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REVIEW

Effectiveness of RCTs Pooling Evidence on Mesenchymal Stem Cell (MSC) Therapeutic Applications During COVID-19 Epidemic: A Systematic Review

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Background: Global pandemic identified as coronavirus disease 2019 (COVID-19) has resulted in a variety of clinical symptoms, from asymptomatic carriers to those with severe acute respiratory distress syndrome (SARS) and moderate upper respiratory tract symptoms (URTS). This systematic review aimed to determine effectiveness of stem cell (SC) applications among COVID-19 patients.

Methods: Multiple databases of PubMed, EMBASE, Science Direct, Google Scholar, Scopus, Web of Science, and Cochrane Library were used. Studies were screened, chosen, and included in this systematic review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart diagram and PRISMA checklist. Included studies' quality was assessed employing Critical Appraisal Skills Programme (CASP) quality evaluation criteria for 14 randomized controlled trials (RCTs).

Results: Fourteen RCTs were performed between the years of 2020 to 2022, respectively, with a sample size n = 574 (treatment group (n = 318); control group (n = 256)) in multiple countries of Indonesia, Iran, Brazil, Turkey, China, Florida, UK, and France. The greatest sample size reported from China among 100 COVID-19 patients, while the lowest sample of 9 COVID-19 patients from Jakarta, Indonesia, and the patient's age ranges from 18 to 69 years. Studies applied to the type of SC were "Umbilical cord MSCs, MSCs secretome, MSCs, Placenta-derived MSCs, Human immature dental pulp SC, DW-MSC infusion, Wharton Jelly-derived MSCs". The injected therapeutic dose was 1×10^6 cells/kg, 1×10^7 cells/kg, 1×10^5 cells/kg, and 1 million cells/kg as per the evidence from the different studies. Studies focused on demographic variables, clinical symptoms, laboratory tests, Comorbidities, respiratory measures, concomitant therapies, Sequential Organ Failure Assessment score, mechanical ventilation, body mass index, adverse events, inflammatory markers, and PaO_2/FiO_2 ratio were all recorded as study characteristics.

Conclusion: Clinical evidence on MSC's therapeutic applications during COVID-19 pandemic has proven to be a promising therapy for COVID-19 patient recovery with no consequences and applied as a routine treatment for challenging ailments.

Keywords: COVID-19, nCoV-19, novel coronavirus, SARS-CoV-2, severe acute respiratory distress syndrome-coronavirus-2, stem cell management, Mesenchymal stem cell applications

Introduction

The treatment (TX) of severe Coronavirus disease 2019 (COVID-19) is extremely difficult.[1] COVID-19, induced by SARS-CoV-2 infection,[2] causes significant lung damage ranging from moderate respiratory symptoms to SARS and death.[3–5] COVID-19 caused widespread fear and apprehension since it is extremely communicable.[6–8] The World Health Organization (WHO) has termed COVID-19 pneumonia a global pandemic and a public health emergency.[9] Because of a lack of clear awareness in the initial days of the epidemic, the number of infected individuals rapidly rose, quickly spreading to more and more continents.[10,11]

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Globally, the number of infected victims is growing constantly.[12] COVID-19 has an incubation period that can differ from 0 to 14 days but is commonly around 3 and 7 days.[13] Fever, headache, dry cough, and breathlessness are the most frequent symptoms.[14–16] A sore throat, diarrhea, nasal congestion, and rhinorrhea are other significant complaints among patients.[17,18] Expiratory Hypertension (HTN) and dyspnea are common in severe individuals one week following the commencement of the illness. According to a biopsy and autopsy investigation, individuals in the most severe instances might have Acute Respiratory Distress Syndrome (ARDS), severe acute lung damage (LD), septic shock, metabolic acidosis, and coagulopathy.[5]

The leading causes of mortality include severe pneumonia, ARDS, pulmonary edema, or multiple organ failure.[4] ARDS is a severe lung injury characterized by an uncontrolled inflammatory process that creates significant alveolar destruction and capillary basement membrane leaking, leading to progressive respiratory distress. There is currently no effective TX for ARDS; however, a variety of TXs, including cell-based therapies, have been proposed.[19,20] Successful repair and regeneration of endothelium and alveolar cells[21] and regulation of excessive inflammatory immune responses may be critical aspects of ARDS recovery in afflicted individuals. COVID-19 has the potential to cause expiratory dyspnea and ARDS. 13.8% of COVID-19 patients had severe cases, 6.1% had critical cases, and roughly 2.3% had fatal outcomes.[22,23]

There are different vaccinations which were approved by the Food and Drug Administration (FDA) for avoiding COVID-19 infections, and a breakthrough in the therapeutic strategy is crucial for the TX of COVID-19, particularly in severely or critically ill patients who may develop ARDS and/or expiratory dyspnea.[24,25] Currently, a few medicines such as remdesivir and dexamethasone have demonstrated intriguing early outcomes in randomized, controlled, open-label clinical studies.[26,27]

In addition to this, some specific medicines have been proven to be successful in the TX of COVID-19. Furthermore, SARS-CoV-2-induced secondary infections have been attributed to multiple organ dysfunction syndrome (MODS) in extremely or critically sick patients and this remains a significant concern globally.[12] Immune dysregulation in both the innate and adaptive immune systems (AIS) has been implicated in disease intensity, lung injury, and long-term functional disability.[28–31]

There are presently some preemptive vaccinations or effective antiviral medicines available to address COVID-19, and COVID-19 patients are managed primarily with symptomatic and supportive therapy.[32] As a result, there is an immediate need for safe and viable TX approaches to reduce inflammatory organ damage. Currently, immunotherapeutic methods in clinical studies include convalescent plasma treatment (CPT), monoclonal antibodies against interleukin-6 (IL-6), including cell therapies.[26,33,34]

The FDA has established forward regulatory procedures to enable the development of COVID-19 vaccines that fulfills the FDA's stringent scientific specifications. The different kinds of vaccinations were as follows:

Pfizer-BioNTech COVID-19 Vaccines: On August 23, 2021, the FDA revealed the first clearance of a COVID-19 vaccine. The vaccine has been known as the Pfizer-BioNTech COVID-19 Vaccine, and the approved vaccine is sold as Comirnaty (monovalent COVID-19 vaccine), for the protection of COVID-19 among individuals who are 12 years of age and older.[35]

Moderna COVID-19 Vaccines: The FDA declared the second clearance of a COVID-19 vaccine on January 31, 2022. The vaccine, previously known as the Moderna COVID-19 Vaccine, will now be sold as Spikevax (monovalent COVID-19 vaccine) for the protection of COVID-19 in people aged 18 and older.[36]

Janssen COVID-19 Vaccine: The Janssen COVID-19 Vaccine is obtainable under the EUA to prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or accepted COVID-19 vaccines are not available or clinically appropriate, as well as individuals 18 years of age and older who select to receive the Janssen COVID-19 Vaccine because they would not otherwise acquire a COVID-19 vaccine.[37]

Novavax COVID-19 Vaccine, Adjuvanted: Novavax COVID-19 Adjuvanted Vaccine is offered under emergency use authorization (EUA) to avoid COVID-19 in people aged 12 and older. The SARS-CoV-2 spike protein and Matrix-M adjuvant are both included in the Novavax COVID-19 Vaccine, Adjuvanted. Adjuvants are added to some vaccines to improve the immune reaction of the immunized person.[38]

In addition to this, remdesivir has shown clinical advantages such as reduced hospitalisation time, lower progression to artificial breathing, and lower utilisation of other hospital facilities; it is uncertain whether it lowers mortality, but one randomised controlled study indicated potential longevity benefits. According to the accessible information, remdesivir has been approved (or authorised for early use) in 48 different countries.[39] Other medications are hydroxychloroquine/chloroquine and azithromycin, favipiravir, interleukin (IL)-6 pathway inhibitor, lopinavir/ritonavir, histamine 2 receptor antagonist (H2RA), interferon (IFN) beta, convalescent plasma (CP), plasma adsorption and exchange.[40]

Stem Cells (SC)

Cellular TXs have considerable potential for the TX of COVID-19.[41] SC TXs are emerging as viable therapeutic techniques that can reduce inflammation and repair LD caused by COVID-19, either alone or in conjunction with existent therapy regimens.[22,42] The SC secretome has been determined to exhibit strong antifibrotic, anti-inflammatory assets, immunomodulatory (IMD), and angiogenic biological functions.[43,44]

The secretome, which can be studied in conditioned medium, consists of growth factors, cytokines, and extracellular vesicles such as microvesicles and exosomes.[45] These components have a multitude of biological functions which can be targeted by a variety of procedures. The secretome is emerging as a potential alternative treatment due to the absence of conventional therapeutics.

These are multi-potent cells that are being applied extensively in regenerative medicine. MSC TX has a large body of preclinical evidence and early, preliminary clinical data indicating its ability to repair and restore the function of injured tissues and organs.[46] MSCs are being studied for their potential application in the TX of ARDS induced by SARS-CoV-2 infection.[47] MSCs are a therapeutic agent that is generally accessible, safe for the patient, and exempt from ethics issues due to their successful acquisition from a wide range of human body tissues, notably bone marrow (BM), adipose cells (AC), synovial surfaces of joints (SSJ), umbilical cord (UC), and placenta.[48]

Mesenchymal Stem Cells (MSCs)

MSCs show extraordinary IMD features, as well as minimal immunogenicity, paracrine characteristics, and the potential to develop into diverse cell lines. These abilities make them attractive therapeutic possibilities for the TX of neurological, cardiovascular, and pulmonary ailments, which may be occupational problems.[49] Preclinical research utilizing experimental animal designs has shown that MSCs have therapeutic implications in illnesses such as silicosis and pulmonary disease. Currently, MSC TXs have the potential to improve the management of the new illness COVID-19.[49] MSCs are non-hematopoietic cells (n-HPC) with a strong proliferative capacity and multi-lineage differentiation abilities.[50,51]

MSCs have been employed for almost 3 decades and have demonstrated tremendous advances.[52] MSCs may help with COVID-19 consequences such as cytokine storm (CS), ARDS, and acute lung injury (ALI).[53] MSCs were observed to generate exosomes that had strong IMD ability for tissue restoration.[54] Intravenous (IV) injection is a common way of administering SC therapy.[55,56] MSCs and their generated extracellular vesicles (ECVs) have the potential to treat COVID-19 because of their capacity to modify the immune response, enhance pathogen clearance, and reduce the degree of organ damage.[57]

Many clinical investigations have found that MSCs and their exosomes (MSCs-Exo) effectively alleviated lung inflammation caused by various forms of LD. So far, they have been employed successfully in multiple trials to treat a variety of illnesses, including Systemic Lupus Erythematosus (SLE), Amyotrophic Lateral Sclerosis (ALS), Graft-Versus-Host Disease (GVHD), and ARDS. In this context, several studies on the usage of these cells for COVID-19 clients have been officially registered, but only a portion of them have been finalized and released their findings.[58]

By the International Society for Cell & Gene Therapy (ISCGT) guidelines for 2019, mesenchymal stem cells should be renamed as mesenchymal stromal cells (MSCs).[59,60] Due to the cells' self-renewing ability, multi-potent possibility, low immunogenicity, anti-inflammatory efficacy, and ability to adhere to injured tissue, MSC-based

cellular TX has been the focus of an increasing number of studies.[61,62] More significantly, MSCs have distinct IMD capabilities that affect both innate and adaptive immune responses (AIRs), making them a highly appealing cell TX tool.[62,63]

MSCs primarily control AIRs by targeting T- and B-lymphocytes, antigen-presenting cells (APCs), dendritic cells (DCs), natural killer (NK) cells, and regulatory T-cells (Tregs).[62] MSCs also have a role in innate immune responses, primarily by targeting DCs, NK cells, innate TH17 cells, neutrophils, monocytes, macrophages, and mast cells.[63] Furthermore, MSC-based TXs have demonstrated promising effects in several clinical investigations across a wide range of diseases.[64,65]

Researchers have observed that after injecting MSCs, the human body activates the host's innate immune cascade mechanism, such as complement and blood coagulation, which is described as the immediate blood-mediated inflammatory response (IBMIR).[66] IBMIR is crucial given the extremely procoagulant state of many critically and severely ill patients requiring MSC treatment.[67]

MSCs can be derived from a variety of sources, such as BM, AT, UC, placenta, menstrual blood (MB), muscles, the dental pulp (DP), Wharton's jelly (WJ), fetal liver, amniotic membranes, amniotic fluid, urine, and others.[65,68,69] Additionally, MSC-based therapy has shown favorable outcomes in investigations on inflammatory lung illness, limiting alveolar collapse, cell death, and collagen aggregation in lung tissues.[70] The angiotensin-converting enzyme-2 (ACE-2) has been recognized as a receptor for SARS-CoV-2 passage into target cells.[71,72] Similarly, studies have shown that MSCs do not express ACE-2 and that MSCs are resilient to SARS-CoV-2 invasion as well as when confronted with SARS-CoV-2 infected cells.[73,74]

Wilson et al[75] also reported no pre-specified adverse effects after infusion of allogeneic MSCs into 9 patients with ARDS, including cardiac arrhythmia (CA), hypoxemia, and ventricular tachycardia (VT). Moreover, the study team revealed that MSC transplantation dramatically reduces mortality in patients with pandemic Influenza A (H7N9) induced ARDS.[76] MSCs may be beneficial in treating COVID-19, particularly in severe and critical patients.[12]

MSCs are n-HPC that have immunological modulatory, regeneration, and differentiation capabilities.[65] In animal models and clinical studies, MSC therapy decreased lung pathology and inhibited the cell-mediated immune inflammatory response caused by the influenza virus.[76–78] MSC has also been studied for its safety and possible effectiveness in ARDS patients.[75,79–81] MSCs' IMD and regenerative characteristics provide a possible cellular TX strategy for lung injury in COVID-19 patients, but they must be validated in RCTs. Since the emergence of the COVID-19 pandemic, several SC TX clinical studies have been conducted, and the findings have shown that MSCs not only reduce LD and recovery time but also enhance patient survival with good tolerance in the early phase.[1,82,83]

The earlier double-blind, randomized, placebo-controlled trial noted the short-term safety and efficacy of UC-MCS TX, from base point to day 28 after TX, and noticed that UC-MCS management greatly decreased the proportions of solid constituent lesion volume in the lungs and quantitatively increased the 6-minute walk test (6-MWD), especially in comparison to the placebo control.[1] MSCs' potential advantages make them suitable for potential new therapy in ARDS patients.[50]

MSCs are safe, ACE-2 negative, and capable of effectively suppressing the overactive immune system in COVID-19 individuals. Furthermore, IV injections of MSCs can rapidly transport a large number of them to the lungs, which are the primary damaged organs in ARDS.[58] Existing clinical trials suggested the potential effectiveness of MSCs-Exo in the treatment of COVID-19.[57] MSCs might be used as an alternative or supplemental therapy. To present, therapeutic trials utilizing MSCs in COVID-19 patients have raised hopes for the safe and beneficial use of this SC type. MSCs might be a viable therapeutic or supplemental agent for COVID-19 therapy.[49]

They are widely used because of factors such as their low immunogenicity. MSCs are not identified by the human Immune System (IS) due to poor expression of Major Histocompatibility Complex (MHC) particles and an undetectable level of MHC-II.[84] Clinical investigations on COVID-19 patients with MSCs indicated their utility in the acute period of the disease.[85]

Umbilical Cord-Derived Mesenchymal Stem Cells (UC-MSCs)

UC-MSCs may have IMD capabilities.[86,87] Regarding the COVID-19 outbreak, MSCs from various sources, particularly UC-MSCs, have been employed in clinical trials.[74,88,89] These UC-MSC features, which may be due to their more primitive origin as compared to adult tissue-derived MSCs,[90] may explain why cord-derived MSCs were the most often employed in a recent evaluation of registered studies investigating MSCs in COVID-19 patients.[91] Another justification for employing UC-MSCs in the setting of SARS-CoV-2-induced severe ARDS is that they do not exhibit the ACE-2 receptor.[74]

Previous study findings indicated that IV of human UC-MSCs was safe and well tolerated in patients with mild to severe COVID-19 in a phase-1 trial.[88] Another study published the findings of a randomized, double-blind, placebo-controlled trial conducted at 2 medical institutions in Wuhan, China, to assess the safety and effectiveness of IV therapy with UC-MSCs in severe COVID-19 patients with LD.[1] A study of 11 patients with COVID-19-associated ARDS found that IV ($60x10^7$ cells) of human UC-MSCs or placental MSCs (PLMSCs) immediately reduced respiratory distress (RD) while also lowering the excessive inflammatory response.[92]

Several randomized, double-blind, placebo-controlled studies found that UC-MSC (a total of $10–12 \times 10^7$ cells) enhanced lung lesion repair in COVID-19 patients without posing any safety risks.[86,93] Anecdotal case reports, small-scale non-randomized or open-label studies, and only 2 recent, single-center, double-blind, Placebo-Controlled Trials (PCTs) have been published thus far in studies investigating UC-MSCs in COVID-19 patients. Overall, the results of those studies corroborated the great tolerance of IV MSC infusions and showed improved clinical outcomes (COs), even though they were small-scale non-randomized or open-label studies, with just 2 contemporary, single-center, double-blind, PCTs. Overall, the findings of those investigations supported the high tolerability of IV MSC infusions and suggested improved COs.[86]

So far, the evidence suggests that allogeneic UC-MSC TX is safe for a wide range of diseases.[94] These cells can be generated from UC that have been discarded after birth and rapidly grown to clinically significant amounts. They display low amounts of human leukocyte antigen (HLA) class-I and class-II, which may diminish alloreactivity.[95]

Menstrual Blood-MSCs (MB-Derived MSCs)

Considering SC-based TX is dose-dependent, and human clinical research normally necessitates millions of SC, a high proliferation rate is critical in therapeutic trials. MB-derived MSCs double in approximately 20 hours, while BM-derived MSCs double in around 40–45 hours. Thus, MSCs obtained from MB had a higher output in a shorter amount of time at early passages.[96,97] More significantly, MB-derived MSCs provide a painless solution that is devoid of the ethical problems that may come with BM-MSC contributions.[98] Thus, MSC-based therapy produced from MB may be a potential TX for COVID-19, especially in fighting the inflammatory CS shown in severe and critical patients.[12]

This is an exploratory trial to determine whether MB-derived MSCs may benefit COVID-19 patients who are severely and chronically unwell. To that effect, researchers evaluated the safety, therapeutic effectiveness, and tolerability of transplanted MSCs during a one-month follow-up following SARS-CoV-2 infection. The research specifically looked at any improvements in pulmonary function. The findings of the study not only shed light on MSCs' potential to cure COVID-19 patients but also imply that MSCs are a promising method for treating acute or chronic pneumonia in future clinical applications.[11] MB-derived MSCs have lately gained a lot of interest due to their exceptional proliferation capacity and absence of ethical issues.[12]

MSC transplantation from MB considerably reduces the death rate of severe and critical SARS-CoV-2-induced patients with COVID-19.[14] MSC-based therapy might be used as an alternate TX for COVID-19 in the future. MB-derived MSCs have been viewed in numerous pre-clinical and clinical studies, including the TX of pulmonary illnesses, in recent decades due to their unique features, such as high proliferation rate, low immunogenicity, and non-invasive periodical acquisition.[99,100]

Bone Marrow MSCs (BM-Derived MSCs)

In children, allogeneic hematopoietic stem cell transplantation (allo-HSCT) from a Human Leukocyte Antigen (HLA) identical family donor is the initial therapy.[101] BM-MSCs have been found to promote lung repair following ventilator-induced LD, to aid in inflammation resolution, and to restore lung function and structure in ARDS patients.[102]

Adipose Tissue-Derived MSCs (AT-Derived MSCs)

Sanchez-Guijo et al revealed the effects of IV injection of AT-derived MSCs in 13 severe COVID-19 pneumonia cases on mechanical ventilation (MV), and the patients were followed up on 16 days following the infusions.[93] The advantages of perinatal MSCs over adult MSCs include their ease of availability, lack of donor site morbidity, cell naivety, the quantity of SC in the main tissue, and a high potential for proliferation.[103]

Given the global severity of COVID-19, one research study evaluated the safety of aerosol inhalation of exosomes derived from human AT-derived MSCs-Exo in the TX of patients with severe COVID-19-related pneumonia, intending to determine the optimal dosage and delivery route of MSCs-based therapy for acute respiratory diseases (ARD). Research utilizing a mouse model of occupational bronchial asthma found that TX of AT-derived MSCs dramatically lowers lung neutrophilic infiltrates and immunoglobulin-E (IgE) levels.[104] AT-derived SC, a common kind of MSCs, has been offered as a therapy option for COVID-19 to minimize morbidity and mortality. AT-derived MSC therapies have the potential to alleviate the strain on crucial hospital resources[41] (Table 1).

Research Questions

1. What is the pooled effectiveness of MSC applications among the COVID-19 population?
2. What are the study characteristics of MSC applications among the COVID-19 population?

Methods

This systematic review (SR) included studies from all across the world. This study was registered in the PROSPERO (CRD42022380088).

Search Strategies

Scopus, Web of Science, PUBMED, EMBASE, Science Direct, Cochrane Library, and Google Scholar were utilized to search for relevant literature. During this time, papers published until December 31, 2022, were sought with key terms on COVID-19, SARS-CoV-2, Novel Coronavirus, nCoV, and Severe Acute Respiratory Syndrome, coronavirus-2, Coronavirus Disease-2019 Virus, 2019-nCoV, 2019 New Coronavirus, Coronavirus, Stem Cells, Stem Cell Management, Therapeutic Stem Cell Management, Stem Cell Applications, Mesenchymal Stem Cell Applications, Mesenchymal Stem Cell Management, Therapeutic Mesenchymal Stem Cell Applications", and Boolean operators were employed.

Eligibility Criteria

Inclusion Criteria

Studies were included in the SR if they fulfil: Studies that reported outcome variables on SC management on COVID-19 patients, studies reported on RCTs, articles published in the English language, and articles published up to December 31, 2022, across all countries.

Exclusion Criteria

Articles that did not assess the outcome variables, articles that were not fully accessible, articles published in a non-English language, articles with non-RCTs, observational studies, case studies, editorials, perspectives, commentary, and poor quality studies were excluded from this SR.

Table 1 Search Databases and Strategies About the Stem Cell Applications Among the COVID-19 Population

Databases	**Search Strategies** **Scopus – 212, Web of Science – 3407, PUBMED – 235, EMBASE – 6818, Science Direct – 804, Cochrane Library – 113, Google Scholar – 978**
Scopus	(covid-19 OR "Coronavirus-19" OR "Novel coronavirus" OR "SARS-CoV-2" OR "Severe acute respiratory distress syndrome-CoV-2" OR "nCOVID-19" OR ncov AND "Mesenchymal stem cell therapy" OR "Mesenchymal stem cell application" OR "Mesenchymal stem cell management" OR "Cell therapies" OR "Mesenchymal stem cell transplantation" OR "MSC applications") AND (LIMIT-TO (OA, "all") OR LIMIT-TO (OA, "publisherfullgold")) AND (LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020)) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "IMMU")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))
PubMed	(("COVID-19" [Title/Abstract] OR "Coronavirus-19" [Title/Abstract] OR "Novel coronavirus" [Title/Abstract] OR "SARS-CoV-2" [Title/Abstract] OR "Virus" [Title/Abstract]) AND ("2017/11/14 00:00":"3000/01/01 05:00"[Date - Publication] AND "loattrfree full text"[Filter] AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms] AND ("losubjtsupplemental materials"[Filter] OR "hasdatabanklist"[All Fields]) AND "english"[Language]) AND ("stem cells"[MeSH Terms] AND ("2017/11/14 00:00":"3000/01/01 05:00"[Date - Publication] AND "loattrfree full text"[Filter] AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms] AND ("losubjtsupplemental materials"[Filter] OR "hasdatabanklist"[All Fields]) AND "english"[Language]))) AND ((y_5[Filter]) AND (ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (data[Filter]) AND (english[Filter]))
EMBASE	(("covid 19"/exp OR "covid 19" OR "coronavirus-19" OR "novel coronavirus" OR "sars-cov-2"/exp OR "sars-cov-2" OR "severe acute respiratory distress syndrome-cov-2" OR "ncovid 19" OR ncov) AND "stem cell applications" OR "stem cell management" OR "stem cell therapy"/exp OR "stem cell therapy" OR "stem cell transplantation"/exp OR "stem cell transplantation" OR "mesenchymal stem cell therapy"/exp OR "mesenchymal stem cell therapy" OR "mesenchymal stem cell application" OR "mesenchymal stem cell management" OR "cell therapies" OR "mesenchymal stem cell transplantation"/exp OR "mesenchymal stem cell transplantation" OR "msc applications") AND ([randomized controlled trial]/lim OR "controlled clinical trial"/de) AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND [humans]/lim AND [abstracts]/lim AND [in process]/lim AND [clinical study]/lim AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim) AND [2019–2022]/py AND [medline]/lim
Cochrane Library	COVID-19 OR "Coronavirus-19" OR "Novel coronavirus" OR "SARS-CoV-2" OR "Severe acute respiratory distress syndrome-CoV-2" OR "nCOVID-19" OR nCoV AND "Mesenchymal stem cell therapy" OR "Mesenchymal stem cell application" OR "Mesenchymal stem cell management" OR "Cell therapies" OR "Mesenchymal stem cell transplantation" OR "MSC applications"
Science Direct	COVID-19 OR "Coronavirus-19" OR "Novel coronavirus" OR "SARS-CoV-2" OR "nCOVID-19" AND "Mesenchymal stem cell therapy" OR "Mesenchymal stem cell application" OR "Mesenchymal stem cell management" OR "Mesenchymal stem cell transplantation"
Web of Science	COVID-19 OR "Coronavirus-19" OR "Novel coronavirus" OR "SARS-CoV-2" OR "Severe acute respiratory distress syndrome-CoV-2" OR "nCOVID-19" OR nCoV AND "Stem cell applications" OR "Stem cell management" OR "Stem cell therapy" OR "Stem cell transplantation" OR "Mesenchymal stem cell therapy" OR "Mesenchymal stem cell application" OR "Mesenchymal stem cell management" OR "Cell therapies" OR "Mesenchymal stem cell transplantation" OR "MSC applications" (All Fields) and Open Access and Open Access and Article (Document Types) and Medicine General Internal or Immunology (Web of Science Categories) and Infectious Diseases (Web of Science Categories) and Article (Document Types) and English (Languages) and Infectious Diseases (Research Areas) and Science Citation Index Expanded (SCI-EXPANDED) (Web of Science Index) and All Open Access (Open Access) (Title) and Open Access and 2019 or 2020 or 2021 or 2022 or 2023 (Publication Years) and Article (Document Types) and Article (Document Types) and Infectious Diseases (Web of Science Categories) and English (Languages) and All
Google Scholar	COVID-19 OR "Coronavirus-19" OR "Novel coronavirus" OR "SARS-CoV-2" OR "Severe acute respiratory distress syndrome-CoV-2" OR nCOVID-19 OR nCoV AND "Stem cell applications" OR "Stem cell management" OR "Stem cell therapy".

Outcome Interest

In this SR, the primary outcome was the effectiveness of MSCs applications among COVID-19 patients. Effectiveness refers to studies that explained positive results on MSC applications among COVID-19 patient studies which were included in this SR.

The secondary outcome was study characteristics that reported on MSC applications among the COVID-19 population.

Data Extraction and Quality Assessment

The retrieved articles from all databases were exported to "Thomson Reuters EndNote version-8". The titles and abstracts of all possible articles to be included in this SR were checked. The standardized data extraction format prepared in a Microsoft Excel worksheet was used to extract the data from the selected articles according to the present inclusion criteria. Author name, publication year, study period, study country, participants, sample size, study design, type of intervention, outcome measurement, study findings, and conclusion of the study were used for the extraction of data from each article.

This SR has included 14 RCTs. The CASP, a critical appraisal tool for SR that could be RCTs on MSC applications among COVID-19 patients was used to assess the included articles, and the CASP for RCTs was used to include the articles in this SR, whereas all articles fulfilling CASP criteria are considered high-quality RCTs and included in this SR and given as a Supplementary 1 File. The CASP methodological quality assessment checklist has been included for each article.

Data Processing and Analysis

This SR adopted a narrative synthesis of the RCTs pooling evidence on MSC therapeutic applications among COVID-19 patients during the epidemic. The data are prepared in the tabular column which includes

> Author, Year, Country, Study Design, Study Duration, Setting of The Study, Population, Sample Size, Sampling Technique, Method of Randomization, Type of SC Applied, Type of Intervention, Duration of Intervention, Study Outcome Measurement, Study Characteristics, Results and Conclusion of the Studies.

Data Synthesis and Reporting

This SR was conducted on the effectiveness of pooling evidence on MSC's therapeutic applications during the COVID-19 epidemic. During this, PRISMA 2020 flowchart diagram and PRISMA 2020 checklist were used for the study screening, selection, and inclusion into this SR. PRISMA 2020 checklist is given in (the Supplementary 2 Files).

Results

Search Results

All related studies done across the world were identified by using diverse databases. From the search made through the mentioned databases, 12,567 studies were found. From this, only 14 studies were meeting the predefined eligibility criteria and were included in this SR (Figure 1).[105]

Study Characteristics

This SR focused on the studies conducted on MSC applications among COVID-19 patients. In this SR, a total of 14 studies were included, comprising studies done on MSC applications on COVID-19 patients.

Results

The study overall records (12,567) are extracted from various databases (Scopus, Web of Science, PUBMED, EMBASE, Science Direct, Cochrane Library, and Google Scholar), and 14 RCTs were included in this SR,[1,58,83,86,88,93,106–113] whereas remaining records were excluded with various reasons and are explained in Figure 1 in detailed. The CASP

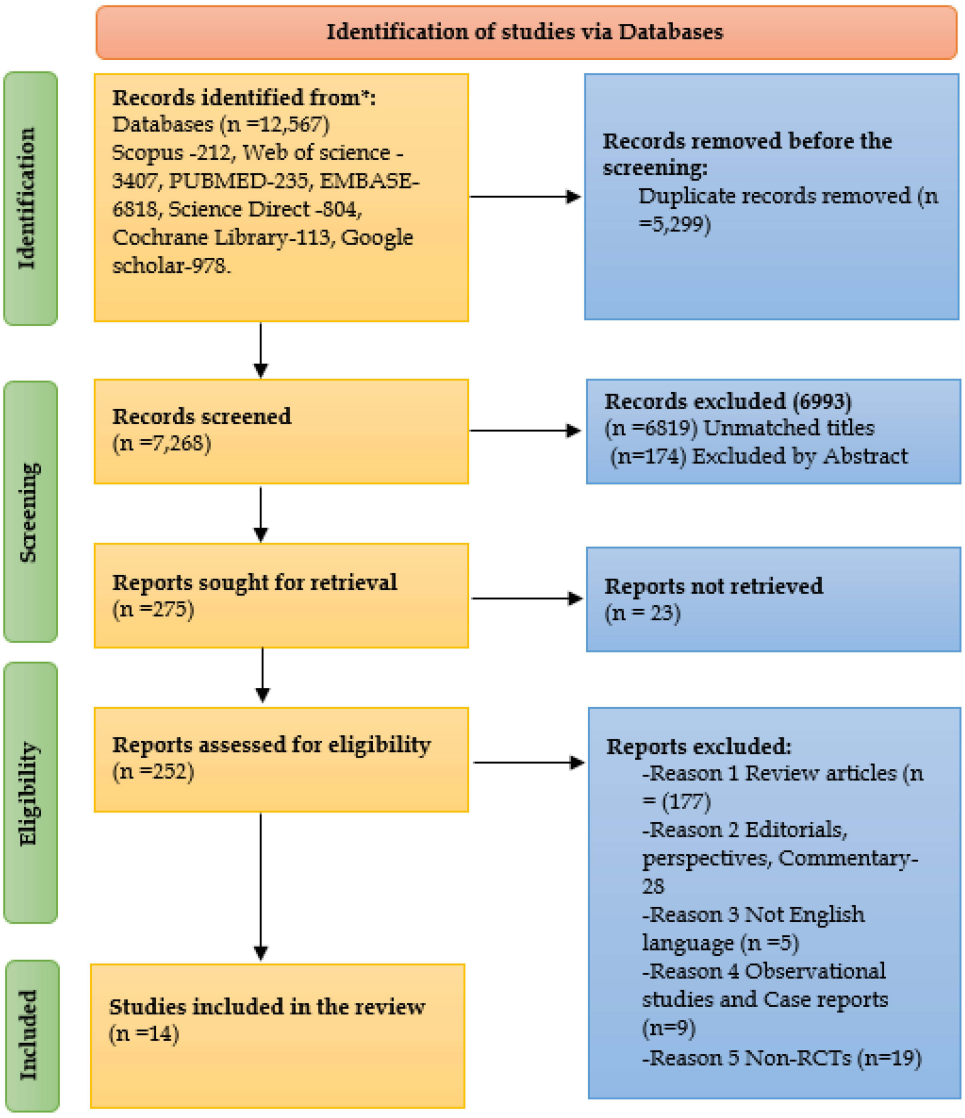

Figure 1 PRISMA flowchart diagram of the study selection for a systematic review on Mesenchymal stem cell therapeutic applications during the COVID-19 epidemic.

checklist criteria were considered for inclusion of the studies and considered as high-quality studies (CASP check attached as Supplementary File 1).

Effectiveness of RCTs on MSC Applications Among COVID-19 Patients

In this systematic review, the included studies conducted on MSC therapeutic applications among COVID-19 patients with RCT clinical trials. The outcome of the each included study was clearly evidenced with positive outcome of the patient prognosis. The RCTs on MSC therapies among COVID-19 patients was progressing and showing promising results with no complication, and these study effective results may evidence early patient recovery with harmful ailments (Table 2).

Demographic Characteristics

The studies were conducted by

Murdani Abdullah, Hamid Reza Aghayan, Najmeh Kafash Farkhad, Rodrigo Pinheiro Araldi, Muhammad Karyana, Antoine Monsel, Carmen Lucia Kuniyoshi Rebelatto, Ayca Sultan Sahin, G Adas, Smail Hadisoebroto Dilogo, Giacomo Lanzoni, Lei Shi, Lei Shi, Fanping Meng.[1,58,83,86,88,93,106–113]

Table 2 RCTs Pooled Evidence on Stem Cell Applications During the COVID-19 Epidemic

Reference and Author	Year	Country	Study Design	Study Duration	The Setting of the Study	Population	Sample Size	Sampling Technique	Randomization	Type of Stem Cells
Murdani Abdullah[83]	2022	Indonesia	Double-blind, multicenter, randomized, PCT	18 February 2021 to 9 July 2021	In 3 COVID-19 referral hospitals in Indonesia's Greater Jakarta region. (Universitas Indonesia Hospital, Dr. Cipto Mangunkusumo Hospital, and Persahabatan National Respiratory Hospital)	COVID-19 patients	40 COVID-19 patients	Using a randomization tool, blocks of 4 were randomly assigned to 2 groups (intervention and control).	Randomized in a 1:1 ratio to an intervention (n=20) and a control (n=20) group	MSCs-secretome
Hamid Reza Aghayan[112]	2022	Iran	Non-blinded phase I clinical study		Patients were randomly assigned to one of 2 groups: TX (n=10) or control (n=10).	COVID-19 has caused ARDS in 20 people (ICU)	COVID-19 caused ARDS in 20 individuals.		COVID-19 Patients were assigned to one of 2 groups: TX (n=10) or control (n=10).	PL-MSCs
Najmeh Kafash Farkhad[51]	2022	Iran	A single-center, open-label, phase I clinical trial	July 2020 to May 2021	Mashhad University of Medical Sciences, Imam Reza Hospital, Mashhad, Iran	COVID-19 individuals suffering from mild-to-moderate ARDS	20 confirmed COVID-19 patients with mild-to-moderate ARDS (intervention n=10; comparator n=10).		The study population was split into 2 groups: control (regular care) and intervention (regular care with UC-MSCs).	UC-MSCs
Rodrigo Pinheiro Araldi[93]	2022	Brazil	Randomized Phase I/II clinical trial		Vera Cruz Hospital (Campinas, Brazil)	90 moderately to critically sick COVID-19 patients	90 patients with moderate to critically ill COVID-19		The patients were randomized into 2 groups of 45 people each: I control/placebo, which received an IV infusion of cell vehicle (saline), and (ii) TX, who received 4 IV infusions of 2×10^7 hIDPSCs/patient on days 1, 3, 5, and 7.	hIDPS (NestaCell® product)

Intervention	Duration	Outcome Measurement	Study Characteristics	Results	Conclusion
MSCs secretome in the experimental group with COVID-19 routine TX (n=20) or the control group with placebo (NaCl 0.9%) and COVID-19 routine therapy (n=20).	MSCs secretome was administered once at a dosage of 15 mL dissolved in 100 mL of NS. Secretome was administered IV for 60 minutes. The COVID-19 standardized therapy delivered to both groups was based on the national COVID-19 therapy regimen.	Secretomes' efficacy and safety assessment as a therapy for severe COVID-19.	Age, year (mean ± SD) =51.25 ± (10.51); Sex= (Male, n (%) =11 (27.5), Female, n (%) =9 (22.5); Smoking, Physical activities, Number of comorbidities, Type of comorbidity, IMs, Post-intervention laboratory characteristics.	On the 14th day following placebo delivery, IL-6 levels in the control group increased considerably [4.110 (2.403–12.820) at baseline to 13.320 (2.958–33.285) on the 14th day after intervention, p=0.017]. On the 14th day following placebo TX, the IL-6/IL-10 ratio in the control group was considerably higher (p=0.036).	MSC secretome can decrease inflammation in patients with severe COVID-19 and has a high safety profile, making it a viable therapy method for severe COVID-19.
Each patient in the intervention group (n=10) received normal care as well as a single IV dosage of $1 10^6$ cells/kg PL-MSCs. The standard therapy was given to the control groups (n=10). The cell suspension was injected slowly (for 15 min)	Patients were examined daily for the first 28 days following transplantation, until discharge or death. They were checked every 2 hours for vital signs (temperature, BP, and HR) and once a day for laboratory values (biochemistry and hematology parameters)	The phase-I clinical trial assessed the safety of allogeneic PL-MSCs administered by IV in patients with COVID-19-induced ARDS.	Age in years, Gender, Hospitalization duration, Weight in kg, presence of disease condition, the time gap between ICU admission and cell injection per day, and Interval between cell injection and death/discharge per day.	The PL-MSC group has experienced no adverse effects. The mean time of hospitalization, serum O_2, and other clinical and laboratory data was not significantly different between the 2 groups (p>0.05).	The findings showed that IV delivery of PL-MSCs in patients with COVID-19-related ARDS is both safe and efficacious.
Every other day, the patients received 3 IV infusions of UC-MSCs ($1x10^6$ cells/kg BW every injection). The infusion period was roughly 30–45 minutes (approximately 50 drops/min)	During the 17-day follow-up period, respiratory parameters, CRP levels, and specific serum cytokines were evaluated 4 times (days 0, 5, 10, and 17).	The safety and potential efficacy of 3 UC-MSC injections in COVID-19-induced ARDS patients were investigated.	Age, gender, co-morbidities, adverse incidences, clinical outcome, and RT-PCR at baseline.	The SPO_2/FIO_2 ratio and serum CRP levels have significantly improved.	Multiple IV transplants of allogenic UC-MSCs in patients with non-severe COVID-19-induced ARDS are a safe TX.
4 IV infusions of $2×10^7$ hIDPSCs/patient on days 1, 3, 5, and 7.	TX group was subjected to 4 IV infusions of $2×10^7$ hIDPSCs/patient on days 1, 3, 5, and 7.	The safety and efficacy of hIDPSCs (NestaCell® product) for the severe COVID-19 pneumonia TX		In moderate to critically ill COVID-19 patients, IV infusions of hIDPSCs with prophylactic enoxaparin administration did not affect D-dimer levels or PT and PTT times.	The findings demonstrate that IV infusions of hIDPSCs (NestaCell® product) are safe, even for individuals at high risk of thromboembolism because it is administered with anticoagulants.

(*Continued*)

Table 2 (Continued).

Reference and Author	Year	Country	Study Design	Study Duration	The Setting of the Study	Population	Sample Size	Sampling Technique	Randomization	Type of Stem Cells
Muhammad Karyana[1]	2022	Jakarta, Indonesia	Phase I double-blind, placebo-controlled, RCT	August 2020 to March 2021	Dr. Wahidin Sudirohusodo Hospital, Makassar	Patients who are at low clinical risk of Infection with COVID-19	9 Patients with low clinical risk of COVID-19 infection	9 subjects were enrolled and randomly assigned to 1 of the 3 groups: TL, TH, and C	Patients were randomly randomized to receive TL (5.0x107 cells), TH ($1.0x10^8$ cells), or C (Cryostor CS10 with dimethyl sulfoxide 10%, sucrose 1%, K+=0.6%, and K+ =0.168%) infusions. All individuals got regular drugs based on their circumstances.	DW-MSC infusion
Antoine Monsel[79]	2022	France	Multicentre, double-blind, randomized, PCT	April 6, 2020, to October 29, 2020	Adults ≥18 years with SARS-CoV-2 had mild to severe ARDS with <96 hours in 10 French centers. 10 ICUs in 8 French university hospitals	COVID-19 affected patients	47 patients	47 participants were randomly allocated to one of 2 TX groups: UC MSCs (n=21) or placebo (n=24).	After recruiting, patients were randomly allocated to receive 3 IV infusions of 10^6 UC-MSCs/kg or a placebo (0.9% NaCl) over 5 days.	UC-MSCs
Carmen Lúcia Kuniyoshi Rebelatto[113]	2022	Brazil	A phase I/II, prospective, single-center, randomized, double-blind, PCT	12 June to 13 July 2020	Complexo Hospital de Clinicas, University dade Federal do Parana, a referral public hospital for the TX of patients with COVID-19	Patients diagnosed with COVID-19	17 patients diagnosed with COVID-19	TX (n=11) or placebo (n=6)	17 eligible patients were enrolled in an approximate 1:2 randomization, according to the randomization table by the R program version 4.1.2	UC-MSCs

Intervention	Duration	Outcome Measurement	Study Characteristics	Results	Conclusion
Subjects in the TL and TH groups received single IV infusions of 5.0×10^7 cells and 1.0×10^8 cells, respectively	The main outcome was the occurrence of TEAE during the 28-day study period	Safety and investigate the efficacy measures of a single dose of IV DW-MSCs in patients with COVID-19	Baseline characteristics of enrolled patients and TEAE-Age, Sex, NEWS-2, Co-existing disease, Vital signs, Chest X-ray, ECG and Laboratory abnormalities, TEAE, Starting the day with duration in days of TEAE.	There were no apparent differences in clinical characteristics between study groups (TL, TH, and C) at baseline. All patients did not show the progression of severity during the study period.	The clinical trial has provided reliable results regarding the safety of MSCs in low clinical-risk COVID-19 subjects treated with MSCs.
Patients were randomly assigned to receive 3 IV infusions of 10^6 UC-MSCs/kg or placebo (0.9% NaCl) over 5 days after recruitment	28 days	To compare the IV infusion of UC-MSCs to saline placebo as add-on TX for SARS-CoV-2-induced ARDS	Baseline parameters of patients include age, gender (male), BMI, obesity, SOFA score, MAP in mm Hg, vasopressors, comorbidities, respiratory features, and ventilation mode.	The UC MSCs and placebo groups did not vary substantially in PaO_2/FiO_2 change between D0 and D7 (medians [IQR] 54.3 [−15.5 to 93.3] vs 25.3 [−33.3 to 104.6], respectively; ANCOVA estimated TX effect 7.4, 95% CI −44.7 to 59.7; P = 0.77).	The D0-to-D7 PaO_2/FiO_2 changes for persons with SARS-CoV-2-induced ARDS who received IV UC-MSCs vs placebo did not significantly differ. Recurrent UC-MSC infusions were not attributed to any major side effects during or after therapy (until D28).
3 doses of 5×10^5 cells/kg UC-MSCs, with a dosing interval of 48 h (n=11) or placebo (n=6) Concomitant corticosteroids and anticoagulants	All patients were evaluated at baseline, as well as at pre-determined follow-up intervals on days 2, 4, 6, and 14, as well as at 2 and 4 months after infusion.	To investigate the safety and long-term effectiveness of 3 IV doses of UC-MSCs	At enrolment, the following baseline parameters were recorded: age, gender, symptoms, and oxygenation index (PaO2/FiO2). Days elapsed between the beginning of symptoms and hospitalization, Days passed between the beginning of symptoms and the first cell injection, Comorbidities, concurrent therapy, the results of a patient's laboratory tests, s Serologic, biochemical, and blood count subgroups of lymphocytes, COVID-19 patient survival status.	On the 14-day, ferritin, IL-6, and MCP1-CCL2 levels decreased in the UC-MSC group. The levels of reactive C-protein, D-dimer, and neutrophils decreased in the 2nd month, whereas TCD3, TCD4, and NK cells increased. In the fourth month, there was a reduction in the extent of lung damage.	Infusion of UC-MSCs is safe and can play a significant role as adjuvant therapy, both in the early phases, averting severe consequences, and in the chronic phase.

(*Continued*)

Table 2 (Continued).

Reference and Author	Year	Country	Study Design	Study Duration	The Setting of the Study	Population	Sample Size	Sampling Technique	Randomization	Type of Stem Cells
Ayca Sultan Sahin[106]	2022	Turkey	Prospective randomized single-center clinical trial	May to July 2020	Health science university, Ka nuni sultan Suleyman education and training hospital, department of anesthesiology and reani mation in Istanbul	COVID-19 patients	21 COVID-19 patients	Patients were detached into 3 groups: those who were intubated without comorbidities (n=7), those who were intubated with comorbidities (n=7), and those who were not intubated (n=7).	Patients were detached into 3 groups: those who were intubated without comorbidities (n=7), those who were intubated with comorbidities (n=7), and those who were not intubated (n=7).	MSCs
G Adas[76]	2021	Turkey	Interventional, prospective, 3 parallel armed, with 2 control arms consisting of moderate and CCC.		Bakirkoy Dr. Sadi Konuk Training and Research Hospital and Istinye University The study protocol was approved by the Clinical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital	Critically-ill COVID-19 patients	30 COVID-19 patients	Group 1 (n = 10) underwent conventional therapy; Group 2 (n = 10) underwent conventional TX; Group 3 (n = 10) underwent conventional TX and MSC transplantation.	Patients with moderate and critical COVID-19 clinical manifestations were categorized into 3 groups: Group 1 (moderate cases, n = 10, treated conventionally), Group 2 (critical cases, n = 10, treated conventionally), and Group 3 (critical cases, n = 10, treated conventionally plus MSCs transplantation therapy of 3 consecutive doses on TX days 0, 3, and 6 (as 3×10^6 cells/kg, IV).	WJ-MSCs
Smail Hadisoebroto Dilogo[88]	2021	Indonesia	Multicentered, double-blind, RCT	May 1 and October 10, 2020	In Jakarta, there are 4 COVID-19 referral hospitals (Sulianti Saroso Infection Disease Hospital, Persahabatan Central General Hospital, Cipto Mangunkusumo National Central General Hospital, and Universitas Indonesia Hospital).	Critically ill patients with COVID-19	A total of 40 people were enrolled in the study, with 20 assigned to the control group and the remaining 20 assigned to the experimental group.	Stratified random sampling and randomization using a computerized random number generator	This is a double-blinded study	UC-MSCs

Intervention	Duration	Outcome Measurement	Study Characteristics	Results	Conclusion
Each group received 1 million cells/kg IV of MSCs on days 0, 2, and 4.	In the days following MSC transplantation, patients' oxygenation and symptoms improved (at days 0, 2, and 4).	The aim of this study is to provide IMD with SCT by reducing the damage caused and COVID-19 infection to tissues and organs.	DC of the SC therapy patients- Age (mean±SD.), Days (mean±SD.), Gender N(%), Discharge status N(%), Blood values (cluster of differences) with no group and time effects: Value Predictors= CD3, CD3+CD4, CD3 +CD4+CD8+, CD4/CD8, NKT.	There was no statistically significant difference between the 3 groups in terms of SC therapy patients' age and exit/discharge days and mortality.	There is a useful effect of MSCs on severe COVID-19 pneumonia showed reversal of hypoxia and downregulation of CS in patients with severe COVID-19 following 3 IV doses with no AEs assignable to the TX.
Group 3/experiment (n =10): Patients in critical condition, intubated and monitored in the ICU with conventional care and systemically transplanted MSCs add-on therapy. Antibiotics (Piperacillin tazobactam 3×2.5gr IV), antivirals (Favipiravir, 2×1600 mg loading dose, and 2×600 mg maintenance), dexamethasone (1 x6 mg IV 5–10 days per required), hydroxychloroquine (2x200 mg 5 days), and enoxaparin were used in the usual TX (2x0.6 mL). Patients in Group 3 were also given 3×10^6 cell/kg MSC by IV infusion over 3 consecutive cures.	MSC transplantation was performed 3 times in a row, on days 0, 3, and 6.	Controlling the CS by giving MSCs to severely sick among COVID-19 patients	Level of IMs in venous blood samples: CRP (mg/L), PCT (ng/mL), D-Dimer (mg/mL), Fibrinogen (mg/dL), Ferritin (mg/L). Level of proinflammatory and anti-Inflammatory cytokines in venous blood samples: Cytokines= proinflammatory cytokines: (IFN-g (pg/mL), IL-6 (pg/mL), IL-17A (pg/mL), IL-2 (pg/mL), IL-12 (pg/mL); anti-inflammatory cytokines -IL-10 (pg/mL); proinflammatory cytokines- IFN-g (pg/mL), IL-13 (pg/mL), IL-1ra (pg/mL).	When the total mortality rates of all cases were calculated, 6 patients in Group 2 and 3 patients in Group 3 died, whereas no patients in Group 1 died. Group-3 had large amounts of proinflammatory cytokines IFN γ, IL-6, IL-17A, IL-2, IL-12, anti-inflammatory cytokines IL-10, IL-13, IL-1ra, and growth factors TGF-b (beta symbol), VEGF, KGF, and NGF. When serum ferritin, fibrinogen, and CRP levels in Group 3 were evaluated, Group 3 had considerably lower values. The levels of CD45 +, CD3 +, CD4 +, CD8 +, CD19 +, HLA-DR +, and CD16 + / CD56 + were all assessed.	The findings revealed that using MSCs on severely sick COVID-19 patients had beneficial systemic and cellular benefits. This impact is significant in the treatment and reduction of mortality in critically sick patients.
On day 8 (ranged from day 2–30) of ICU care, the experimental group received a single IV infusion of 1×106 /kg BW UC-MSCs in 100 mL saline (0.9%) solution, whereas the control group received a placebo (100 mL saline [0.9%] solution).	During the 15-day observation period, laboratory assessments were performed on days 0 and 1, and then once every 3 days for normal laboratory examination, whilst particular markers were tested only on days 0 and 7.	Evaluation of UC-MSCs as essential COVID-19 adjuvant TX.	Subject demographics: age, gender, comorbidities (n); cytokine-IL-6, VEGF, ferritin, IL-10, LIF.	The survival rate in the UC-MSCs group was 2.5 times greater than in the control group (P =0.047), with 10 patients in the UC-MSCs and 4 patients in the control groups, correspondingly.	The use of IV UC-MSCs as adjuvant therapy for critically sick patients with COVID-19 improves survival by regulating the immune system.

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Table 2 (Continued).

Reference and Author	Year	Country	Study Design	Study Duration	The Setting of the Study	Population	Sample Size	Sampling Technique	Randomization	Type of Stem Cells
Giacomo Lanzoni[86]	2021	Florida	A double-blind, phase 1/2a, RCT	25 April 2020, to 21 July 2020	U Health System/ Jackson Health System (UHS/ JHS), in Miami, Florida.	COVID-19 ARDSpatients	24 subjects were randomized 1:1 to either UC-MSC TX (n = 12) or the control group (n = 12).		Randomization and stratification by ARDS severity were used to foster balance among groups. All subjects were analyzed to treat design. 24 subjects were randomized 1:1 to either UC-MSC treatment (n = 12) or the control group (n = 12)	UC-MSC
Lei Shi[109]	2021	China	Randomized, double-blind, and PCT	5 March 2020 and 28 March 2020	2 hospitals in Wuhan city.	Severe COVID-19 patients	100 severe COVID-19 patients with LD-UC-MSCs (n = 65) or placebo (n = 35)	To assess the efficacy and safety of human UC-MSCs to treat severe COVID-19 patients with LD	Randomized in a 2:1 ratio (66 to the UC-MSC group and 35 to the placebo group)	Human UC-MSCs
Lei Shi[114]	2021	China	A prospective, longitudinal, cohort study	April 8, 2020, to March 31, 2021	In the outpatient clinic of the General Hospital of Central Theater Command in Wuhan, Hubei, China	Severe COVID-19 patients	100 patients −66 to the UC-MSC group and 35 to the placebo group		Randomly assigned in a 2:1 ratio to receive either UC-MSCs or the placebo	Human UC-MSC

Intervention	Duration	Outcome Measurement	Study Characteristics	Results	Conclusion
Subjects in the UC-MSC TX group received 2 IV infusions (at days 0 and 3) of 100 ± 20×10^6 UC-MSCs; controls received 2 infusions of vehicle solution. Both groups received the best standard of care.	The primary endpoint was safety (AEs) within 6 hours; cardiac arrest or death within 24 hours post-infusion). 2ndry endpoints included patient survival at 31 days after the first infusion and time to recovery.	Safety and explore the efficacy of UC-MSC infusions in subjects with COVID-19 ARDS.	Characteristics and TX- Sex, n (%), Age, mean ± SD, years, Race, n (%), Ethnicity, n (%), PaO2/FiO2 ratio at enrollment, median (IQR), ARDS severity stratification, n (%), BMI, mean ± SD, kg/m^2, Smoker (former), n (%), Comorbidities, n (%), Concomitant TX, n (%), Number of AEs reported, Number of subjects with AEs, Number of SAEs reported, Number of subjects with SAEs, Number of AEs by severity, Subjects with AEs by severity, Number of AEs by relatedness to TX, Subjects with AEs by relatedness to TX.	No serious AEs were observed related to UC-MSC infusions. -UC-MSC infusions in COVID-19 ARDS were found to be safe. -TX was associated with significantly improved patient survival (91% vs 42%, P = 0.015), SAE-free survival (P = 0.008), and time to recovery (P = 0.03).	UC-MSC infusions are safe and could be beneficial in treating subjects with COVID-19 ARDS
Randomly assigned at a 2:1 ratio to receive either UC-MSCs (4×10^7 cells per infusion) or placebo on days 0, 3, and 6	28 days The primary endpoint was an altered proportion of whole lung lesion volumes from baseline to day 28	Randomly assigned at a 2:1 ratio to receive either UC-MSCs (4×10^7 cells per infusion) or placebo on days 0, 3, and 6	Baseline patient characteristics- Age, years, Sex—no. (%) -Men, Women, BMI, Kg/m^2, Time from symptom onset to baseline (days), any comorbidities, Concomitant medication, Lesion proportion (%), Solid component lesion proportion (%), Laboratory investigations, Primary and secondary outcomes in the mITT population, Adverse events that occurred in the enrolled population of the trial.	UC-MSCs administration exerted numerical improvement in whole lung lesion volume from baseline to day 28 compared with the placebo (the median difference was −13.31%, 95% CI −29.14%, 2.13%, P = 0.080). UC-MSCs significantly reduced the proportions of solid component lesion volume compared with the placebo (median difference: −15.45%; 95% CI −30.82%, −0.39%; P = 0.043). The 6-MWT showed an increased distance in patients treated with UC-MSCs (difference: 27.00 m; 95% CI 0.00, 57.00; P = 0.057).	These results suggest that UC-MSCs TX is a safe and potentially effective therapeutic approach for COVID-19 patients with LD
Patients received either UC-MSCs (n = 65) or placebo (n = 35) in addition to standard care.	Prospectively followed up at 3-month intervals for 1 year to evaluate the long-term safety and effectiveness of UC-MSC TX 1-year follow-up	Effect of Human MSCs TX for severe COVID-19: 1-year follow-up results	Baseline characteristics-Age, years, Sex - no. (%), BMI, Kg/m^2, Time from symptom onset to baseline (days), Any comorbidities, Concomitant medication, Lesion proportion (%), Solid component lesion proportion (%), Change in the total lesion proportion (%) of the whole lung volume from baseline, Change in solid component lesion proportion (%) of whole lung volume from baseline, Number of normal chest CT images, Symptoms and health-related quality of life between MSC and placebo groups throughout 1-year follow-up visit, AEs that occurred between MSC and placebo groups throughout 1-year follow-up visit.	MSC administration improved in whole-lung lesion volume compared with the placebo with a difference of −10.8% (95% CI: −20.7%, −1.5%, p = 0.030) on day 10.	UC-MSC administration achieves a long-term benefit in the recovery of lung lesions and symptoms in COVID-19 patients

(*Continued*)

Table 2 (Continued).

Reference and Author	Year	Country	Study Design	Study Duration	The Setting of the Study	Population	Sample Size	Sampling Technique	Randomization	Type of Stem Cells
Fanping Meng[110]	2020	London, UK	A parallel assigned controlled, non-randomized, phase I clinical trial			Hospitalized patients with COVID-19	18 hospitalized patients with COVID-19	The study enrolled 18 hospitalized patients with COVID-19 (n = 9 for each group)		Human UC-MSCs

Abbreviations: SD, standard deviation; IL-6, interleukin-6; COVID-19, coronavirus disease-19; MSCs, mesenchymal stem cells; ARDS, acute respiratory distress syndrome; n, sample size; PL-MSCs, placenta-derived MSCs; IV, intravenous; BP, blood pressure; HR, heart rate; O_2, oxygen; UC-MSCs, umbilical cord-derived MSCs; BW, body weight; CRP, C-reactive protein; RT-PCR, reverse transcription polymerase chain reaction; FIO_2, fraction of inspired oxygen; hIDPS, human immature dental pulp stem cells; PT, prothrombin time; PTT, partial thromboplastin time; TL, low dose; TH, high dose; C, placebo; TEAE, treatment-emergent adverse events; NEWS-2, National Early Warning Score-2; ECG, electrocardiogram; SARS-CoV-2, severe acute respiratory syndrome; NaCl, sodium chloride; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; PCT, placebo controlled trial; ANCOVA, analysis of covariance; CI, confidence interval; IQR, interquartile range; MCP1, monocyte chemoattractant protein-1; NK, natural killer cell; CD, cluster of differentiation; IMs, inflammation markers; DC, demographic characteristics; SCT, stem cell transplantation; CS, cytokine storm; WJ-MSCs, Wharton's jelly MSCs; IFN, interferons; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; LIF, leukemia inhibitory factor; AEs, adverse events; SAEs, serious adverse events; mITT, modified intention-to treat; 6-MWT, 6-minute walk test; TX, treatment; MAP, mean arterial pressure; NKT, natural killer-T cells; CCC, critical clinical cases; LD, lung damage; MV, mechanical ventilation.

RCT published studies included in the year 2022 were 8; [58,86,106–111] in 2021 were 5; [1,83,93,112,113] in 2020 one study.[88] The RCTs published from different countries were Indonesia-3; [106,109,112] Iran-2; [58,107] Brazil −2; [108,110] Turkey-2; [83,111] China-2; [1,113] Florida-1; [93] UK-1.[88]

The total pooled sample size was 574 (treatment group (318), control group (256)).[1,58,83,86,88,93,106–113] The highest sample size was reported from China, ie, 100 (100 severe COVID-19 patients with lung damage with UC-MSCs (n = 65) or placebo (n = 35)).[1] The lowest sample size was recorded from Jakarta, Indonesia, ie, 9 patients with low clinical risk COVID-19 infection, and 9 subjects were enrolled and randomly assigned to 1 of the 3 groups: TL, TH, and C.[109]

The reported highest age of the patient category was 69 years,[108] and the lowest age category was 18 years,[106] and the identified age (mean ± SD) is intubated/no comorbidity (48 ± 10.8781), intubated/with comorbidity (62.2857 ± 8.2606), no intubated (56.8571 ± 13.2718); UC-MSC group (n = 65) 60.72 (9.14), placebo group (n = 35) 59.94 (7.79).[111,113] The recorded BMI (body mass index), Kg/m2, of the patient is UC-MSC group (n = 65) 24.71 (3.19), placebo group (n = 35) 25.01 (3.12); UC-MSC (n = 12) 34.5 ± 4.5, control (n = 12) 29.6 ± 3.5; UC-MSC (n = 21) 28.6 (3.5), placebo (n = 24) 28 (5.5).[1,86,93]

Different study measurements were recorded on comorbidities; [1,58,88,93,106,107,110,112,113] SOFA score; [86] PaO_2/FiO_2 ratio; [86,93] laboratory values; [1,88,106,107,109–111,113] mechanical ventilation; [86,88] clinical symptoms; [88,110] inflammatory markers; [83,106,111,112] body mass index; [1,86,93,113] concomitant treatment; [1,93,110,113] adverse events.[1,86,113]

The type of MSCs applied in the studies was MSCs-secretome (1); [106] MSCs (1); [111] PL-MSCs; [107] human immature dental pulp stromal cells (hIDP-SCs) (1);[108] DW-MSC infusion (1); [109] WJ-MSCs (1); [83] majority of the studied transfused UC-MSCs (8).[1,58,86,88,93,110,112,113] The transfused interventional dosage was 1×10^6 cells/kg (6); [58,83,86,93,107,112] 1×10^7 cells/kg (4); [1,88,108,109] 1×10^5 cells/kg (1);[110] 1 million cells/kg (1).[111]

The reported laboratory measurements are haemoglobin, haematocrit, white blood cells (WBC), platelets, erythrocyte, basophils, eosinophils, neutrophils, lymphocytes, monocytes, neutrophils lymphocytes ratio, ureum, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, direct bilirubin, indirect bilirubin, procalcitonin, C-reactive protein (CRP), albumin, glomerular filtration rate (GFR), D-dimer, sodium (Na+), potassium (K+), chloride, ferritin, troponin-I.[1,106,110]

The recorded clinical symptoms are fever, fatigue, cough, shortness of breath (SOB), nausea or vomiting, diarrhea, loss of taste or smell, disorientation, and confusion.[88,110] The documented inflammatory markers are interleukin (IL)-6, IL-10, LIF, VEGF, and ferritin.[1,106,113] The findings on the Sepsis-related Organ-Failure Assessment score (SOFA) are

Intervention	Duration	Outcome Measurement	Study Characteristics	Results	Conclusion
The TX group received 3 cycles of IV infusion of UC-MSCs (3 × 107 cells per infusion) on days 0, 3, and 6. Both groups received standard COVID-19 TX regimens.	UC-MSCs transfusion on days 0, 3, and 7	To evaluate the safety of human UC-MSCs infusions in the TX of patients with moderate and severe COVID-19 pulmonary disease.		No serious UC-MSCs infusion-associated AEs were observed. 2 patients receiving UC-MSCs developed transient facial flushing and fever, and one patient developed transient hypoxia at 12 h post-UC-MSCs transfusion. MV was required in one patient in the TX group compared with four in the control group.	IV UC-MSCs infusion in patients with moderate and severe COVID-19 is safe and well tolerated.

UC-MSC (n = 21) 5.5 (2.7) and placebo (n = 24) 5.9 (2.7).[86] The used concomitant medications are antiviral drugs, immunomodulatory drugs, steroids treatment, antibiotics, corticosteroids, heparin (anticoagulant), only prophylactic dose heparin, therapeutic dose heparin, remdesivir, convalescent plasma, corticosteroids, tocilizumab, hydroxychloroquine, alteplase.[1,86,88,93,110,113]

The observed comorbidities are obesity, diabetes mellitus (DM), heart disease, hypertension (HTN), atrial fibrillation, coronary artery disease (CAD), dyslipidemia, encephalitis, stroke, asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, tuberculosis (TB), stress ulcer, dyspepsia syndrome with alarm sign, kidney disease, sepsis, autoimmune diseases, adenomyosis, mild anemia, fatty liver disease, schizophrenia, cancer[1,86,93,106,110,113] (Table 2 and Table 3).

Discussion

COVID-19, caused by SARS-CoV-2, was first identified in December 2019 as the source of a cluster of respiratory infections.[4,114] There is currently no viable TX for COVID-19.[14] MSC-based therapy might be a potential alternative TX for severe and serious COVID-19.[12] The number of ventilator-free and organ-failure-free days in patients with ARDS was statistically lower in the MSC group than in the placebo group.[75,79] MSCs have been studied in various clinical trials; however, they face hurdles such as carcinogenic risk and particular storage conditions, as well as limited evidence regarding their mode of action. The core of MSCs' distinctive features is attributable to their paracrine activity, notably their exosomes.[53]

The aim of the study was "to identify the effectiveness of RCTs pooling evidence on MSC therapeutic applications during the COVID-19 epidemic". The articles were extracted around 12,567 from the different databases from 1st December 2022 to 31st December 2022. As per the PRISMA checklist, the articles were screened, and find 14 relevant RCTs which reported on MSC applications among COVID-19 patients during the pandemic. The articles were evaluated by the CASP quality assessment tool. The included articles were published between the years 2019–2022.

The included 14 RCTs, the highest 8 studies were conducted in the year 2022 and one study was conducted in the year 2020, and 5 studies were published in the year 2021 with a pooled sample size of n = 574 (treatment group (n = 318) + control group (n = 256) in different countries). The majority of 3 studies were recorded from Indonesia, 2 studies from Iran, 2 studies from Brazil, 2 studies from Turkey, 2 studies from China, 1 study from Florida, 1 study from the UK, and 1 study from France.

Table 3 Demographic Factors of MSC Applications on COVID-19 Patients

Reference	Abdullah[99]		Rebelato[105]		Lanzoni[108]		Monsel[104]		Shi[109]		Shi[86]	
Name of the Comorbidity	Intervention Group	Control Group	UC-MSC	Placebo	UC-MSC	Control	UC-MSC	Placebo	UC-MSC Group	Placebo Group	UC-MSC Group	Placebo Group
	(n=20)	(n=20)	(n=11)	(n=6)	(n = 12)	(n = 12)	(n=21)	(n=24)	(n = 65)	(n = 35)	(n = 65)	(n = 35)
Obesity(BMI>30)	15 (37.5)	13 (32.5)	6 (54.5)	3 (50)	11 (91.7)	5 (41.7)	–	–				
Diabetes mellitus	9 (22.5)	6 (15)	4 (36.4)	3 (50)	5 (41.7)	6 (50)	–	–	12 (18.46%)	5 (14.29%)	12 (18.46%)	5 (14.29%)
Heart disease	11 (27.5)	6 (15)	–	–	1 (8.3)	3 (25)	–	–	–	–		
Hypertension	9 (22.5)	7 (17.5)	6 (54.5)	3 (50)	7 (58.3)	9 (75)	11/15 (73.3%)	10/15 (66.7%)	17 (26.15%)	10 (28.57%)	17 (26.15%)	10 (28.57%)
Atrial fibrillation	–	–	–	–	–	–	2/15 (13.3%)	0 (0%)	–	–	–	–
Coronary artery disease	–	–	–	–	–	–	2/15 (13.3%)	2/15 (13.3%)	–	–	–	–
Dyslipidemia	0 (0)	(2.5)	–	–	–	–	–	–	–	–	–	–
Encephalitis	1 (2.5)	0 (0)	–	–	–	–	–	–	–	–	–	–
Stroke	1 (2.5)	0 (0)	–	–	–	–	2/15 (13.3%)	1/15 (6.7%)	–	–	–	–
Asthma	1 (2.5)	0 (0)	–	–	–	–	-	-	–	–	–	–
COPD			0 (0)	1 (16.7)	–	–	0 (0%)	1/15 (6.7%)	2 (3.08%)	0 (0.00%)	2 (3.08%)	0 (0.00%
Chronic bronchitis			–	–	–	–	–	–	2 (3.08%)	3 (8.57%)	2 (3.08%)	3 (8.57%)
Tuberculosis	1 (2.5)	1 (2.5)	–	–	–	–	–	–	–	–	–	–
Stress ulcer	1 (2.5)	0 (0)	–	–	–	–	–	–	–	–	–	–
Dyspepsia syndrome with alarm sign	0 (0)	1 (2.5)	–	–	–	–	–	–	–	–	–	–
Kidney disease	3 (7.5)	1 (2.5)	1 (9.1)	0 (0)	–	–	–	–	–	–	–	–
Sepsis	2 (5)	0 (0)	–	–	–	–	–	–	–	–	–	–
Autoimmune	1 (2.5)	1 (2.5)	–	–	–	–	–	–	–	–	–	–
Adenomyosis	0 (0)	1 (2.5)	–	–	–	–	–	–	–	–	–	–
Mild anemia	–	–	–	–	–	–	–	–	–	–	–	–
Fatty liver disease	–	–	–	–	–	–	–	–	–	–	–	–

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Schizophrenia	–	–	1 (9.1)	0 (0)	–	–	–	–	–	–	–	–
Cancer	–	–	–	–	0 (0)	1 (8.3)	–	–	–	–	–	–
BMI (Body Mass Index), Kg/m^2	**Shi**[109]		Lanzoni[108]		Monsel[104]		–	–	–	–	–	–
	UC-MSC group (n = 65) 24.71 (3.19)	Placebo group (n = 35) 25.01 (3.12)	UC-MSC (n = 12) 34.5 ± 4.5	Control (n = 12) 29.6 ± 3.5	UC-MSC (n=21) 28.6 (3.5)	Placebo (n=24) 28 (5.5)	–	–	–	–	–	–
Age (mean±SD)	Sahin[110]			**Shi**[109]			–	–	–	–	–	–
	Intubated/no comorbidity (48 ±10.8781)	Intubated/with comorbidity (62.2857±8.2606)	No intubated (56.8571 ±13.2718)	UC-MSC group (n = 65) 60.72 (9.14)	Placebo group (n = 35) 59.94 (7.79)	–	–	–	–	–	–	–
Concomitant medication n(%)	Meng[110]		Rebelato[105]		Lanzoni[108]		Monsel[104]		**Shi**[109]		**Shi**[86]	
	UC-MSCs treatment group (n = 9)	Control group (n = 9)	UC-MSC (n=11)	Placebo (n=6)	UC-MSC (n = 12)	Control (n = 12)	UC-MSC (n=21)	Placebo (n=24)	UC-MSC group (n = 65)	Placebo group (n = 35)	UC-MSC group (n = 65)	Placebo group (n = 35)
Antiviral drugs	Lopinavir/Ritonavir	Lopinavir/ Ritonavir	2 (18.2)	0 (0)	–	–	–	–	32 (49.23%)	20 (57.14%)	32 (49.23%)	20 (57.14%)
Immunomodulatory drugs	–	–	–	–	–	–	2/17 (11.8%)	0 (0%)	–	–	–	–
Steroids treatment	Glucocorticoid	Glucocorticoid	11 (100)	6 (100)					–	–	–	–
Antibiotics			2 (18.2)	1 (16.7)	–	–	–	–	27 (41.54%)	12 (34.29%)	27 (41.54%)	12 (34.29%)
Corticosteroids	–	–			–	–	–	–	13 (20.00%)	9 (25.71%)	13 (20.00%)	9 (25.71%)
Heparin Anticoagulant	–	–	11 (100)	6 (100)	12 (100)	12 (100)	–	–	–	–	–	–
Only a prophylactic dose of heparin	–	–	–	–	9 (75)	7 (58.3)	–	–	–	–	–	–
Therapeutic dose heparin	–	–	–	–	3 (25)	5 (41.7)	–	–	–	–	–	–
Remdesivir	–	–	–	–	9 (75)	7 (58.3)	–	–	–	–	–	–
Convalescent plasma	–	–	–	–	3 (25)	4 (33.3)	–	–	–	–	–	–
Corticosteroids	–	–	–	–	10 (83.3)	9 (75)	–	–	–	–	–	–
Tocilizumab	–	–	–	–	1 (8.3)	4 (33.3)	–	–	–	–	–	–

(*Continued*)

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Table 3 (Continued).

Reference	Abdullah[99]		Rebelato[105]		Lanzoni[108]		Monsel[104]		Shi[109]		Shi[86]	
Name of the Comorbidity	**Intervention Group**	**Control Group**	**UC-MSC**	**Placebo**	**UC-MSC**	**Control**	**UC-MSC**	**Placebo**	**UC-MSC Group**	**Placebo Group**	**UC-MSC Group**	**Placebo Group**
	(n=20)	**(n=20)**	**(n=11)**	**(n=6)**	**(n = 12)**	**(n = 12)**	**(n=21)**	**(n=24)**	**(n = 65)**	**(n = 35)**	**(n = 65)**	**(n = 35)**
Hydroxychloroquine	–	–	–	–	1 (8.3)	2 (18.2)	–	–	–	–	–	–
Alteplase	–	–	–	–	0 (0)%	2 (16.7)	–	–	–	–	–	–
Inflammatory Markers	Abdullah[99]		**Shi**[109]		**Shi**[86]							
Median Interquartile	Intervention Group Day 7 (n=17)	Control group Day 7 (n=18)	–	–	–	–	–	–	–	–	–	–
IL-6	2.270 (1.495–4.455)	2.700 (1.670–8.118)	7.86 (5.63, 9.84)	8.76 (6.54, 11.77)	7.86 (5.63,9.84)	8.76 (6.54,11.77)	–	–	–	–	–	–
IL-10	1.450 (1.240–1.800)	1.615 (1.350–2.018)	–	–	–	–	–	–	–	–	–	–
LIF	6.770 (5.480–8.040)	7.405 (6.770–8.040)	–	–	–	–	–	–	–	–	–	–
VEGF	55.160 (32.775–115.615)	50.055 (27.570–96.773)	–	–	–	–	–	–	–	–	–	–
Ferritin	203 (89.500–401.500)	330.500 (198–552.750)	–	–	–	–	–	–	–	–	–	–
Laboratory parameters	Abdullah[99]		Rebelatto[105]		**Shi**[109]		**Shi**[86]		–	–	–	–
	Intervention group	Control group	UC-MSC (n=11)	**Placebo (n=6)**	–	–	–	–	–	–	–	–
Haemoglobin (16/17)	13.500 (12.150–15.275)	13.400 (11.950–15.150)	13.35±1.69	12.68±2.56	122.68 (14.44)	124.26 (11.83)	122.68 (14.44)	124.26 (11.83)				
Haematocrit (16/17)	37.500 (34.500–43.675)	37.400 (36.300–42.600)	41±5	38±7	–	–	–	–	–	–	–	–
WBC (16/17)	13,190 (9830–17,832.500)	17,110 (10,760–20,240)	10,959.73 ±4591.77	9605 ±3998.52	–	–	–	–	–	–	–	–
Platelets (16/17)	289,500 (191,000–405,500)	336,000 (204,500–378,500)	271,690.91 ±75,889.73	296,500 ±54,013.89	214.00 (174.00, 255.00)	210.00 (176.00, 247.00)	214.00 (174.00,255.00)	210.00 (176.00,247.00)	–	–	–	–

Erythrocyte (16/17)	4.580 (4.253–5.125)	4.680 (4.235–5.115)	–	–	–	–	–	–	–	–	–	–
Basophils (13/15)	0.300 (0.200–0.400)	0.300 (0.200–0.500)	–	–	–	–	–	–	–	–	–	–
Eosinophils (13/15)	0.100 (0–1.900)	0.100 (0–1.100)	–	–	–	–	–	–	–	–	–	–
Neutrophils (13/15)	83.300 (64.950–93.300)	87.300 (73.500–91.700)	9899.73 ±4354.47	8266 ±3671.02	3.48 (2.91, 4.32)	3.83 (2.85, 4.48)	3.48 (2.91,4.32)	3.83 (2.85,4.48)	–	–	–	–
Lymphocytes (13/15)	9.700 (4.100–18.800)	7.400 (4.600–16.300)	737 ±299.55	1652.33 ±2032.80	1.39 (1.19, 1.80)	1.47 (1.24, 1.84)	–	–	–	–	–	–
Monocytes (13/15)	5.900 (2.400–10.700)	4.600 (3–9.400)	–	–	–	–	–	–	–	–	–	–
Neutrophils Lymphocytes Ratio (7/10)	14.090 (8.090–50.580)	13.195 (5.723–23.458)	–	–	–	–	–	–	–	–	–	–
Ureum (12/12)	57.450 (42.175–77.200)	46 (36.500–98.375)	–	–	–	–	–	–	–	–	–	–
Creatinine (12/12)	0.880 (0.713–1.208)	0.700 (0.600–0.923)	2.07±1.71	1.92±1.84	–	–	–	–	–	–	–	–
AST (14/16)	29.500 (21.750–55.250)	29 (23.500–40)	60±33	45±19	–	–	–	–	–	–	–	–
ALT (14/16)	54 (38.250–89.750)	61 (37–91)	49±40	29±14	–	–	–	–	–	–	–	–
Total Bilirubin (mg/dL)	–	–	0.84±1.41	0.33±0.12	–	–	–	–	–	–	–	–
Direct bilirubin (mg/dL)	–	–	0.59±1.17	0.18±0.06	–	–	–	–	–	–	–	–
Indirect bilirubin (mg/dL)	–	–	0.24±0.28	0.15±0.10	–	–	–	–	–	–	–	–
Procalcitonin (14/12)	0.200 (0.050–0.958)	0.130 (0.045–0.323)	–	–	–	–	–	–	–	–	–	–
CRP (16/15)	8.150 (3.025–11.875)	12 (1.500–23.400)	38±81	9±5	1.95 (0.84, 3.53)	1.38 (0.68, 2.26)	1.95 (0.84,3.53)	1.38 (0.68,2.26)				
Albumin (4/9)	3170 (2773–3350)	3030 (2905–3305)	–	–	–	–	–	–	–	–	–	–
GFR (12/12)	92.350 (70.550–110.475)	98.400 (84.100–131.850)	–	–	–	–	–	–	–	–	–	–
D-dimer (14/17)	1765 (581.203–4560)	1500 (488.265–4805)	7.75±10.81	6.45±4.83	0.58 (0.36, 1.11)	0.56 (0.31, 1.12)	0.58 (0.36,1.11)	0.56 (0.31,1.12)	–	–	–	–

(*Continued*)

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Table 3 (Continued).

Reference	Abdullah[99]		Rebelato[105]		Lanzoni[108]		Monsel[104]		Shi[109]		Shi[86]	
Name of the Comorbidity	**Intervention Group**	**Control Group**	**UC-MSC**	**Placebo**	**UC-MSC**	**Control**	**UC-MSC**	**Placebo**	**UC-MSC Group**	**Placebo Group**	**UC-MSC Group**	**Placebo Group**
	(n=20)	**(n=20)**	**(n=11)**	**(n=6)**	**(n = 12)**	**(n = 12)**	**(n=21)**	**(n=24)**	**(n = 65)**	**(n = 35)**	**(n = 65)**	**(n = 35)**
Sodium (14/14)	138.500 (135.750–140.250)	136 (132.750–139.250)							–	–	–	–
Potassium (14/14)	4.110 (3.778–4.493)	4.205 (3.660–4.685)	–	–	–	–	–	–	–	–	–	–
Chloride (14/14)	105.250 (102.825–106.850)	102.600 (100.925–103.800)	–	–	–	–	–	–	–	–	–	–
Ferritin (ng/mL)	–	–	2760.53 ±3167.67	1600.38 ±1258.86		–	–	–	–	–	–	–
Troponin-I (pg/mL)	–	–	218±655	132±209	–	–	–	–	–	–	–	–
Sepsis-related Organ-Failure Assessment score (SOFA)	Monsel[104]					–	–	–	–	–	–	–
	UC-MSC (n=21) 5.5 (2.7)	Placebo (n=24) 5.9 (2.7)			–	–	–	–	–	–	–	–
Clinical Symptoms	Meng[110]		Rebelatto[105]									
	UC-MSCs treatment group (n = 9)	Control group (n = 9)	UC-MSC (n=11)	Placebo (n=6)	–	–	–	–	–	–	–	–
Fever	5/9	2/9	8 (72.7)	5 (83.3)	–	–	–	–	–	–	–	–
Fatigue	4/9	5/9			–	–	–	–	–	–	–	–
Cough	4/9	8/9	9 (81.8)	4 (66.6)	–	–	–	–	–	–	–	–
Nausea or vomiting	–	–	3 (27.3)	2 (33.3)	–	–	–	–	–	–	–	–
Diarrhea	–	–	4 (36.4)	0 (0)	–	–	–	–	–	–	–	–
Loss of taste or smell	–	–	4 (36.4)	3 (50)	–	–	–	–	–	–	–	–
SOB	–	–	9 (81.8)	3 (50)	–	–	–	–	–	–	–	–
Disorientation and confusion	–	–	2 (18.2)	0 (0)	–	–	–	–	–	–	–	–

Abbreviations: SOB, shortness of breath; SOFA Score, Sepsis-related Organ-Failure Assessment score; UC-MSCs, umbilical cord-mesenchymal cells; SD, standard deviation; BMI, body mass index.

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The application of MSCs by the different studies among 14 RCTs was that the majority 8 studies experimented on UC-MSCs among COVID-19 patients and MSC secretome, MSCs, PL-MSCs, hIDPSC, DW-MSC infusion, and WJ-MSCs were experimented by another study. The highest studies' interventional dosage of 1×10^6 cells/kg was used by 6 studies, 1×10^7 cells/kg was used by 4 studies, 1×10^5 cells/kg was used by one study, and 1 million cells/kg was applied by one study. The studies focused on DV, CS, LT, comorbidities, RM, CT, SOFA score, MV, BMI, AEs, IMs, and PaO_2/FiO_2 ratio were all recorded as study characteristics. There is a promising result on pooled evidence of RCTs on MSC applications among COVID-19 patients and may be used in the management of severe infectious disease.

Limitations of the Study

The studies included in this SR were RCT studies published on MSC applications among COVID-19 patients, studies limited to the English language, from the year 2019–2022, and full-text articles.

Conclusion

COVID-19, caused by SARS-CoV-2, was discovered in December 2019 and has since expanded globally. ARDS is a catastrophic consequence of the new COVID-19 pandemic, and it is directly connected to high levels of inflammatory cytokines. MSCs offer a viable therapy against this illness due to their IDM properties. Clinical evidence presented on MSC's therapeutic applications during the COVID-19 pandemic has proven to be a promising therapy for COVID-19 patient recovery with no side consequences, and it may be applied as a routine TX for the prevention of challenging disorders. The study results were explained the good progress of the patient condition during the COVID-19 pandemic times with MSC application with RCT trials. These methods are dramatically brought the progressed effective results among patients with COVID-19.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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