Research Results in Pharmacology

Research Results in Pharmacology 9(2): 75-84
UDC: 615.038
DOI 10.18413/rrpharmacology.9.10031

Review Article

The therapeutic potential of mesenchymal stem cells in COVID-19: Present and future

Mutiara Indah Sari[1], Imam Budi Putra[1], Dadik Wahyu Wijaya[1]

1 Universitas Sumatera Utara, Jl. Dr. Mansyur No. 5 Medan, North Sumatra, Indonesia 20155

Corresponding author: Mutiara Indah Sari (mutiara@usu.ac.id)

Academic editor: Tatyana Pokrovskaia ♦ **Received** 12 February 2023 ♦ **Accepted** 21 May 2023 ♦ **Published** 19 June 2023

Citation: Sari MI, Putra IB, Wijaya DW (2023) The therapeutic potential of mesenchymal stem cells in COVID-19: Present and future. Research Results in Pharmacology 9(2): 75–84. https://doi.org/10.18413/rrpharmacology.9.10031

Abstract

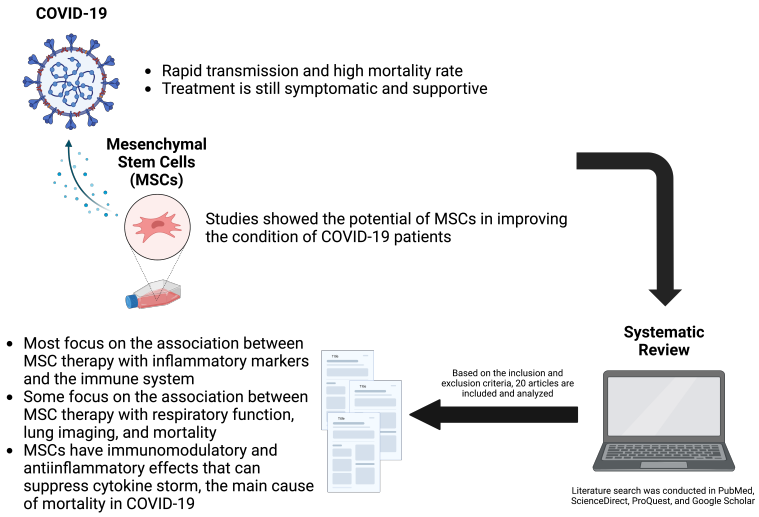
Introduction: Coronavirus disease 2019 (COVID-19) was first reported in 2019 and has since become a health concern due to its rapid spread and high mortality rate. With the discovery of vaccines, there has been a reduction in disease occurrence, transmission, mortality, and morbidity in a population. However, with the emergence of new variants, the available vaccines show varying efficiencies depending on the population and variants, while the present drugs may lose their effectiveness, hence the urgent need to explore effective therapies. Mesenchymal stem cells (MSCs) have been widely studied for their anti-inflammatory and immunomodulatory effects as COVID-19 treatment and shown their potential to improve the condition of COVID-19 patients. This systematic review aims to assess the therapeutic potential of MSCs as anti-inflammatory and immunomodulatory agent in COVID-19.

Materials and Methods: A literature search is performed on PubMed, ScienceDirect, ProQuest, and Google Scholar and potentially relevant studies to review, based on the inclusion and exclusion criteria we have determined. We identified 14,090 publications from our search and excluded duplicates as well as irrelevant studies from title, abstract, and full-text screening. Data extraction and analysis were then performed in the 20 eligible studies.

Results and Discussion: Results show that MSCs improve immune system dysregulation through immunomodulatory and anti-inflammatory effects, through reducing blood C-reactive protein (CRP) and IL-6 levels.

Conclusion: We conclude that MSC is one of the promising treatments in COVID-19 regardless of variants.

Graphical abstract:



Keywords

anti-inflammatory, cell therapy, immunomodulatory, inflammation, virus

Introduction

The respiratory disease caused by novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV) coronavirus disease 2019 (COVID-19) was first reported in China (Guo et al. 2020). Although the details of the virus emergence, such as its origins and transmission potential on humans, are unknown, the increasingly dire cases are thought to come from human-to-human transmission (Munster et al. 2020). COVID-19 could lead to various symptoms, ranging from asymptomatic infection to severe pneumonia as well as multisystem failure that can lead to death (Garcia 2020). COVID-19 has a mortality rate of 30-40% and often causes intensive care unit (ICU) admission. The main cause of death is the immune system dysregulation that will evolve into acute respiratory distress syndrome (ARDS). Up to 90% of ICU patients with ARDS require mechanical ventilation (COVID-ICU Group 2020).

COVID-19 patients are reported to increase in number, with more than 61.8 million cumulative cases and 1.4 million deaths globally (Dilogo et al. 2021). Per January 24, 2020, at least 830 cases had been diagnosed in nine countries in Asia and America. There were 26 deaths, mainly in patients with severe underlying diseases (Guo et al. 2020).

The first COVID-19 case in Indonesia was reported on March 2, 2020. The two patients, aged 31 and 64, were the country's first two cases. It was proposed that COVID-19 had entered Indonesia in the third week of January 2020. On May 21, 2020, 973 new cases of COVID-19 were reported in Indonesia. Indonesia has reported 1,278 cases of COVID-19 death, 6.3% of the country's COVID-19 cases, mainly in four provinces, namely East Java, Jakarta, West Java, and North Sumatra (Sari et al. 2021).

With the discovery of vaccines, there has been a reduction in disease occurrence, transmission, morbidity, and mortality in a population (Alencar et al. 2021). A study by Liang et al. (2021) on a longitudinal data set of 90 countries over 25 weeks showed that an increase in vaccine coverage was associated with a reduction in case fatality ratio (CFR). A systematic review on seven studies involving a total of 1,366,700 participants by Huang and Kuan (2022) also shows that all types of COVID-19 vaccines could effectively prevent the occurrence of severe diseases.

However, with the emergence of new variants, the available vaccines show varying efficiencies (Rabaan et al. 2022). These variants contain mutations in the spike proteins, which many COVID-19 vaccines were based on (Rubin 2021). For example, the Omicron variant has at least 30 amino acid substitutions, with 15 of them located in the receptor-binding portion (Liu et al. 2022). An experiment of incubating the virus from the convalescent sera of patients infected with prior subtypes by Zhang et al. (2021) showed that the sera has relatively low neutralization ability against the Omicron variant. Moreover, the rapid mutation of the virus may cause the present drugs to lose their effectiveness against SARS-CoV-2 spread, hence the urgent need to explore effective clinical therapies (Yin et al. 2022). Currently, there are hundreds of on-going clinical trials of potential COVID-19 drugs. The therapeutic effects of these drugs range from preventing the virus from entering cells, inhibiting viral RNA-dependent RNA polymerase or proteases activities, to maintaining the equilibrium of the immune system of the host and reducing inflammation (Beeraka et al. 2020; Zhou et al. 2021; Yin et al. 2022).

Mesenchymal stem cells (MSCs) from the umbilical cord tissue, placental cells, bone marrow, adipose tissue, and dental pulp have been extensively studied for their anti-inflammatory effects (Galipeau and Sensébé 2018). Mesenchymal stem cells with conditioned media are

called secretomes which function as an effective alternative therapy, mediating their therapeutic effects by retaining trophic molecules in the form of a number of factors (Gwam et al. 2021). Biological factors secreted from cells into the extracellular space can be in the form of dissolved proteins, free nucleic acids, lipids, extracellular vesicles (EV), apoptotic bodies, microparticles, and exosomes (Daneshmandi et al. 2020). MSCs is known to modulate the immune response by cell-to-cell contact and soluble secretory factors. Currently, the immunomodulatory effects of MSCs are mostly attributed to the paracrine activity of MSCs (Weiss et al. 2020).

Since the COVID-19 pandemic, clinical trials using stem cell therapy have been carried out. These studies have reported that MSCs reduce inflammatory cell infiltration and improve lung damage and recovery time as well as the survival of patients in the early phase (Tang et al. 2020). MSCs also show immunomodulatory potential, but the safety and long-term effectiveness of using MSC therapy for severe COVID-19 remains unknown (Tang et al. 2020; Shi et al. 2022).

In this systematic review, we assess the therapeutic potential of MSCs in COVID-19 by reviewing previous studies on MSC therapy in COVID-19.

Materials and Methods

A literature search was conducted in PubMed, Science Direct, ProQuest, and Google Scholar from April 15, 2022 to May 3, 2022. The search was conducted using keywords based on MesH to find research subjects for studies published in the last 3 years (2019-2022) in English language.

Case control, cohort, clinical trials, randomized controlled trials, cross-sectional, retrospective, prospective, pilot, meta-analyses, and observational studies are included. Review articles, comments, abstracts, book excerpts, case reports, bulletin reviews, dissertations and master theses as well as studies in animals and pediatric populations are excluded. The relevance of the study was determined using the inclusion criteria formulated using PICO (Population, Intervention, Comparison and Outcomes), as presented in Table 1.

Table 1. List of questions used for inclusion and exclusion of studies during screening stage

Screening Stage	Questions	Results
Title and abstract screening	· Is this study focused on COVID-19? · Does the study population consist of adult humans? · Is the population of this study treated with MSCs? · Has this study been published within the last 3 years? · Is this study in English? · Is the study design a case control, cohort, clinical trial, randomized controlled trial, cross-sectional, retrospective, prospective, pilot, meta-analysis, or observational study?	Literature included if all questions are answered with 'yes'
Full text screening	· Is there full access to this study? · Does this study have a control group as a comparison?	Literature included if all questions are answered with 'yes'

Results

We identified 14,090 publications related to mesenchymal stem cells and COVID-19 in the PubMed, ScienceDirect, ProQuest, and Google Scholar databases. 10,872 duplicates were identified and excluded. Titles and abstracts were then screened. We found 3,182 irrelevant studies and performed full text screening on studies that were not excluded. Data extraction and analysis were performed on 22 eligible studies. These data are illustrated in Figure 1.

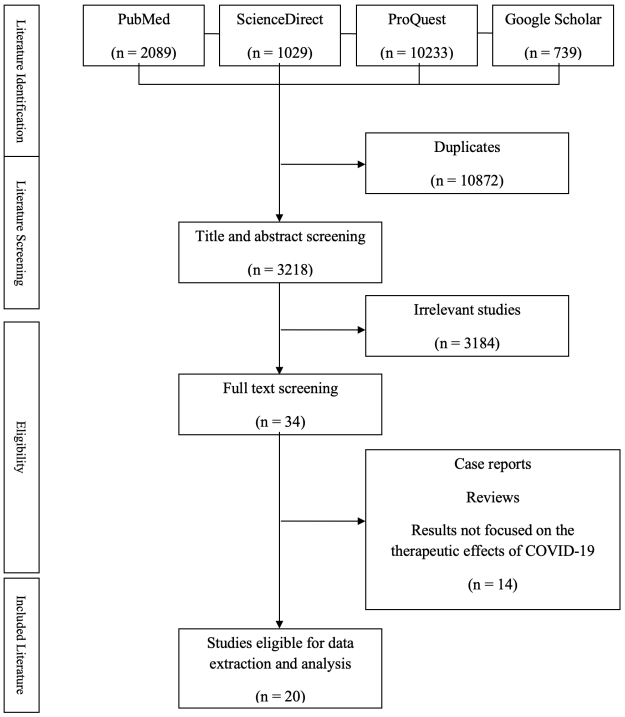


Figure 1. Study selection flowchart

The study design, number of cases, and outcome of the selected articles are summarized in Table 2. Most studies focus on the association between MSC therapy with inflammatory markers and the immune system, though there are several studies that focus on the association between MSC therapy with respiratory function, lung imaging, and mortality.

Discussion

From various sources of MSCs, umbilical cord MSCs can be obtained and cultured easily. These MSCs have demonstrated immunomodulating and tissue repairing effects with low immunogenicity, making them ideal candidates for allogeneic adoptive transfer therapy (Liang et al. 2020). Processing and collection of MSCs from the umbilical cord are simple as well. Cord blood collection can be performed before or after delivery of the placenta and is painless for both the mother and the child. In addition, the number of cells per unit volume in umbilical cord blood is higher than that in bone marrow (Alatyyat et al. 2020). Many studies in this systematic review used the umbilical cord as a source of MSCs for the therapy (Feng et al. 2020; Meng et al. 2020; Shu et al. 2020;

Table 1. Summary of the included studies

Reference	Study Design	Patients	MSC Source	Outcome
Adas et al. (2021)	Prospective Study	30 patients with moderate and critical COVID-19 clinical manifestations; First group (n=10), moderate COVID-19 with conventional treatment. Second group (n = 10), critical COVID-19 with conventional treatment. Third group (n=10), critical COVID-19, with conventional treatment plus MSCs transplantation therapy	Wharton's Jelly	· Statistically lower mortality rate in Group 3 (p<0.001) than in Group 2 · Duration of stay in hospital and ICU of Group 2 and Group 3 were not statistically different (p>0.05) · Duration of stay in the ICU were significantly lower in Group 3 compared to Group 2 (p<0.05) · Lower serum ferritin, fibrinogen, and CRP levels in Group 3 than Group 2 (p<0.05)
Dilogo et al. (2021)	Randomized Controlled Trial	40 COVID-19 patients; 20 UC-MSC group, 20 control group	Umbilical Cord	· Higher survival rate in the UC-MSC group than in the control group (p=0.047) · No significant difference in duration of ICU and ventilator usage · Lower IL-6 in the UC-MSC group (p=0.023)
Fathi-Kazeeroni et al. (2022)	Randomized Controlled Trial	30 COVID-19 patients; 15 given MSC-Secretome, 15 control	Menstrual Blood	· Significantly higher survival rate in the intervention group (p<0.001) · Significant improvement in the percentage of pulmonary involvement of the intervention group (p<0.0001)
Feng et al. (2020)	Pilot Study	16 COVID-19 patients; 8 severe type patients and 7 critically severe type patients	Umbilical Cord	· Overall death rate was 6.25%, whereas the historical mortality rate was 45.4% · Improved oxygenation index after UC-MSCs transplantation · No statistical significance between the D28 mortality rate of severe type and critically severe type (p=1.0000)
Feng et al. (2022)	Cohort Study	28 COVID-19 patients; 8 patients in hUC-MSC group, 20 patients included in control group	Umbilical Cord	· Higher mean FEV1 in hUC-MSC group compared to control group (p<0.01) · Significantly higher FEV1/FVC ratio of the hUC-MSC group than the control group (p<0.05) · Significantly lower rate of wheezing in the hUC-MSC group than the control group (p<0.05) · No significant differences in CT scores between the two groups (p=0.917)
Häberle et al. (2021)	Case Control Study	23 patients with severe COVID-19 ARDS; 5 treated with MSC, 18 control	Unspecified	· No statistically significant difference in ICU stay length in both groups (p=0.07) · Lower mortality rate in MSC group (p=0.32) · No significant difference in CRP and IL-6 between the groups · MSC group had lower number of leukocytes and neutrophils than controls at discharge · Significant increase in ferritin levels in the MSC group
Karyana et al. (2022)	Randomized Controlled Trial	9 COVID-19 patients; 3 given high dose DW-MSC, 3 given low dose DW-MSC, 3 given placebo	Unspecified	· No statistically significant differences among the three groups based on the WHO ordinal scale, PaO2/ FiO2 ratio, NEWS2, or chest X-ray data
Lanzoni et al. (2020)	Randomized Controlled Trial	24 COVID-19 patients; 12 patients in UC-MSC group, 12 patients in control group	Umbilical Cord	· Significantly improved survival rate in the treatment group than the control group (p=0.015) · Significantly improved SAE-free survival rate in the treatment group than the control group (p=0.0081) · Significantly shorter time to recovery in the treatment group than the control group (p=0.0307) · Lower median values and significant differences in the concentration (p<0.05) of various cytokines in the treatment group · Statistically significant decrease in inflammatory cytokine concentrations from day 0 to day 6 in the treatment group · Insignificant differences in viral load between groups at day 0 (p=0.196) or day 6 (p=0.136)
Meng et al. (2020)	Clinical Trial	18 COVID-19 patients; 9 patients in UC-MSC treatment group, 9 patients in control group	Umbilical Cord	· No significant difference in the duration from admission to discharge in both groups (p=0.306) · Numerical, but not statistical decrease in median IgG (p=0.174) and IgM (p=0.114) antibodies titer in UC-MSC treatment group compared to control group
Monsel et al. (2022)	Randomized Controlled Trial	47 COVID-19 patients; 22 assigned to receive UC-MSCs, 25 assigned to receive the placebo	Umbilical Cord	· Insignificant difference in PaO_2/FiO_2-ratio change between day 0 and day 7 between treatment and control group · Significantly lower inflammatory markers in the treatment group · No significant difference in SOFA scores, PaO2/FiO2 ratios, compliance, driving pressure change between day 0 and day 7 and day 14, organ-failure–free days, ventilation-free days, duration of ventilation, time to weaning, time to ICU discharge, time to reach PaO2/FiO2 > 200 or > 300, and mortality to D28 between two groups
Montanucci et al. (2021)	In Vitro Study	18 COVID-19 patients and 14 healthy subjects as control; blood samples collected from the patients	Wharton's Jelly	· In COVID-19 patients, co-culture with free, but mostly microencapsulated hUCMS, was associated with an higher percentage of live cells and lymphocytes · Percentage of the apoptotic peripheral blood mononuclear cell (PBMC) cells significantly raised upon co-culture with both, microencapsulated and hUCMS free cells, as compared to controls
Rebelatto et al. (2022)	Randomized Controlled Trial	17 COVID-19 patients; 11 UC-MSC group, 6 placebo group	Umbilical Cord	· No significant difference in the reduction of viral load over time in both groups · Significantly lower D-dimer value in treatment group than controls (p=0.01) · Lower number of neutrophils in the treatment group than the controls in the second month (p=0.03) and fourth month (p=0.01) · Different IL-6 level in treatment group between baseline and the fourteenth day (p=0.02), second month (p=0.01) and fourth month (p=0.01) · Higher IL-6 values in the treatment group than controls at baseline (p=0.01), day 2 (p=0.01) and day 4 (p=0.04) · Significantly lower IL-6 in the treatment group and higher IL-6 level in the controls at the fourth month (p=0.01) · Higher IL-8 values until the fourteenth day in the treatment group than the controls, a large reduction in values in both groups at the second and fourth months (treatment group, baseline vs 2 months, p=0.01; baseline vs 4 months, p=0.01; control group, baseline vs 2 months, p=0.01, baseline vs 4 months, p=0.01) · No significant difference in chest CT abnormalities between groups

Table 1. Summary of the included studies (continue)

Reference	Study Design	Patients	MSC Source	Outcome
Saleh et al. (2021)	Pilot Study	5 severe COVID-19 patients treated with WJ- MSC	Wharton's Jelly	· Increased percentage of lymphocytes, absolute lymphocyte count, and CD4 and CD8 T cell ratio after cell therapy · Increased SDF-1 and IL-10 levels after cell therapy · Decreased VEGF, TGF-β, IFN-γ, IL-6, and TNFα levels after cell therapy
Sengupta et al. (2020)	Clinical Trial	Patients who met acceptance criteria were enrolled into the following three study cohorts: Cohort A, 1 COVID-19 outpatient with fever and dyspnea with objective vitals of respiratory rate (RR) ≥20 and/or SpO2 <94% on room air (RA); Cohort B, 20 in-patients with hypoxemia as defined by SpO2 ≤90% on RA or patients who require supplemental oxygen to maintain SpO2 ≥94%, who require noninvasive oxygen support; Cohort C, 3 intubated COVID-19 patients with hypoxic respiratory failure on mechanical ventilation	Bone Marrow	· The survival rate in the study was 83%. · Average PaO2/FiO2 ratio increase was 191% (p<0.001) · Mean reductions of CRP, ferritin, and D-dimer were 77%, 43%, and 42% (p<0.001; p<0.001; p<0.05), respectively · Mean reduction of ANC was 32% (p < 0.001) · Total lymphocyte count increased by 36% (p<0.05) with CD3+, CD4+, and CD8+ T lymphocytes increased by 46% (p<0.05), 45% (p<0.05), and 46% (p<0.001), respectively
Shi et al. (2021)	Randomized Controlled Trial	100 severe COVID-19 patients; 65 UC-MSC group, 35 placebo group	Umbilical Cord	· Numerical improvement in whole lung lesion volume from baseline to the twenty-eighth day in the treatment group compared with the controls (p=0.080) · Significant reduction in the proportions of solid component lesion volume in the treatment group compared to the control group (p=0.043)
Shi et al. (2021)	Cohort Study	100 severe COVID-19 patients; 65 UC-MSC group, 35 placebo group	Umbilical Cord	· Improvement in whole lung lesion volume in treatment group compared to control group (p=0.030) · Reduction in the proportions of solid component lesion volume compared to the controls (p=0.013)
Shu et al. (2020)	Randomized Controlled Trial	41 COVID-19 patients; 12 patients in the hUC-MSC treatment group and 29 patients assigned to placebo group	Umbilical Cord	· Shorter median time to clinical improvement in the treatment group (9.0 days) vs. the control group (14.0 days), p=0.006 · Lower day 28 death rate in the treatment group (p=0.543) · Shorter hospital stay in the treatment group (p=0.054) · Significant decrease in CRP and IL-6 levels after the third day in treatment group compared to control group · Significantly better CT scores in treatment group compared to control group
Xu et al. (2021)	Clinical Trial	44 COVID-19 patients; 26 included for experimental group, 18 included for control group	Menstrual Blood	· Lower death rate in experimental group (p=0.048) · Significant improvement in dyspnea while undergoing MSC infusion on the first (p=0.016), third (p=0.040), and fifth (p=0.031) day · No significant improvement in dyspnea while undergoing MSC infusion on the seventh (p=0.631), fourteenth (p=0.635), and thirtieth (p=1.000) day · No significant differences in CRP (p=0.486), IL-6 (p=0.375), FiO2 (p=0.174), and SaO2 (p=0.068) before and after MSC infusion · Significantly improved SpO2 (p<0.001) and PaO2 (p=0.015) after MSC infusion
Zhu et al. (2021)	Randomized Controlled Trial	58 COVID-19 patients; 29 MSC group, 29 placebo group	Umbilical Cord	· Shorter hospital stay in MSC-treatment group (p=0.0198) · Less time required for symptoms remission (p=0.0194) · Significant decrease in CRP levels in MSC group on the third (p=0.044) and fifth (p=0.0035) day · Substantially lower levels of plasma pro-inflammatory cytokines at the twenty-eighth day in MSC group than in placebo group (p<0.05)
Zhu et al. (2022)	Pilot Study	7 severe COVID-19 patients receive aerosol inhalation of haMSC-Exos	Adipose Tissue	· An increase in lymphocyte counts in all patients · A decrease in CRP (6 out of 7), IL-6 (5 out of 7), LDH (6 out of 7) · Different degrees of resolution of pulmonary lesions in all patients

Dilogo et al. 2021; Lanzoni et al. 2021; Shi et al. 2021; Zhu et al. 2021; Monsel et al. 2022; Rebelatto et al. 2022; Shi et al. 2022).

Three studies used Wharton's jelly as a source of MSCs (Montanucci et al. 2020; Adas et al. 2021; Saleh et al. 2022). Wharton's jelly is a gelatinous tissue in the umbilical cord that surrounds two arteries and veins and contains myofibroblast-like stromal cells (Kim et al. 2013; Alatyyat et al. 2020). Neonatal tissues, including the placenta, umbilical cord, amnion, and umbilical cord blood, are readily available, therefore, avoiding invasive procedures and ethical issues (Kim et al. 2013).

Studies by Fathi-Kazerooni et al. (2022) and Xu et al. (2021) used menstrual blood as a source of MSCs. Menstrual blood MSCs show pluripotency and easily accessible and developed (Meng et al. 2007). These cells are a good alternative to MSCs from other sources such as bone marrow, adipose, and postpartum tissue because they have high proliferation rate and can be easily obtained, without the need for surgical procedures or hospitalization. These cells are also free from ethical dilemmas and exhibit novel properties when compared to stem cells derived from adult tissues (Khoury et al. 2014).

Research by Sengupta et al. (2020) used bone marrow as a source of MSCs. MSCs from bone marrow take a long time to collect and process, and are more expensive. Anesthesia and hospitalization are also required for the post-collection pain (Alatyyat et al. 2020). However, MSCs from bone marrow have better osteogenic and chondrogenic differentiation capacities compared to MSCs from adipose tissue, so it is necessary to consider the selection of MSC sources for specific clinical applications (Li et al. 2015).

One study used MSC secretome (Fathi-Kazerooni et al. 2022). MSCs maintain and repair damaged tissue, and secrete factors for tissue regeneration. These are

known as the secretome. Secretome exhibits immunomodulating, anti-inflammatory, pro-angiogenic, and anti-protease properties (de Witte et al. 2018). Compared to MSCs, secretome has advantages in terms of production, storage, management, shelf-life, and potential as a ready-to-use biological product (Vizoso et al. 2017).

A number of studies found that mortality was lower in patients treated with MSCs (Feng et al. 2020; Shu et al.2020; Adas et al. 2021; Häberle et al. 2021; Xu et al. 2021). COVID-19 patients with ARDS and multi-organ dysfunction experience a higher risk of death (Que et al. 2022). Several studies show that this is associated with cytokine release syndrome (CRS), which is sometimes called the cytokine storm. A prior study reported that excessive amounts of pro-inflammatory cytokines were found in the deceased COVID-19 patients (Huang et al. 2019). Another previous study reported that IL-1β, IFN-γ, IL-10, and Monocyte Chemoattractant Protein (MCP)-1 levels were elevated in patients with COVID-19 when compared to healthy controls, while IP-10, MCP-1, MIP1a, and TNF-α levels were elevated in ICU patients compared to non-ICU patients, indicating that disproportionate cytokine production may be associated with severe COVID-19 (Bassetti et al. 2020). However, a systematic review and meta-analysis by Halim et al. (2022) reported that no definitive results could be drawn regarding the association of TNF-α with the severity and mortality of COVID-19.

CRS is one of the main contributing factors in COVID-19 mortality. Pro-inflammatory cytokines produced by immune cells in a positive feedback process cause CRS. Cytokine storms potentially cause organ damage, acute respiratory distress failure, acute heart injury, and secondary infection, which potentially lead to mortality. Therefore, avoiding cytokine storms and neutralizing the key inflammatory factors in CRS may play an important role in reducing mortality in severe cases (Atluri et al. 2020; Zhang et al. 2020).

MSC therapy has often been associated with inflammatory markers and immune function in COVID-19. Several studies have found that MSC therapy lowers IL-6 levels (Shu et al. 2020; Dilogo et al. 2021; Lanzoni et al. 2021; Saleh et al.2021; Rebelatto et al. 2022; Zhu et al. 2022). Cytokine storm plays a contributing role in severe COVID-19 cases. SARS-CoV-2 binds and enters alveolar epithelial cells. The innate and adaptive immune systems are activated by the virus and released numerous cytokines, including IL-6. IL-6 is one of the main mediators in acute inflammatory response and is considered to be the main marker of severe systemic inflammation in patients with SARS-CoV 2 (Zhang et al.2020; Bacca et al. 2021). A systematic review and meta-analysis by Halim et al. (2022) analyzed IL-6 as an independent prognostic factor in COVID-19 severity and mortality.

Systemic inflammation and hypoxic respiratory failure in COVID-19 are associated with an increase in pro-inflammatorymolecules including C-reactive protein (CRP), D-dimer, ferritin, and cytokines (Bacca et al. 2021). Some studies in this systematic review found that MSC therapy caused a decrease in blood CRP levels (Adas et al. 2021; Häberle et al. 2021; Sengupta et al. 2020; Shu et al. 2020; Zhu et al. 2021; Zhu et al. 2022). Elevated serum CRP, a protein whose production is affected by IL-6, had been found to lead to severe clinical manifestations in COVID-19 (Melo et al. 2021).

In the current pandemic, the inflammation due to COVID-19 infection may be the main mechanism for increased CRP, which activates the macrophage complement system and induces an unrestrained inflammatory response. CRP has been studied and found to play a role in acute and chronic inflammation, dysfunction of endothelial cell, formation of thrombus, and activation of coagulation cascade, and will eventually lead to organ failure (Noris et al. 2020; Luan et al.2021). The cytokine storm in severe COVID-19 is highly correlated with elevated CRP (Luan et al. 2021; Stringer et al. 2021).

Studies by Sengupta et al. (2020) and Rebelatto et al. (2022) found that MSC therapy led to a decrease in blood D-dimer levels. Elevated levels of D-dimer may play a role in COVID-19 deaths, but the mechanism is unknown (Li et al. 2021). Various studies have differing opinions, such as an increase in D-dimer levels is due to the development of COVID-19. One study proposed that SARS-CoV-2 infection is often accompanied by a hyperinflammation, which led to endothelial cell dysfunction and damage, which in turn caused increased D-dimer and excessive thrombin production (Levi and van der Poll 2017).

Xu et al. (2021) found a reduction in mortality after MSC therapy, but without a significant change in inflammatory factor levels. However, it is hard to draw a strong conclusion due to the limited size of the study. There may also be a difference in the consistency of service standards at the two different hospitals where this experiment was conducted.

Several studies have found an increase in lymphocytes in patients treated with MSC (Sengupta et al. 2020; Montanucci et al. 2021; Saleh et al. 2021; Zhu et al. 2022). Lymphopenia is found to lead to poorer prognosis in COVID-19 and younger patients (Huang and Pranata, 2020). COVID-19 patients generally exhibit lymphopenia, which is often associated with severe COVID-19 and had a poor outcome, and the deceased patients were reported to have significantly lower lymphocyte counts (Huang et al. 2020; Ruan et al. 2020; Yang et al. 2020). According to streaming mass cytometry results, viral infection causes total lymphocyte dysfunction, even the entire immune system. MSCs are involved in the repair of the lymphocyte population generally through dendritic cells (Leng et al. 2020).

MSCs exhibit good immunomodulatory abilities and are involved in both innate and adaptive immune system (Kavianpour et al. 2020). The interaction mechanism is associated with cell-to-cell contact and induces MSC-regulated immunomodulation (Kean et al. 2013). Immunosuppressive ligands such as Fas ligand (Fas-L) and programmed death-ligand 1 (PD- L1) bind to receptors on immune cells, leading to the loss of immune cell function (Strasser et al.2009; Ostrand-Rosenberg et al. 2014). At the molecular level, both MSC phenotypes can switch between pro- and anti-inflammatory regulation (Becerra and Duran 2021).

Indoleamine 2,3-dioxygenase (IDO) is a rate-limiting enzyme, which degrades tryptophan (Trp) to N-formylkynurenine (Nasef et al. 2007). Human MSCs, stimulated by IFNγ, TNFα or IL-1, express IDO. This leads to immunosuppressive effect. IFNγ triggers MSCs to express IDO in a Signal Transducer and Activator of

Transcription 1 (STAT1)-dependent manner. T-cell suppression in vitro is known to be caused by STAT-1 overexpression, mediated by an increase in MSC (Mounayar et al. 2015). Silencing IDO in human MSCs will lead to immunostimulation, and increase PBMC proliferation at low and high cell density (Li et al. 2012).

In several studies, MSC therapy has been associated with improvements in lung imaging outcome (Fathi-Kazerooni et al.2022; Shi et al. 2021; Shi et al. 2022; Zhu et al. 2022). Studies have also shown improvement in lung function after MSC therapy (Feng et al. 2020; Feng et al. 2021; Monsel et al. 2022). In addition to having immunomodulatory properties to suppress injury due to immune reactions, MSCs can also suppress ARDS exacerbations, repair damaged tissue, and inhibit pulmonary fibrosis (Irmak and Karaoz 2021). MSCs enter the body through the intravenous route and are concentrated in the lungs. This leads to better lung microenvironment, alveolar cell protection, lung function and alsoprevent lung fibrosis (Sinclair et al. 2013).

Various anti-inflammatory mediators are released into the pulmonary microenvironment through various activating receptors. Toll-like receptors (TLRs) are receptors found in many immune cells which could bind to unmethylated CpF-DNA and viral RNA (TLR 9 and TLR3, respectively), leading to downwards cellular signaling pathways. Growth factors such as angiopoietin-1 (Ang-1) and keratinocyte growth factor (KGF) help repair the impaired alveolar-capillary barrier caused by the pathogenesis of ARDS (Levi and van der Poll 2020; Rajarshi et al. 2020; Chouw et al. 2022).

TSG-6, an amino acid glycoprotein 277 produced in response to pro-inflammatory factors by various cells, gives MSCs a notable anti-inflammatory property for repairing acute lung injury (Danchuk et al. 2011). Deposition of metabolites such as lactic acid due to relative hypoxic conditions and metabolism of immune cells at inflammatory locations forms anacidic environment, drawing TSG-6 to the injured site (Han et al. 2022).

However, several studies found that MSC therapy did not lead to significant improvements in pulmonary imaging outcomes (Feng et al. 2021; Karyana et al. 2022; Rebelatto et al. 2022). Administration of MSCs is done intravenously in general. MSCs will end up in the pulmonary microvasculature and many will disappear within 24 hours (Eggenhofer et al. 2011). A study in mice demonstrated that monocytes and neutrophils contribute to MSC clearance from the lung through phagocytosis. Then, these cells will migrate through the bloodstream to the other parts of the body, especially the liver. MSCs may lack the time to secrete adequate levels of immunomodulatory factors before they are lost, but the disintegration of MSCs may lead to the release of intracellular cytokines and growth factors (de Witte et al. 2018).

MSCs are resistant to viral infection. This is because viruses are unable to enter MSCs due to the presence of IFN-stimulated genes (ISG) that can prevent viruses from entering cells. MSCs also secrete IDO, which has antiviral properties (Rocha et al. 2021). However, studies by Lanzoni et al. (2021) and Rebelatto et al. (2022) found no significant difference in viral load between MSC-treated patients and controls.

The rationale of using MSCs to treat COVID-19 is their immunomodulatory effects, which are achieved through autocrine, paracrine, and endocrine pathways (Xu et al. 2022). As the viral variants evade the immune system through the mutations in the spike proteins, with MSCs targeting the regulatory dynamics in the hosts, this approach can be versatile in treating the manifestations caused by the new probable variants (Rubin 2021; Karakaş et al. 2022).

Conclusion

MSCs possess immunomodulatory and anti-inflammatory effects that can suppress cytokine storm, the main cause of mortality in COVID-19, making it a promising treatment for COVID-19. Along with the regenerative properties, MSCs are also capable of improving the lung functions and imaging outcome in the patients. While further studies are needed, we believe MSCs therapy may serve in future clinical applications in treating COVID-19 regardless of variants.

Conflicts of Interests

The authors have no conflict of interests.

References

- Adas G, Cukurova Z, Yasar KK, Yilmaz R, Isiksacan N, Kasapoglu P, Yesilbag Z, Koyuncu ID, Karaoz E (2021) The systematic effect of mesenchymal stem cell therapy in critical covid-19 patients: A prospective double controlled trial. Cell Transplantation 30: 1–14. https://doi.org/10.1177/09636897211024942 [PubMed] [PMC]
- Alencar CH, Cavalcanti LPG, Almeida MM, Barbosa PPL, Cavalcante KKS, Melo DN, de Brito Alves BCF, HeukelbachJ (2021) High effectiveness of SARS-CoV-2 vaccines in reducing COVID-19-related deaths in over 75-year-olds, cearástate, Brazil. Tropical Medicine and Infectious Disease 6(3): 129. https://doi.org/10.3390/tropicalmed6030129 [PubMed] [PMC]
- Alatyyat SM, Alasmari HM, Aleid OA, Abdel-maksoud MS, Elsherbiny N (2020) Umbilical cord stem cells: Background, processing and applications. Tissue and Cell 65: 101351. https://doi.org/10.1016/j.tice.2020.101351 [PubMed]
- Atluri S, Manchikanti L, Hirsch JA (2020) Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically Ill COVID-19 patients: The Case for compassionate use. Pain Physician 23(2): E71–E83. [PubMed]
- Bacca E, Digaetano M, Meschiari M, Franceschini E, Menozzi M, Cuomo G, Mussini C (2021) Immunomodulation for the management of severe SARS-CoV2 infections. State of the art and review of the literature. Biochemical and Biophysical Research Communications 538: 151–155. https://doi.org/10.1016/j.bbrc.2020.11.084 [PubMed] [PMC]
- Bassetti M, Vena A, Giacobbe DR (2020) The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm. European Journal of Clinical Investigation 50(3): e13209. https://doi.org/10.1111/eci.13209 [PubMed] [PMC]
- Becerra J, Duran I (2021) Inflammation, a common mechanism in frailty and COVID-19, and stem cells as a therapeutic approach. Stem Cells Translational Medicine 10(11): 1482–1490. https://doi.org/10.1002/sctm.21-0074 [PubMed] [PMC]
- Beeraka NM, Sadhu SP, Madhunapantula SV, Rao Pragada R, Svistunov AA, Nikolenko VN, Mikhaleva LM, Aliev G (2020) Strategies for targeting SARS CoV-2: Small molecule inhibitors-the current status. Frontiers in Immunology 11: 552925. https://doi.org/10.3389/fimmu.2020.552925 [PubMed] [PMC]

- Chouw A, Milanda T, Sartika CR, Kirana MN, Halim D, Faried A (2022) Potency of mesenchymal stem cell and its secretome in treating COVID-19. Regenerative Engineering and Translational Medicine 8(1): 43–54. https://doi.org/10.1007/s40883-021-00202-5 [PubMed] [PMC]
- COVID-ICU Group (2021) Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: Aprospective cohort study. Intensive Care Medicine 47(1): 60–73. https://doi.org/10.1007/s00134-020-06294-x [PubMed] [PMC]
- Danchuk S, Ylostalo JH, Hossain F, Sorge R, Ramsey A, Bonvillain RW, Lasky JA, Bunnell BA, Welsh DA, Prockop DJ, Sullivan DE (2011) Human multipotent stromal cells attenuate lipopolysaccharide-induced acute lung injury in mice via secretion of tumor necrosis factor-α-induced protein 6. Stem Cell Research &Therapy 2(3): 27. https://doi.org/10.1186/scrt68 [PubMed] [PMC]
- Daneshmandi L, Shah S, Jafari T, Bhattacharjee M, Momah D, Saveh-Shemshaki N, Lo KW, Laurencin CT (2020) Emergence of the stem cell secretome in regenerative engineering. Trends in Biotechnology 38(12): 1373–1384. https://doi.org/10.1016/j.tibtech.2020.04.013 [PubMed] [PMC]
- de Witte SFH, Luk F, Sierra Parraga JM, Gargesha M, Merino A, Korevaar SS, Shankar AS, O'Flynn L, Elliman SJ, Roy D, Betjes MGH, Newsome PN, Baan CC, Hoogduijn MJ (2018) Immunomodulation by therapeutic mesenchymal stromal cells (MSC) is triggered through phagocytosis of MSC by monocytic cells. Stem Cells 36(4): 602–615. https://doi.org/10.1002/stem.2779 [PubMed]
- Dilogo IH, Aditianingsih D, Sugiarto A, Burhan E, Damayanti T, Sitompul PA, Mariana N, Antarianto RD, Liem IK, Kispa T, Mujadid F, Novialdi N, Luviah E, Kurniawati T, Lubis AMT, Rahmatika D (2021) Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: A randomized controlled trial. Stem Cells TranslationalMedicine 10(9): 1279–1287. https://doi.org/10.1002/sctm.21-0046 [PubMed] [PMC]
- Eggenhofer E, Benseler V, Kroemer A, Popp FC, Geissler EK, Schlitt HJ (2012) Mesenchymal stem cells are short-lived and do not migrate beyond the lungs after intravenous infusion. Frontiers in Immunology 3: 297. https://doi.org/10.3389/fimmu.2012.00297 [PubMed] [PMC]
- Fathi-Kazerooni M, Fattah-Ghazi S, Darzi M, Makarem J, Nasiri R, Salahshour F, Dehghan-Manshadi SA, Kazemnejad S(2022) Safety and efficacy study of allogeneic human menstrual blood stromal cells secretome to treat severe COVID-19 patients: clinical trial phase I & II. Stem Cell Research & Therapy 13(1): 96. https://doi.org/10.1186/s13287-022-02771-w [PubMed] [PMC]
- Feng G, Shi L, Huang T, Ji N, Zheng Y, Lin H, Niu C, Wang Y, Li R, Huang M, Chen X, Shu L, Wu M, Deng K, Wei J, Wang X, Cao Y, Yan J (2021) Human umbilical cord mesenchymal stromal cell treatment of severe COVID-19 patients: a 3-month follow-up study following hospital discharge. Stem Cells and Development 30(15): 773–781. https://doi.org/10.1089/scd.2021.0015 [PubMed]
- Feng Y, Huang J, Wu J, Xu Y, Chen B, Jiang L, Xiang H, Peng Z, Wang X (2020) Safety and feasibility of umbilical cord mesenchymal stem cells in patients with COVID-19 pneumonia: A pilot study. Cell Proliferation 53(12): e12947. https://doi.org/10.1111/cpr.12947 [PubMed] [PMC]
- Galipeau J, Sensébé L (2018) Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell 22(6): 824–833. https://doi.org/10.1016/j.stem.2018.05.004 [PubMed] [PMC]
- Garcia LF (2020) Immune response, inflammation, and the clinical spectrum of COVID-19. Frontiers inImmunology 11: 1441. https://doi.org/10.3389/fimmu.2020.01441 [PubMed] [PMC]
- Gwam C, Mohammed N, Ma X (2021) Stem cell secretome, regeneration, and clinical translation: a narrative review. Annals of Translational Medicine 9(1): 70. https://doi.org/10.21037/atm-20-5030 [PubMed] [PMC]
- Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research 7(1): 11. https://doi.org/10.1186/s40779-020-00240-0 [PubMed] [PMC]
- Häberle H, Magunia H, Lang P, Gloeckner H, Körner A, Koeppen M, Backchoul T, Malek N, Handgretinger R, Rosenberger P, Mirakaj V (2021) Mesenchymal stem cell therapy for severe COVID-19 ARDS. Journal of Intensive Care Medicine 36(6): 681–688. https://doi.org/10.1177/0885066621997365 [PubMed] [PMC]
- Halim C, Mirza AF, Sari MI (2022) The association between TNF-α, IL-6, and vitamin D levels and COVID-19 severity and mortality: A Systematic review and meta-analysis. Pathogens 11(2): 195. https://doi.org/10.3390/pathogens11020195 [PubMed] [PMC]
- Han Y, Yang J, Fang J, Zhou Y, Candi E, Wang J, Hua D, Shao C, Shi Y (2022) The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduction and Targeted Therapy 7(1): 92. https://doi.org/10.1038/s41392-022-00932-0 [PubMed] [PMC]
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223): 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5 [PubMed] [PMC]
- Huang I, Pranata R (2020) Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. Journal of Intensive Care 8: 36. https://doi.org/10.1186/s40560-020-00453-4 [PubMed] [PMC]
- Huang YZ, Kuan CC (2022) Vaccination to reduce severe COVID-19 and mortality in COVID-19 patients: a systematic review and meta-analysis. European Review for Medical and Pharmacological Sciences 26(5): 1770–1776. https://doi.org/10.26355/eurrev_202203_28248 [PubMed]
- Irmak DK, Karaoz E (2021) Cellular therapy as promising choice of treatment for COVID-19, and stem cells as a therapeutic approach. IntechOpen. https://doi.org/10.5772/intechopen.96900
- Karakaş N, Üçüncüoğlu S, Uludağ D, Karaoğlan BS, Shah K, Öztürk G (2022) Mesenchymal stem cell-based COVID-19 therapy: Bioengineering perspectives. Cells 11(3): 465. https://doi.org/10.3390/cells11030465 [PubMed] [PMC]
- Karyana M, Djaharuddin I, Rif'ati L, Arif M, Choi MK, Angginy N, Yoon A, Han J, Josh F, Arlinda D, Narulita A, Muchtar F, Bakri RA, Irmansyah S (2022) Safety of DW-MSC infusion in patients with low clinical risk COVID-19 infection: a randomized, double-blind, placebo-controlled trial. Stem Cell Research & Therapy 13(1): 134. https://doi.org/10.1186/s13287-022-02812-4 [PubMed] [PMC] Kaushal K, Kaur H, Sarma P, Bhattacharyya A, Sharma DJ, Prajapat M, Pathak M, Kothari A, Kumar S, Rana S, Kaur M, Prakash A, Mirza AA, Panda PK, Vivekanandan S, Omar BJ, Medhi B, Naithani M (2022) Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. Journal of Critical Care 67: 172–181. https://doi.org/10.1016/j.jcrc.2021.09.023 [PubMed] [PMC]
- Kavianpour M, Saleh M, Verdi J (2020) The role of mesenchymal stromal cells in immune modulation of COVID-19: focus on cytokine storm. Stem Cell Research & Therapy 11(1): 404. https://doi.org/10.1186/s13287-020-01849-7 [PubMed] [PMC]
- Kean TJ, Lin P, Caplan AI, Dennis JE (2013) MSCs: Delivery routes and engraftment, cell-targeting strategies, and immune modulation. Stem Cells International 2013: 732742. https://doi.org/10.1155/2013/732742 [PubMed] [PMC]
- Khoury M, Alcayaga-Miranda F, Illanes SE, Figueroa FE (2014) The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy. Frontiers in Immunology 5: 205. https://doi.org/10.3389/fimmu.2014.00205 [PubMed] [PMC]
- Kim DW, Staples M, Shinozuka K, Pantcheva P, Kang SD, Borlongan CV (2013) Wharton's jelly-derived mesenchymal stem cells: Phenotypic characterization and optimizing their therapeutic potential for clinical applications. International Journal of Molecular Sciences 14(6): 11692–11712. https://doi.org/10.3390/ijms140611692 [PubMed] [PMC]
- Lanzoni G, Linetsky E, Correa D, Cayetano SM, Alvarez RA, Kouroupis D, Alvarez Gil A, Poggioli R, Ruiz P, Marttos AC, Hirani K, Bell CA, Kusack H, Rafkin L, Baidal D, Pastewski A, Gawri K, Leñero C, Mantero AMA, Metalonis SW, Wang X, Roque L, Masters B, Kenyon NS, Ginzburg E, Xu X, Tan J, Caplan AI, Glassberg MK, Alejandro R, Ricordi C (2021) Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. STEM CELLS Translational Medicine 10(5): 660–673. https://doi.org/10.1002/sctm.20-0472 [PubMed] [PMC]
- Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, Fan J, Wang W, Deng L, Shi H, Li H, Hu Z, Zhang F, Gao J, Liu H, Li X, Zhao Y, Yin K, He X, Gao Z, Wang Y, Yang B, Jin R, Stambler I, Lim LW, Su H, Moskalev A, Cano A, Chakrabarti S,

Min KJ, Ellison-Hughes G, Caruso C, Jin K, Zhao RC (2020) Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging and Disease 11(2): 216–228. https://doi.org/10.14336/AD.2020.0228 [PubMed] [PMC]

- Levi M, van der Poll T (2017) Coagulation and sepsis. Thrombosis Research 149: 38–44. https://doi.org/10.1016/j.thromres.2016.11.007
- Li CY, Wu XY, Tong JB, Yang XX, Zhao JL, Zheng QF, Zhao GB, Ma ZJ (2015) Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. Stem Cell Research & Therapy 6(1): 55. https://doi.org/10.1186/s13287-015-0066-5 [PubMed] [PMC]
- Li W, Ren G, Huang Y, Su J, Han Y, Li J, Chen X, Cao K, Chen Q, Shou P, Zhang L, Yuan ZR, Roberts AI, Shi S, Le AD, Shi Y (2012) Mesenchymal stem cells: a double-edged sword in regulating immune responses. Cell Death & Differentiation 19(9): 1505–1513. https://doi.org/10.1038/cdd.2012.26 [PubMed] [PMC]
- Li Y, Deng Y, Ye L, Sun H, Du S, Huang H, Zeng F, Chen X, Deng G (2021) Clinical significance of plasma D-dimer in COVID-19 mortality. Frontiers in Medicine (Lausanne) 8: 638097. https://doi.org/10.3389/fmed.2021.638097 [PubMed] [PMC]
- Liang B, Chen J, Li T, Wu H, Yang W, Li Y, Li J, Yu C, Nie F, Ma Z, Yang M, Xiao M, Nie P, Gao Y, Qian C, Hu M (2020) Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. Medicine 99(31): e21429. https://doi.org/10.1097/MD.0000000000021429 [PubMed] [PMC]
- Liang LL, Kuo HS, Ho HJ, Wu CY (2021) COVID-19 vaccinations are associated with reduced fatality rates: Evidence from cross-county quasi-experiments. Journal of Global Health 11: 05019. https://doi.org/10.7189/jogh.11.05019 [PubMed] [PMC]
- Liu Y, Yu Y, Zhao Y, He D (2022) Reduction in the infection fatality rate of Omicron variant compared with previous variants in South Africa. International Journal of Infectious Diseases 120: 146–149. https://doi.org/10.1016/j.ijid.2022.04.029 [PubMed] [PMC]
- Luan YY, Yin CH, Yao YM (2021) Update advances on C-Reactive protein in COVID-19 and other viral infections. Frontiers in Immunology 12: 720363. https://doi.org/10.3389/fimmu.2021.720363 [PubMed] [PMC]
- Melo AKG, Milby KM, Caparroz ALMA, Pinto ACPN, Santos RRP, Rocha AP, Ferreira GA, Souza VA, Valadares LDA, Vieira RMRA, Pileggi GS, Trevisani VFM (2021) Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: A living systematic review and meta-analysis. PLoS One 16(6): e0253894. https://doi.org/10.1371/journal.pone.0253894 [PubMed] [PMC]
- Meng F, Xu R, Wang S, Xu Z, Zhang C, Li Y, Yang T, Shi L, Fu J, Jiang T, Huang L, Zhao P, Yuan X, Fan X, Zhang JY, Song J, Zhang D, Jiao Y, Liu L, Zhou C, Maeurer M, Zumla A, Shi M, Wang FS (2020) Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. Signal Transduction and Targeted Therapy 5(1): 172. https://doi.org/10.1038/s41392-020-00286-5 [PubMed] [PMC]
- Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, Wang H, Ge W, Bogin V, Chan KW, Thébaud B, Riordan NH (2007) Endometrial regenerative cells: A novel stem cell population. Journal of Translational Medicine 5: 57. https://doi.org/10.1186/1479-5876-5-57 [PubMed] [PMC]
- Monsel A, Hauw-Berlemont C, Mebarki M, Heming N, Mayaux J, Tchoumba ON, Diehl JL, Demoule A, Annane D, Marois C, Demeret S, Weiss E, Voiriot G, Fartoukh M, Constantin JM, Mégarbane B, Plantefève G, Malard-Castagnet S, Burrel S, Rosenzwajg M, Tchitchek N, Boucher-Pillet H, Churlaud G, Cras A, Maheux C, Pezzana C, Diallo MH, Ropers J, Menasché P, Larghero J; APHP STROMA–CoV-2 Collaborative Research Group (2022) Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: a multicenter randomized double-blind trial. Critical Care 26(1): 48. https://doi.org/10.1186/s13054-022-03930-4 [PubMed] [PMC]
- Montanucci P, Pescara T, Greco A, Francisci D, Basta G, Calafiore R (2021) Microencapsulated Wharton Jelly-derived adult mesenchymal stem cells as a potential new therapeutic tool for patients with COVID-19 disease: an in vitro study. American Journal of Stem Cells 10(3): 36–52. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8449139/ [PubMed] [PMC]
- Mounayar M, Kefaloyianni E, Smith B, Solhjou Z, Maarouf OH, Azzi J, Chabtini L, Fiorina P, Kraus M, Briddell R, Fodor W, Herrlich A, Abdi R (2015) PI3kα and STAT1 interplay regulates human mesenchymal stem cell immune polarization. Stem Cells 33(6): 1892–1901. https://doi.org/10.1002/stem [PubMed] [PMC]
- Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E (2020) A novel coronavirus emerging in China — key questions for impact assessment. The New England Journal of Medicine 382(8): 692–694. https://doi.org/10.1056/NEJMp2000929 [PubMed]
- Nasef A, Chapel A, Mazurier C, Bouchet S, Lopez M, Mathieu N, Sensebé L, Zhang Y, Gorin NC, Thierry D, Fouillard L (2007) Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. Gene Expression 13(4-5): 217–226. https://doi.org/10.3727/000000006780666957 [PubMed] [PMC]
- Noris M, Benigni A, Remuzzi G (2020) The case of complement activation in COVID-19 multiorgan impact. Kidney International 98(2): 314–322. https://doi.org/10.1016/j.kint.2020.05.013 [PubMed] [PMC]
- Ostrand-Rosenberg S, Horn LA, Haile ST (2014) The programmed death-1 immune suppressive pathway: Barrier to anti-tumor immunity. The Journal of Immunology 193(8): 3835–3841. https://doi.org/10.4049/jimmunol.1401572 [PubMed] [PMC]
- Que Y, Hu C, Wan K, Hu P, Wang R, Luo J, Li T, Ping R, Hu Q, Sun Y, Wu X, Tu L, Du Y, Chang C, Xu G (2022) Cytokine release syndrome in COVID-19: a major mechanism of morbidity and mortality. International Reviews of Immunology 41(2): 217–230. https://doi.org/10.1080/08830185.2021.1884248 [PubMed] [PMC]
- Rabaan AA, Mutair AA, Hajissa K, Alfaraj AH, Al-Jishi JM, Alhajri M, Alwarthan S, Alsuliman SA, Al-Najjar AH, Al Zaydani IA, Al-Absi GH, Alshaikh SA, Alkathlan MS, Almuthree SA, Alawfi A, Alshengeti A, Almubarak FZ, Qashgari MS, Abdalla ANK, Alhumaid S (2022) A comprehensive review on the current vaccines and their efficacies to combat SARS-CoV-2 variants. Vaccines (Basel) 10(10): 1655. https://doi.org/10.3390/vaccines10101655 [PubMed] [PMC]
- Rajarshi K, Chatterjee A, Ray S (2020) Combating COVID-19 with mesenchymal stem cell therapy. Biotechnology Reports 26: e00467. https://doi.org/10.1016/j.btre.2020.e00467 [PubMed] [PMC]
- Rebelatto CLK, Senegaglia AC, Franck CL, Daga DR, Shigunov P, Stimamiglio MA, Marsaro DB, Schaidt B, Micosky A, de Azambuja AP, Leitão CA, Petterle RR, Jamur VR, Vaz IM, Mallmann AP, Carraro Junior H, Ditzel E, Brofman PRS, Correa A (2022) Safety and long-term improvement of mesenchymal stromal cell infusion in critically COVID-19 patients: a randomized clinical trial. Stem Cell Research & Therapy 13(1): 122. https://doi.org/10.1186/s13287-022-02796-1 [PubMed] [PMC]
- Rocha JLM, de Oliveira WCF, Noronha NC, Dos Santos NCD, Covas DT, Picanço-Castro V, Swiech K, Malmegrim KCR (2021) Mesenchymal stromal cells in viral infections: Implications for COVID-19. Stem Cell Reviews and Reports 17(1): 71–93. https://doi.org/10.1007/s12015-020-10032-7 [PubMed] [PMC]
- Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine 46(5): 846–848. https://doi.org/10.1007/s00134-020-05991-x [PubMed] [PMC]
- Rubin R (2021) COVID-19 vaccines vs variants-determining how much immunity is enough. Journal of the American Medical Association 325(13): 1241–1243. https://doi.org/10.1001/jama.2021.3370 [PubMed]
- Saleh M, Vaezi AA, Aliannejad R, Sohrabpour AA, Kiaei SZF, Shadnoush M, Siavashi V, Aghaghazvini L, Khoundabi B, Abdoli S, Chahardouli B, Seyhoun I, Alijani N, Verdi J (2021) Cell therapy in patients with COVID-19 using Wharton's jelly mesenchymal stem cells: a phase 1 clinical trial. Stem Cell Research & Therapy 12(1): 410. https://doi.org/10.1186/s13287-021-02483-7 [PubMed] [PMC]
- Sari DK, Amelia R, Dharmajaya R, Sari LM, Fitri NK (2021) Positive correlation between general public knowledge and attitudes regarding COVID-19 outbreak 1 month after first cases reported in Indonesia. Journal of Community Health 46(1): 182–189. https://doi.org/10.1007/s10900-020-00866-0 [PubMed] [PMC]
- Sengupta V, Sengupta S, Lazo A, Jr., Woods P, Nolan A, Bremer N (2020) Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. Stem Cells and Development 29(12): 747–754. https://doi.org/10.1089/scd.2020.0080 [PubMed] [PMC]
- Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, Wang S, Zhang C, Yuan X, Xu Z, Huang L, Fu JL, Li Y, Zhang Y, Yao WQ, Liu T, Song J, Sun L, Yang F, Zhang X, Zhang B, Shi M, Meng F, Song Y, Yu Y, Wen J, Li Q, Mao Q, Maeurer M, Zumla A, Yao C, Xie WF, Wang FS (2021) Effect of human umbilical cord-derived mesenchymal

stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduction and Targeted Therapy 6(1): 58. https://doi.org/10.1038/s41392-021-00488-5 [PubMed] [PMC]

- Shi L, Yuan X, Yao W, Wang S, Zhang C, Zhang B, Song J, Huang L, Xu Z, Fu JL, Li Y, Xu R, Li TT, Dong J, Cai J, Li G, Xie Y, Shi M, Li Y, Zhang Y, Xie WF, Wang FS (2022) Human mesenchymal stem cells treatment for severe COVID-19: 1-year follow-up results of a randomized, double-blind, placebo-controlled trial. EBioMedicine 75: 103789. https://doi.org/10.1016/j.ebiom.2021.103789 [PubMed] [PMC]
- Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, Ji N, Zheng Y, Chen X, Shi L, Wu M, Deng K, Wei J, Wang X, Cao Y, Yan J, Feng G (2020) Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Research & Therapy 11(1): 361. https://doi.org/10.1186/s13287-020-01875-5 [PubMed] [PMC]
- Sinclair K, Yerkovich ST, Chambers DC (2013) Mesenchymal stem cells and the lung. Respirology 18(3): 397–411. https://doi.org/10.1111/resp.12050 [PubMed]
- Strasser A, Jost PJ, Nagata S (2009) The many roles of FAS receptor signaling in the immune system. Immunity 30(2): 180–192. https://doi.org/10.1016/j.immuni.2009.01.001 [PubMed] [PMC]
- Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, Quinn TJ, Vilches-Moraga A, Stechman MJ, Pearce L, Moug S, McCarthy K, Hewitt J, Carter B (2021) COPE Study collaborators. The role of C-reactive protein as a prognostic marker in COVID-19. International Journal of Epidemiology 50(2): 420–429. https://doi.org/10.1093/ije/dyab012 [PubMed] [PMC]
- Tang L, Jiang Y, Zhu M, Chen L, Zhou X, Zhou C, Ye P, Chen X, Wang B, Xu Z, Zhang Q, Xu X, Gao H, Wu X, Li D, Jiang W, Qu J, Xiang C, Li L (2020) Clinical study using mesenchymal stem cells for the treatment of patients with severe COVID-19. Frontiers in Medicine 14(5): 664–673. https://doi.org/10.1007/s11684-020-0810-9 [PubMed] [PMC]
- Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R (2017) Mesenchymal stem cell secretome: Toward cell-free therapeutic strategies in regenerative medicine. International Journal of Molecular Sciences 18(9): 1852. https://doi.org/10.3390/ijms18091852 [PubMed] [PMC]
- Weiss ARR, Lee O, Eggenhofer E, Geissler E, Korevaar SS, Soeder Y, Schlitt HJ, Geissler EK, Hoogduijn MJ, Dahlke MH (2020) Differential effects of heat-inactivated, secretome-deficient MSC and metabolically active MSC in sepsis and allogenic heart transplantation. Stem Cells (Dayton, Ohio) 38(6): 797–807. https://doi.org/10.1002/stem.3165 [PubMed]
- Xu R, Feng Z, Wang FS (2022) Mesenchymal stem cell treatment for COVID-19. EBioMedicine. 77: 103920. https://doi.org/10.1016/j.ebiom.2022 [PubMed] [PMC]
- Xu X, Jiang W, Chen L, Xu Z, Zhang Q, Zhu M, Ye P, Li H, Yu L, Zhou X, Zhou C, Chen X, Zheng X, Xu K, Cai H, Zheng S, Jiang W, Wu X, Li D, Chen L, Luo Q, Wang Y, Qu J, Li Y, Zheng W, Jiang Y, Tang L, Xiang C, Li L (2021) Evaluation of the safety and efficacy of using human menstrual blood-derived mesenchymal stromal cells in treating severe and critically ill COVID-19 patients: An exploratory clinical trial. Clinical and Translational Medicine 11(2): e297. https://doi.org/10.1002/ctm2.297 [PubMed] [PMC]
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. The Lancet Respiratory Medicine 8(5): 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5 [PubMed] [PMC]
- Yin J, Li C, Ye C, Ruan Z, Liang Y, Li Y, Wu J, Luo Z (2022) Advances in the development of therapeutic strategies against COVID-19 and perspectives in the drug design for emerging SARS-CoV-2 variants. Computational and Structural Biotechnology Journal 20: 824–837. https://doi.org/10.1016/j.csbj.2022.01.026 [PubMed] [PMC]
- Zhang C, Wu Z, Li JW, Zhao H, Wang GQ (2020) Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. International Journal of Antimicrobial Agents 55(5): 105954. https://doi.org/10.1016/j.ijantimicag.2020.105954 [PubMed] [PMC]
- Zhang X, Wu S, Wu B, Yang Q, Chen A, Li Y, Zhang Y, Pan T, Zhang H, He X (2021) SARS-CoV-2 Omicron strain exhibits potent capabilities for immune evasion and viral entrance. Signal Transduction and Targeted Therapy 6(1): 430. https://doi.org/10.1038/s41392-021-00852-5 [PubMed] [PMC]
- Zhou YW, Xie Y, Tang LS, Pu D, Zhu YJ, Liu JY, Ma XL (2021) Therapeutic targets and interventional strategies in COVID-19: mechanisms and clinical studies. Signal Transduction and Targeted Therapy 6(1): 317. https://doi.org/10.1038/s41392-021-00733-x [PubMed] [PMC]
- Zhu R, Yan T, Feng Y, Liu Y, Cao H, Peng G, Yang Y, Xu Z, Liu J, Hou W, et al (2021) Mesenchymal stem cell treatment improves outcome of COVID-19 patients via multiple immunomodulatory mechanisms. Cell Research 31(12): 1244–1262. https://doi.org/10.1038/s41422-021-00573-y [PubMed] [PMC]
- Zhu YG, Shi MM, Monsel M, Dai C, Dong XC, Shen H, Li SK, Chang J, Xu CL, Li P, Wang J, Shen M-P, Ren CJ, Chen DC, Qu JM (2022) Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: A pilot study. Stem Cell Research & Therapy 13(1): 220. https://doi.org/10.1186/s13287-022-02900-5 [PubMed] [PMC]

Author Contributions

- **Mutiara Indah Sari**, MD, Department of Biochemistry, Faculty of Medicine, Universitas Sumatera Utara; e-mail: mutiara@usu.ac.id; **ORCID ID** https://orcid.org/0000-0001-6510-2196. The author created the concept and the methodology of the study and participated in drafting the manuscript.

- **Imam Budi Putra**, MD, PhD, Department of Dermatology & Venereology, Faculty of Medicine, Universitas Sumatera Utara; e-mail: imam_65@yahoo.com. The author drafted, revised, edited, and finalized the manuscript.

- **Dadik Wahyu Wijaya**, MD, PhD, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara; e-mail: dadikwahyuwijaya@yahoo.com. The author analyzed the data, participated in revising the manuscript, and provided the final conclusions.