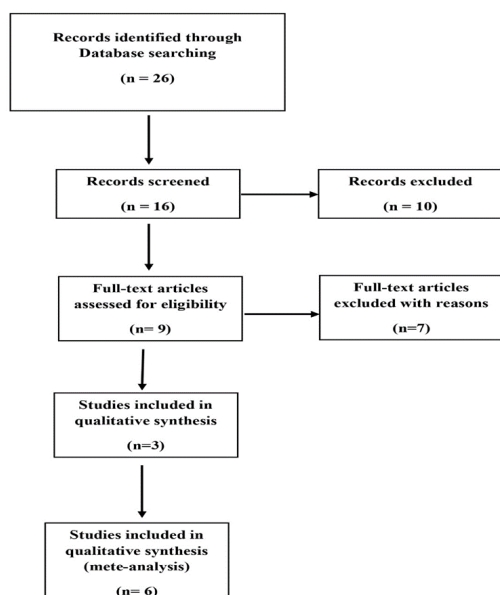


Fig. 1. A flowchart depicting the process of searching for, reviewing, and identifying the studies that were examined using the systematic review.

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Results

Literature search

Twenty articles were found during the initial search of the complete electronic database. Using the citation manager tool Zotero 5.0 to check for duplicated articles, 16 articles were confirmed to be unique. We evaluated publications based on their titles and abstracts, and only nine articles were suitable. Two studies were excluded from the meta-analysis due to their lack of standards (comparators) and failure to produce data that

aligned with the predetermined outcomes for this study.

Study characteristics

The study comprised six interventional studies involving a combined number of 136 participants. Randomization was only used in one out of the six investigations. Shu et al. used a dosage of 2×10^6 cells per kilogram of MSC therapy, whereas Xu et al. and Adas et al. used a dosage of 3×10^6 cells per kilogram of body weight cells. Sadeghi et al. delivered a dose of 1×10^6 cells per kilogram of body weight. Saleh and his colleagues administered 150 million cells with every injection. Other experiments did not clearly specify the dose of MSCs administered. The research excluded pediatric subjects. The mean age of the study subjects exceeded 40 years.

Bias-risk assessment

By employing the RoB and ROBINS-I tools to evaluate bias, it was ascertained that each study that made up the analysis had a level of quality ranging from medium to excellent (Fig. 2). The studies carried out by Singh et al., Saleh et al., and Xu et al. were classified as moderately quality since the group feature assessment did not show any significant differences. This could lead to the introduction of a confounding bias. Furthermore, Shu et al.'s study did not implement blinding, which led to competence prejudice, recognition bias, and dropout bias.

Clinical Aspects of MSC Therapy in COVID-19 Patients

We analyzed the clinical findings for CRP, IL-6, and oxygenation index (Fig 3-5). Moreover, we reviewed mortality, serious adverse events, and Ventilation in the test population which we will

discuss in the following. Results of our search in www.clinicaltrial.gov and www.who.int/clinical-trials-registry-platform have also been demonstrated in Fig. 6.

Mortality

Mortality was reported in five studies. Among these five studies, two comparative studies were performed between the control and treatment groups. Which showed a reduction in mortality in the MSC treatment group.

Serious adverse events

The security of a product may be determined by the variables of adverse events. After MSC delivery, or after a placebo or MSC carrier (without MSC), complications included urticaria, pulsations, or pulmonary edema (within six hours) and/or cardiac arrest (within 24 hours).

Meng et al. noted that two MSC recipients experienced a brief face flush and fever right away after injection, which went away on their own after four hours; another moderately unwell patient experienced a brief fever within two hours, which went away after 24 hours (16). Another case described by Lanzoni et al. was of an individual whose bradycardia got worse after receiving an injection and needed temporary vasopressin therapy (17).

Ventilation

Ventilation as one of the important parameters in the field of studies related to Covid-19 has always been special importance, which has been investigated in two invasive and non-invasive manners according to the phase of the disease. Many studies have documented ventilation as an inclusion

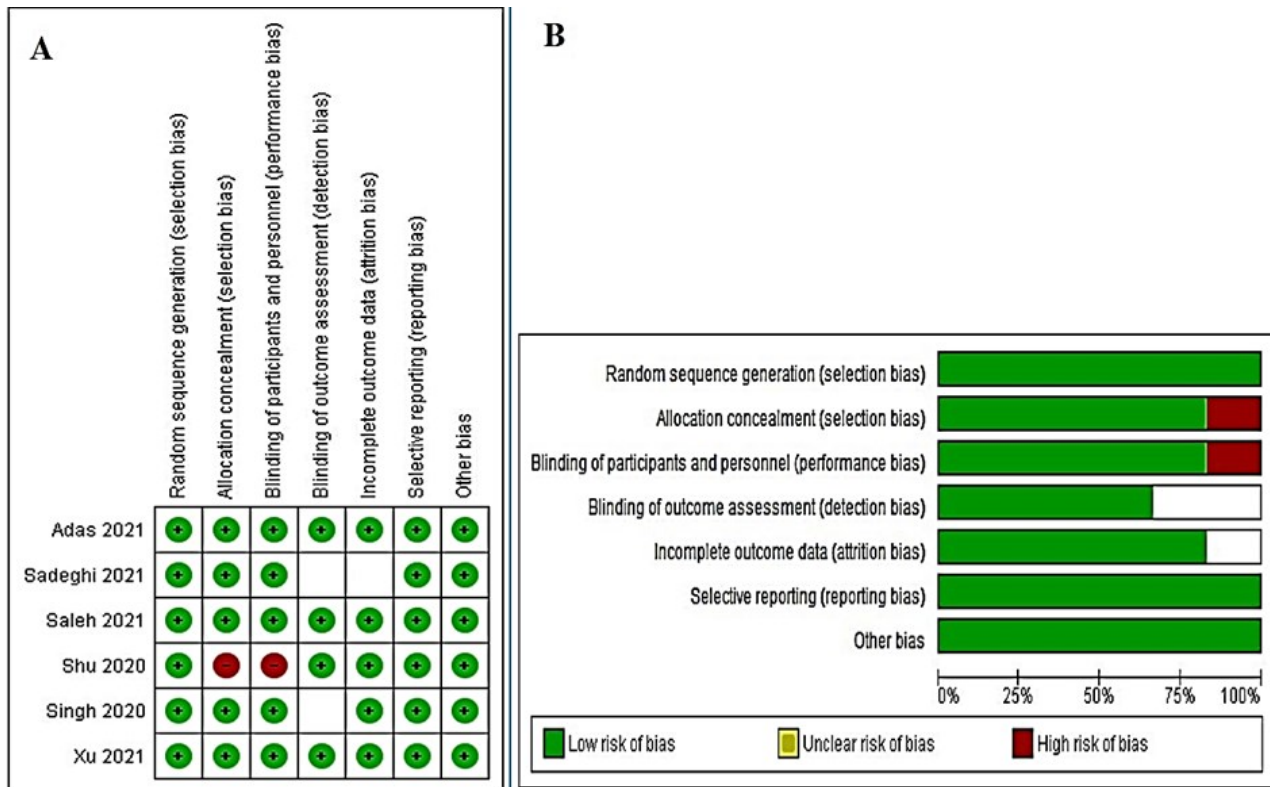


Figure 2. **A:** displays a summary of the risk of bias, indicating the review writers' evaluations of each risk of bias factor for every investigation contained in the review. **B:** The risk of bias graph shows the proportions of each risk of bias element for each study that made up the research, as determined by the review's writers.

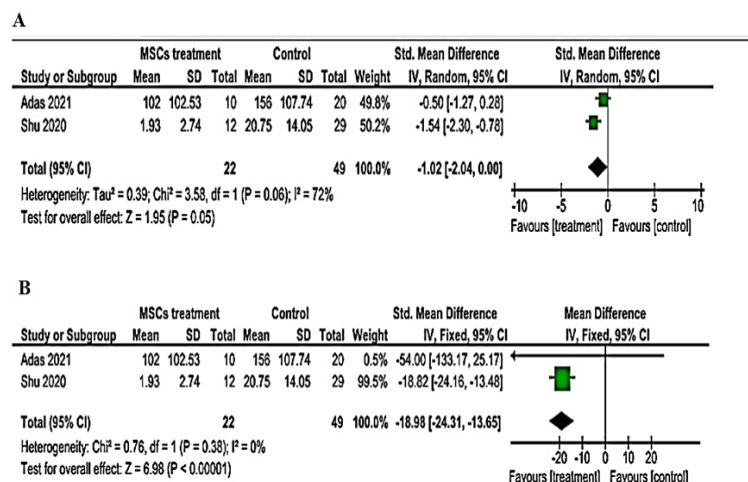


Fig. 3. **A:** The forest plot shows CRP in participants with MSC medication with CONTROL - 1.02 [95% CI: -2.04, 0.00] (std) (Forest plot of comparison: MSC therapy and control of COVID-19 patients, outcome: CRP). **B:** The forest plot indicates CRP in individuals receiving MSC treatment with CONTROL -1.02 [95% CI: -2.04, 0.00] (mean).

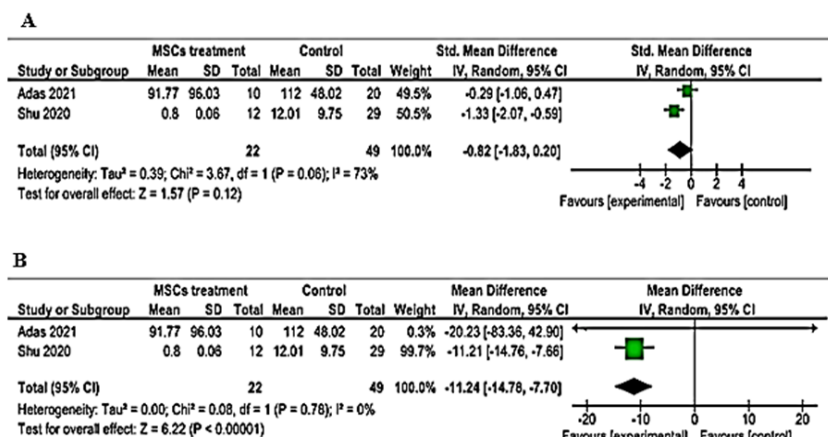


Fig. 4. **A:** The forest plot displays IL-6 in CONTROL-treated individuals receiving MSC treatment -0.82 [95% CI: -1.83, 0.20] (std) OR Forest plot of comparison: MSCs therapy and control of covid-19 patients, outcome: IL-6. **B:** The forest plot displays IL-6 in CONTROL-treated patients receiving MSC treatment -0.82 [95% CI: -1.83, 0.20]

(mean)

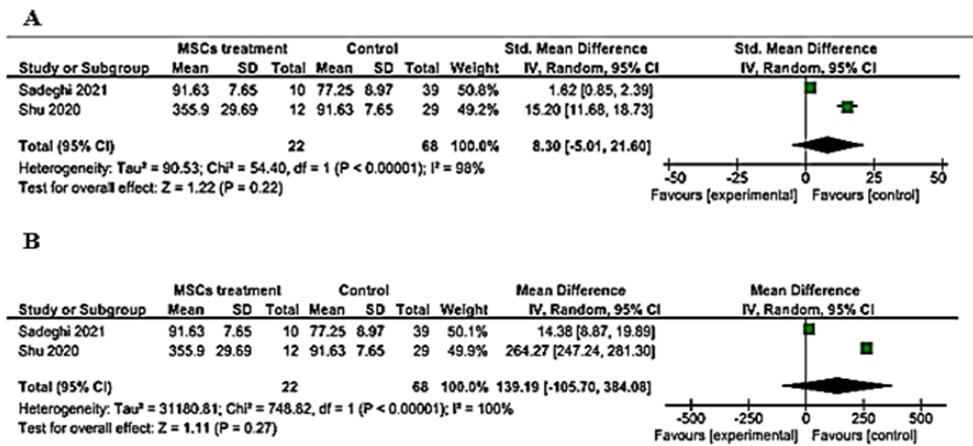


Fig. 5. A: The forest plot shows oxygenation index in patients with MSC therapy with CONTROL 8.30 [95% CI: -5.01, 21.60] (std) OR Forest plot of comparison: MSCs therapy and control of covid-19 patients, outcome: oxygenation index. **B:** The forest plot shows oxygenation index in patients with MSC therapy with CONTROL 8.30 [95% CI: -5.01, 21.60] (mean)

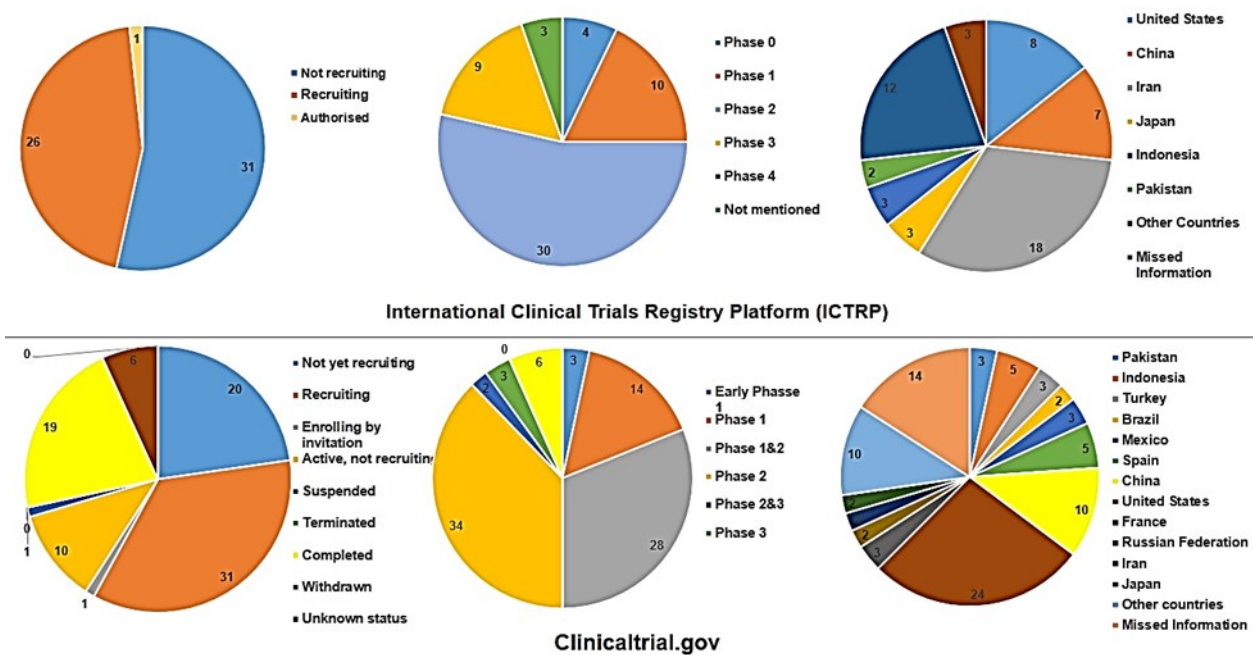


Fig. 6. A brief overview of the COVID-19 therapy cell-based clinical trials registered on www.clinicaltrial.gov and www.who.int/clinical-trials-registry-platform.

criterion and as a treatment for seriously ill individuals brought to the intensive care unit for treatment. Nevertheless, the use of MSCs as a new therapeutic tool has been noticed and various studies have shown that the injection of MSCs to patients significantly reduces the need of patients for this treatment method and increases the rate of recovery of patients.

Stem cell sources

Pre-natal sources

Umbilical cord tissue

One vein and two arteries, backed up by connective tissue known as Wharton's jelly (WJ), make up the umbilical cord (UC), a newborn tissue.

Rich in easily expandable and accessible MSCs, WJ is also extensively employed for MSC gathering. Furthermore, out of all the allogenic tissues, WJ has the greatest MSC content per milliliter. Generally multipotent, MSCs from WJ release more growth factors (GFs), anti-inflammatory cytokines (CKs), and extracellular vesicles (EVs) that include exosomes than from other donors. As it is evident, the UC and the WJ inside it can be acquired without requiring an individual to have an intrusive operation, as can opposing supplies like bone marrow (BM), dental pulp (DP), and adipose tissue (AT). Infusion of allogeneic UC-MSC has been shown to be safe in a wide range of conditions. Low quantities of class I and class II human leukocyte antigen (HLA) are represented by them, which could reduce alloreactivity (18).

It was shown that the present MSCs had important moderators of activated T cells, which explains their remarkable capacity for immunosuppression and regulation of the intrinsic and adoptive immune responses. Due to all the previously mentioned qualities, the UC and/or WJ may thus be an ideal allogenic repository of MSCs for the medical management of COVID-19 individuals (19). A double-blind phase 1/2a randomized controlled trial (RCT) including twenty-four participants with COVID-19-associated acute respiratory distress syndrome (ARDS) in the USA was conducted by Lanzoni et al. The patients received two intravenous injections of UC-derived MSCs.

This RCT had as its major goal assessing both the safety and effectiveness of UC-MSCs in treating COVID-19 patients (ClinicalTrials.gov identifier: NCT04355728) (20). A 1:1 randomization was used to assign the subjects—12 for the UC-MSC therapy and 12 for the control group. Participants in the UC-MSC treatment group received a pair of

intravenous treatments on days 0 and 3 of $100 \pm 20 \times 10^6$ UC-MSCs, whereas controls received two injections of diluent solution. Patient longevity at 31 days following the initial injection and recovery time showed no difference between groups in terms of infusion-associated adverse events (AEs). Furthermore, UC-MSC infusions for individuals with COVID-19-associated ARDS were shown to be effective, as no major adverse events were linked to the infusion. Reduction in inflammatory components linked to the COVID-19 "cytokine storm," including cytokines, RANTES chemokines, and IFN- γ , IL-6, and TNF- α , is one of the main characteristics of the response in the UC-MSC therapy groups. In this research, by day six, the inflammatory cytokines were noticeably reduced in the UC-MSC-treated patients. In addition, there was a decrease in PDGF-BB and GM-CSF, the stimulators of the proinflammatory M1 macrophage phenotype. As a result, UC-MSC treatment was linked to a significant decrease in death rates, SAEs, and recovery time compared to the control (20). Eighteen individuals suffering from moderate to severe COVID-19 had been included and split into two groups in another RCT phase I (NCT 04252118) carried out by Meng et al. in China (21). On days 0 through 6, the nine participants in the therapy group had three rounds of intravenous injections of UC-MSCs (3×10^7 cells). Though no major side effects from UC-MSCs were documented, two patients in the therapy group experienced brief face flushing and fever, and one patient experienced brief hypoxia 12 hours after UC-MSC transfusion, which cleared on its own within 24 hours. Although four patients in the untreated group needed ventilation, one patient in the therapy group had mechanical ventilation. Remarkably, after obtaining UC-MSCs, the patient with the greatest IL-6 level across the four patients with severe illness

demonstrated the most decrease in the IL-6 level and improvement of the oxygenation index. As this milieu might enhance the immunomodulatory impacts of MSCs, UC-MSCs may consequently be the most advantageous for those with elevated levels of inflammatory cytokines. Remarkably, TNF- α , IFN- γ , IL-1, IL18, IL-8, and IL-6 receptor levels were decreased in patients receiving UC-MSCs after 14 days of administration. A phase II clinical trial (NCT0428802) was suggested and will be conducted to assess the effectiveness, lower fatalities, and enhance long-term therapeutic outcomes as infusion of UC-MSCs is safe and tolerated in patients with COVID-19, together with indications of prospective efficiency (21). An additional investigation by Shu et al. in China demonstrated that intravenous hUC-MSC donation is a secure and efficient method that can be regarded as a lifesaver and the primary therapy choice for acute COVID-19. In three days after hUC-MSC infusion, IL-6 and CRP levels were considerably observed to be lower, as in previous studies. The hUC-MSC therapy group therefore had a quicker time to therapeutic improvement than the control group (22). In a phase 1 experiment conducted in Iran, Hashemian et al. also published the outcomes of intravenous injection of a large dose of placental MSCs (PL-MSCs) and UC-MSCs. Patients with acute hypoxemia who needed mechanical ventilation got three intravenous infusions (200×10^6 cells) each day, totaling 600×10^6 UC-MSCs or PL-MSCs. Seven individuals had decreased dyspnea and higher SpO₂ three days following the initial injection. Out of these seven individuals, five were released from the intensive care unit within two to seven days; one patient with severe hepatic and renal failure was released on day 18, and the final patient unexpectedly experienced cardiac arrest on day seven following the cell infusions. Five individuals

passed away 4–19 days following the initial cell injection. Six survivors showed substantial drops in TNF- α , IFN- γ , IL-8, IL-6, and CRP levels. The results of this phase 1 experiment imply that while all six patients were healthy on day 60 following infusion and had no complaints of dyspnea, patients with sepsis or multi-organ failure might not be suitable choices for stem cell therapy (22). They have also proposed that, in order to identify the precise therapeutic possibilities of MSC in COVID-19-induced ARDS, massive randomized multicenter clinical trials are necessary. In this sense, a number of case report investigations have been conducted, and the findings showed the therapeutic outcome and good tolerability of allogenic UC/WJ-derived MSCs transfer. No major adverse events were linked to the MSC injection (23). Table 1 indicated the studies utilizing MSCs for COVID-19 treatment.

Adult-derived stem cells

Menstrual blood-derived stem cells (MenSCs)

Ever since their announcement in 2007, MenSCs have drawn increasing interest as a new resource for MSCs. MenSCs offer an appropriate substitute resource for investigation and use in regenerative medicine because they exhibit some special features of recognized adult-derived stem cells and have no ethical dilemma (24). Without any other supplies of MSCs, these cells exhibit outstanding proliferation, amazing adaptability, and recurrent recruitment in a non-invasive way.

Moreover, the practical properties and medicinal potential of MenSCs were reported in a number of disorders, such as diabetes, stroke, liver disease, Duchenne muscular dystrophy, myocardial infarction, ovarian-related disease, Alzheimer's disease, Asherman syndrome, endometriosis, acute lung

injury, neurodegenerative disorders, and cutaneous injury(25). Tang et al. employed MenSCs in experimental pilot research in Wuhan, China, to cure two individuals with severe COVID-19 (26). The 37-year-old woman in the first instance had dyspnea for four days and a fever for nine days. Even while the patient received complementary therapies throughout hospitalization, including oseltamivir, blood pressure reduction, and arbidol hydrochloride, fever and dyspnea were strikingly noticeable. Three times, on February 5, 6, and 8, 2020, the patient had intravenous injections of MenSCs. In the second case, a man 71 years old had a fever for 20 days and cough and dyspnea for 4 days. He was treated in the hospital with ribavirin, arbidol hydrochloride, cefoperazone-sulbactam, blood pressure reduction, and other symptomatic supporting therapies, much as in the first episode. Concurrently, the patient had three intravenous injections of MenSCs on February 8, 9, and 11, 2020. Several restrictions exist in this medical experiment. For instance, the sample size is insufficient; just two patients got MSC therapy, and the inflammatory cytokines following the third intravenous injection were not examined (26). Lu et al. verified in a different investigation the advantages of MenSCs in the management of the first COVID-19 patient found in Hangzhou, China(27). The individual in this trial had intravenous MenSCs on hospital days 11, 12, and 14, accordingly, at 3000, 2000, and 3000 U. Over these three days, the patient's breathing got better, his chest congestion subsided, and his fever dropped to 37.4 °C. Inflammatory cytokines, including IL-6 and IL-10, dramatically decreased after the third infusion. Moreover, no untoward events were linked to the infusion, suggesting that these cells may be useful in offering a viable COVID-19 treatment (27). Though the role of MenSCs in these two studies offers a promising

approach to addressing COVID-19, more therapeutic information is needed to validate their application in future medical treatments.

Adipose tissue derived mesenchymal stromal cells (AT-MSC)

Adipose tissue (AT) has a greater ability to preserve MSC content than any other human tissue, depending on the donor's maturity. It includes adipose-derived stem cells (ADSCs), multipotent stem/stromal cells that have been extensively studied for their differentiation and proliferation capacity. The accessibility of the subcutaneous adipose tissue and its easily removed quantity make a large number of these cells possible to obtain. ADSCs can be allogeneic or autologous. Several human clinical trials have confirmed the notable anti-inflammatory effects. Better immunomodulatory actors without MHC class II were found in these cells, which has opened the door to allogenic medicinal studies (28). These properties have highlighted the application of ADSC as a successful approach to the management of COVID-19 patients. For example, Sanchez-Guijo et al. in Spain were able to conclude that giving these individuals AT-MSC is both healthy and possibly beneficial (29). Intravenous allogeneic AT-MSC therapy was administered to thirteen patients who were on intensive mechanical ventilation and had already undergone antiviral and/or anti-inflammatory medication. Of the patients, ten got two doses, two got one, and just one got three. The first injection of AT-MSC was given around seven days after mechanical ventilation. There were no unfavorable effects from the cell treatment. Nine patients (70% of them) showed improvement sixteen days following the first dose. Four patients were kept on intubation, two passed away, and seven patients were released from the intensive care unit.

Like in earlier research, patients who recovered showed lower levels of inflammatory markers such as IL-6, CRP, LDH ferritin, and D-dimer. Still, there was a rise in lymphocytes, especially in the individuals who showed clinical enhancement. These findings demonstrating the absence of negative effects from intravenous AT-MSC infusion may be linked to clinical and biological improvement in certain patients who need mechanical ventilation. Moreover, a phase 2 randomized controlled trial is currently in progress, according to the findings of this work (29). Two clinical trials are now approved (<https://clinicaltrials.gov>) to assess mesenchymal stem cells generated from adipose tissue as a medical procedure for COVID-19 patients. The current article, "Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19," highlights the findings of these trials (30).

ACE2- Mesenchymal Stem Cells

Through examination of the immune system profile following MSC transplantation, Leng et al. in Beijing YouAn Hospital, China, found that MSCs were ACE2- and TMPRSS2-positive, indicating these cells are without COVID-19 contamination (7). Ten seriously ill patients were included as participants; three were placebo controls, and seven were SARS-CoV-2 positive and receiving MSC transplants. All of the patients suffered from pneumonia, dyspnea, low oxygen saturation, and elevated temperatures prior to the MSC infusion. Every one of the seven patients received intravenous clinical-grade human MSCs. The pulmonary performance and every symptom the patients had prior to the infusion improved without any side effects two to four days after MSC treatment. Peripheral lymphocytes grew, CRP dropped, and excessively stimulated cytokine-secreting immune cells

(CXCR3+ CD4+ T cells, CXCR3+ CD8+ T cells, CXCR3+ NK cells, and TNF- α) disappeared or declined three to six days after donation. Still, IL-10 and regulatory DC were higher than in the placebo control group. Peripheral blood CyTOF (mass cytometric) analysis demonstrated that, following the transplant, peripheral lymphocytes increased and shifted towards the regulatory phenotype for both CD4+ T cells and dendritic cells. Actually, upon transplantation, the patients with severe symptoms had higher numbers of regulatory T cells and dendritic cells. Moreover, none of the three severe control patients who received enrollment for placebo treatment showed any appreciable increase in CXCR3-dendritic cells. In addition, the gene expression of the MSCs indicated that MSCs, being ACE2 and TMPRSS2, were a safe and efficient COVID-19 medication (7).

Mesenchymal Stem Cells derived exosomes:

Small nanovesicles ranging in size from 30 to 150 nm, exosomes are released by several cell types and identified by their function in cell communication. Proteins and microRNAs are only two examples of the biological molecules that these exosomes can move. The originating cell from which exosomes are released determines their composition. Exosomes bind with the target cell thanks to the presence of adhesion molecules on their surface. By enclosing and transferring active biomolecules like proteins, peptides, and RNA species to the sick tissues and cells, exosomes generated from MSCs exhibit biological operations comparable to those of these cells (31). Furthermore, there are a few benefits to using MSC-derived exosomes as cell-free therapeutics as opposed to their biological equivalents, including less immunogenicity, superior stability, and simplicity in maintenance. Exosomes are an excellent carrier for drug

special characteristics, which include the possibility of off-the-shelf accessibility, bilipid membrane structure, and biocompatibility (32). These fascinating characteristics of exosomes have therefore generated a strong interest in evaluating their possible application as a medicinal and pharmacological treatment in the current COVID-19 pandemic. A multitargeted, new, next-generation biologic substance, bone marrow-derived exosomes, are an intricate mixture of signaling nanovesicles released by BM-MSCs that may be the key to changing the inhibition of host antiviral barriers and to downregulating the cytokine storm that describes COVID-19. Bone marrow-derived exosomes have been shown to have helpful advantages in animal models of ARDS, lung injury, asthma, and other inflammatory diseases. Analysis has shown reduced alveolar inflammation, increased edema clearance, restoration of leaky epithelial membranes, and other cytokine storm outcomes (22–24). In this regard, Sengupta et al. in the USA presented an upcoming nonrandomized open-label cohort study to assess the feasibility and safety of exosomes (ExoFloTM) produced from allogeneic BM-MSCs as a therapy for acute COVID-19. The bmMSC-derived exosome drug ExoFloTM was given intravenously to 24 medically deteriorating SARS-CoV-2-linked ARDS patients. Efficacy and safety were evaluated in patients from days 1 to 14 following a single (15 mL) infusion. Twenty individuals in the present trial lived, and no adverse effects were noted within the 72 hours after ExoFloTM delivery. The oxygenation and clinical condition of the patients improved after the first injection. The average level of CD3+, CD4+, and CD8+ lymphocytes increased while the degree of neutrophils, CRP, ferritin, and D-dimer decreased, as shown by laboratory values. In conclusion, RCTs are needed to assess ExoFloTM's therapeutic potential, even though it is a prom-

ising treatment option for severe COVID-19 since it can restore oxygenation, reduce cytokine storms, and restore the immune system (16).

Conclusion

The safety and effectiveness of MSC therapy for COVID-19 treatment, particularly in acute form, are thoroughly assessed in this systematic review. Based on the synthesised data, MSC treatment shows promising safety profiles and positive medical results as a possible therapeutic strategy for COVID-19 patients. The requirement for cautious assessment is nevertheless highlighted by the heterogeneity between the selected studies and the limits of the existing data. The best utilization of MSC therapy in COVID-19 management must be clarified by more excellent randomized controlled trials with bigger sample sizes, consistent methodologies, and longer monitoring times. To maximize patient choice and therapeutic results, future studies should also concentrate on investigating the processes of action underlying MSC therapy and discovering possible predictors of treatment success. Notwithstanding the present drawbacks, MSC therapy is a prospective approach to creating efficient treatments for severe COVID-19 and should be further investigated in properly planned clinical trial research.

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Conflict of interest

Authors claim to have no conflicting interests.

Table 1. Clinical trials of MSCs in COVID-19 management

Source of MSCs	Study details	Type of cells	Delivery approaches	Country	Results	Ref
Umbilical cord	(RCT) double-blind, phase 1/2a; 24	Allogenic	2doses of $10^6 \times 20 \pm 100$ cells, IV administration	USA	No unfavorable actions, lowering GM-CSF, TNF- α , IL-6, and IFN- γ	[33]
Umbilical cord	RCT phase 1; 18	Allogenic	3doses of $10^7 \times 3$ cells, IV administration	China	No negative effects, lowering IL-6, IL-1, TNF- α , and IFN- γ	[21]
Umbilical cord	RCT; 41	Allogenic	3doses of $10^6 \times 2$ cells/kg, IV administration	China	No adversative effects, reducing CRP and IL-6	[17]
Umbilical cord and placental	RCT phase 1; 11	Allogenic	3doses of $10^6 \times 200$ cells, IV administration	Iran	No serious adverse events, falling TNF- α , IFN- γ , IL-8, IL-6, and CRP	[34]
Umbilical cord	RCT phase 2; 101	Allogeneic	3doses of 4×10^7 cells, IV administration	China	No negative reactions, smaller volumes of solid element injury, higher aerobic activity.	[35]
Umbilical cord	Phase 1, multi-center, parallel armed trial; 210	Allogeneic	Single dose of $1-2 \times 10^6$ cells/kg, IV administration	Turkey	No harmful events, the higher survival rate, improved the SaO ₂ parameter, restored oxygenation, and suppressed CSS	[36]
Umbilical cord	RCT phase 2; 40	Allogeneic	Single dose of 1×10^6 cells/kg, IV administration	Indonesia	No negative happens, decreased IL-6 levels in the recovered patients	[37]
Umbilical cord	Phase 1, single-armed, open-label trial; 31	Allogeneic	Single dose of 1×10^6 cells/kg, IV administration	China	No adverse proceedings, restored oxygenation and suppressed CSS	[38]
Umbilical cord	Phase 1, open label, parallel controlled pilot trial; 10	Allogeneic	Single dose of $10^6 \times 1$ cells/kg, IV administration	China	No side effects, lower CRP and TNF- α , higher IL-10, immune cell groups returning to normal.	[7]
Umbilical cord	Pilot study; 17	Allogeneic	4doses, with a one-day interval of 10^8 cells/kg, IV administration	China	Safe therapy, two side effects linked to therapeutic advantages and modifications in immunological and inflammatory responses.	[39]

Table 1. Clinical trials of MSCs in COVID-19 management (continue)

Umbilical cord	Case report	Allogeneic	3doses of 1×10^6 cells , IV administration	China	No negative events, higher PaO ₂ and relative lymphocyte counts, lower absolute neutrophil counts and IL-6 values	[40]
Umbilical cord	Case report	Allogeneic	3doses of 5×10^7 cells, IV administration	China	No negative reactions, effectively permitted, lower CRP, relief of pneumonia.	[41]
Umbilical cord	Case report	Allogeneic	2dose of $10^7 \times 5$ cells, IV administration	Brazil	No negative effects, modification of several mediators in conjunction with peripheral blood modification, notably a decrease in inflammatory monocytes.	[42]
Umbilical cord	Case report	Allogeneic	$10^6 \times 1$ cells /kg, IV administration	China	No adverse events, the normal level of SpO ₂ ,and increasing lymphocytes	[43]
Umbilical cord	Case report	Allogeneic	2dose of 0.7×10^6 cells/kg IV administration / $10^6 \times 0.3$ cells/kg intratracheal	Turkey	No adverse events, disappearing acidosis, electrolyte imbalance , improving hypoxemia, and regressing the level of CRP	[44]
Wharton's Jelly	Phase 1, interventional, prospective, three- parallel armed trial (partial randomized) ; 30	Allogeneic	3doses of 3×10^6 cells , IV administration	Turkey	No adverse events, the lower mortality rate (30%), decrease levels of serum ferritin, fibrinogen and CRP	[45]
Wharton's Jelly	Single-armed, open-label, single-center pilot trial; 5	Allogeneic	3doses of 1.5×10^8 cells , IV administration	Iran	No adverse events, increased the levels of IL-10 and SDF-1, decreased the levels of VEGF, TGF- β , IFN- γ , IL-6, and TNF α	[46]
Wharton's Jelly	Case report	Allogeneic	$10^6 \times 1$ cells/kg, IV administration	China	No untoward occurrences, fever and dyspnea gone, and IL-6 and TNF- α levels down.	[47]
MenSCs	Pilot clinical trial; 2	Allogeneic	3dose of 1×10^6 cells /kg, IV administration	China	FiO ₂ ¹ reduced, SaO ₂ ² and PO ₂ ³ heightened, and absorbing lesions of lung exudate bilaterally	[48]

Table 1. Clinical trials of MSCs in COVID-19 management (continue)

MenSCs	Phase 1 multicenter, open-label, nonrandomized, parallel-controlled exploratory trial 44	Allogeneic	3dose of 3×10^7 cells /kg, IV administration	China	No adverse events, lower mortality rate , ameliorated dyspnea, improved SpO ₂ and chest imaging results	[26]
MenSCs	Case report	Allogeneic	3dose at 3000-2000U IV administration	China	No side effects, assessment of immunomodulation effect lowering IL-10 and IL-6 and including both non-specific and specific immunological functions of MenSCs.	[27]
AT-MSC	RCT phase 1; 13	Allogeneic	1) 3patient), 10) 2patients), and 1 (2 patients) dose of 1×10^6 cells/kg IV administration	Spain	No side effects; lowers IL-6, CRP, LDH ferritin, and D-dimer; raises lymphocytes	[29]
MSC	Case series/ retrospective study; 25	Allogeneic	3~1doses of 1×10^6 cells /kg, IV administration	China	Three cases reported increased efficacy, adverse effects from the medication, and serum values of CK-MB, cTnT, and LAC.	[49]
MSC	Case series; 14	Allogeneic	Single dose of $10^8 \times 1$ cells / kg, IV administration	USA	No adverse events, improved PaO ₂ /FiO ₂	[50]
MSC	Case series; 10	Allogeneic	Single dose of $10^6 \times 1$ cells / kg, IV administration	Brazil	Less TNF- α , less chest infiltration, more CD44 T cells and dendritic cells, anti-inflammatory genes, and nutritive components of circulation are all benefits. There are also no negative effects.	[51]

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