



# REGENERATIVE MEDICINE APPROACHES FOR TREATING COVID-19 DISEASE: A COMPREHENSIVE REVIEW

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## Abstract:

COVID-19 disease is an acute respiratory infectious disease that is caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In 2020, over 79 million reported cases and over 1.7 million deaths globally. The novel coronavirus has gained a lot of attention worldwide. The most common symptoms of COVID-19 are fever, chills, sore throat, severe fatigue or tiredness, new and persistent cough, tight chest or chest pain, and shortness of breath. Various studies were carried out to find the best therapeutic approach for the management of diseases. Regenerative medicine provides various cell-tissue therapeutics products like stem cell therapy, exosomes, Chimeric antigen receptor T-cell therapy, and natural killer cell therapy. IL-6 signaling pathways are the major pathways for the management of COVID-19 disease by a trans-signaling pathway. This article reveals the underlying mechanisms for the pathogenesis of coronavirus, and available therapeutic regenerative medicine approaches, and searches for better and more effective medicine in view of the management of the COVID-19 disease.

**Key point:** COVID-19 Disease, Regenerative medicine, Mesenchymal stem cell therapy, Exosomes

## Introduction:

At the end of December 2019, the novel coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) [1]. As of the second week of November 2020, there were about 53.5 million confirmed cases of COVID-19 worldwide, with 1,350,000 deaths [2]. The virus was evolving quickly. Since SARS-CoV-2 was isolated and identified, several kinds of research investigations have been conducted in order to better understand the virus's epidemiological characteristics and mode of

transmission, as well as to establish diagnostic tools and emergency treatment approaches. Approximately 80% of individuals infected with SARS-CoV-2 are asymptomatic or display mild flu-like symptoms, such as fever, sore throat, cough, myalgia, dyspnoea, and fatigue. However, there have also been reports of new symptoms such as ageusia, anosmia, and CNS and gastrointestinal issues [3, 4]. Approximately 15% of infected patients develop severe pneumonia, and 5% develop acute respiratory distress syndrome (ARDS), the most severe COVID-19 complication characterized by diffuse alveolar-capillary damage [5, 6]. Although the specific root cause of the life-threatening condition of COVID-19 is unknown, severe inflammation triggered by a high level of pro-inflammatory cytokines is thought to be the main reason for disease severity and death [7].

On further investigation, it was found that pneumonia is an acute respiratory infectious disease brought on by the novel  $\beta$ -coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that had never before been documented [8]. CoVs are enveloped viruses with polyadenylated and capped 27–32 kb genomic RNA [9]. They are separated into the following four groups: beta, gamma, delta, and alpha [10]. The symptoms of the common cold (fever, chills, sore throat, new and persistent cough, tightness in the chest with chest pain, and shortness of breath) in the COVID-19 disease have been triggered by the CoV species such as HKU1, NL63, OC43, and 229E. Middle East Respiratory Coronavirus and SARS-CoV are serious respiratory viruses responsible for the illness called COVID-19. The third member of the CoV family of viruses is SARS-CoV-2 which can infect a wide range of people and cause potentially fatal illness [11].

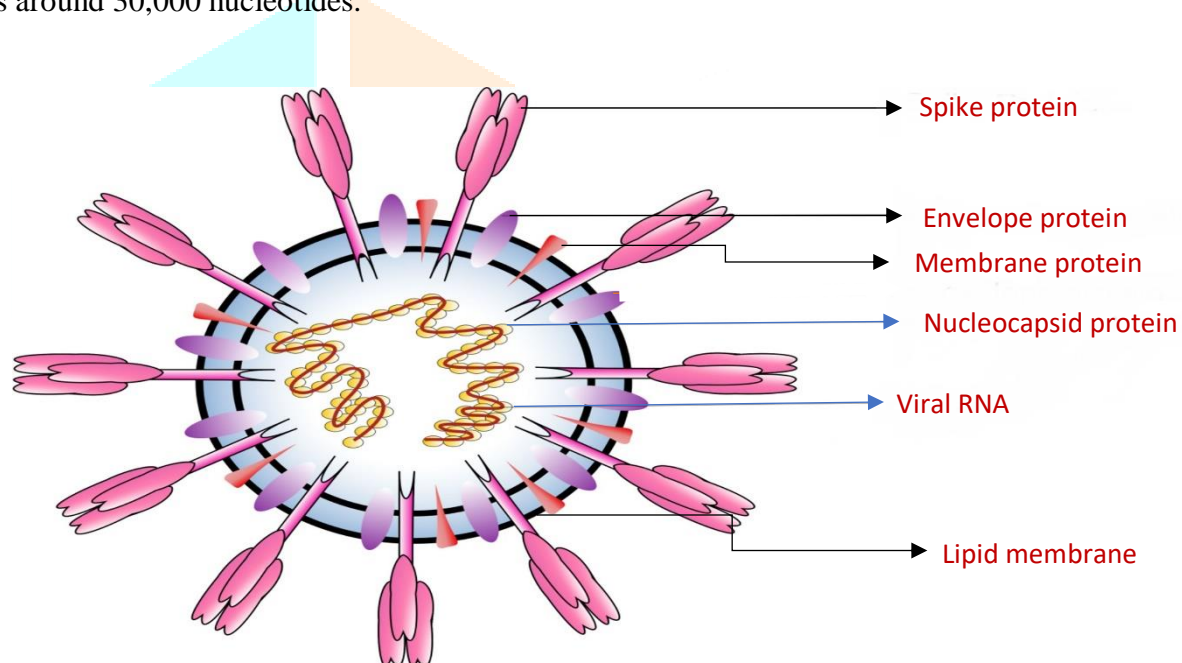
Numerous cell-tissue therapies and associated products are available through regenerative medicine. It tackles the utilization of cells directly as therapeutic agents or as a way of delivering other therapeutic agents, including cytokines. Mesenchymal stem cells are of special relevance to this topic because they have the potential to be employed in regenerative medicine and have exhibited promising results in the regulation of inflammatory responses [12]. Moreover, Mesenchymal stem cells have the ability to release exosomes which are tiny extracellular membrane vesicles [13]. Exosomes are generated from cells that function as carriers of cell therapy by influencing intercellular communication through a range of macromolecules they can carry. Notably, exosomes have significant effects on immune modulation as a result, they may find use in cancer treatment [14, 15].

A notable anti-tumor impact has also been revealed by natural killer (NK) cell therapy, which is mostly explained by the direct impact of NK cells on the immune system [16]. Regenerative medicine can therefore be used to treat COVID-19, a virus linked to immunological dysregulation, by means of its immunoregulatory actions [17].

## ❖ Overview of SARS-CoV-2 virus

The recent outbreak of COVID-19 caused by a novel beta-coronavirus (CoV) was a major worldwide medical and economic challenge. Therefore, specifying the therapeutic approaches and the mechanisms of action that lead to these strategies. Reviewing the published papers in regard to the mechanisms and we have tried to draw an overall concept of the involved mechanism and the related therapeutic approaches. The type of documents used to obtain the data were original articles, review articles, and HTML documents from official websites (e.g., WHO). Search terms included MeSH (Medical Subject Headings) terms, “coronavirus, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, along with focusing on novel therapeutic approaches”. The registered and active clinical trials were found on ClinicalTrials.gov and the index of studies of novel coronavirus pneumonia in the Chinese Clinical Trial Registry [18].

The coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2) has spread rapidly across the entire world. The single-stranded RNA genome of SARS-CoV-2, an enveloped, plus-stranded RNA virus, offers around 30,000 nucleotides.

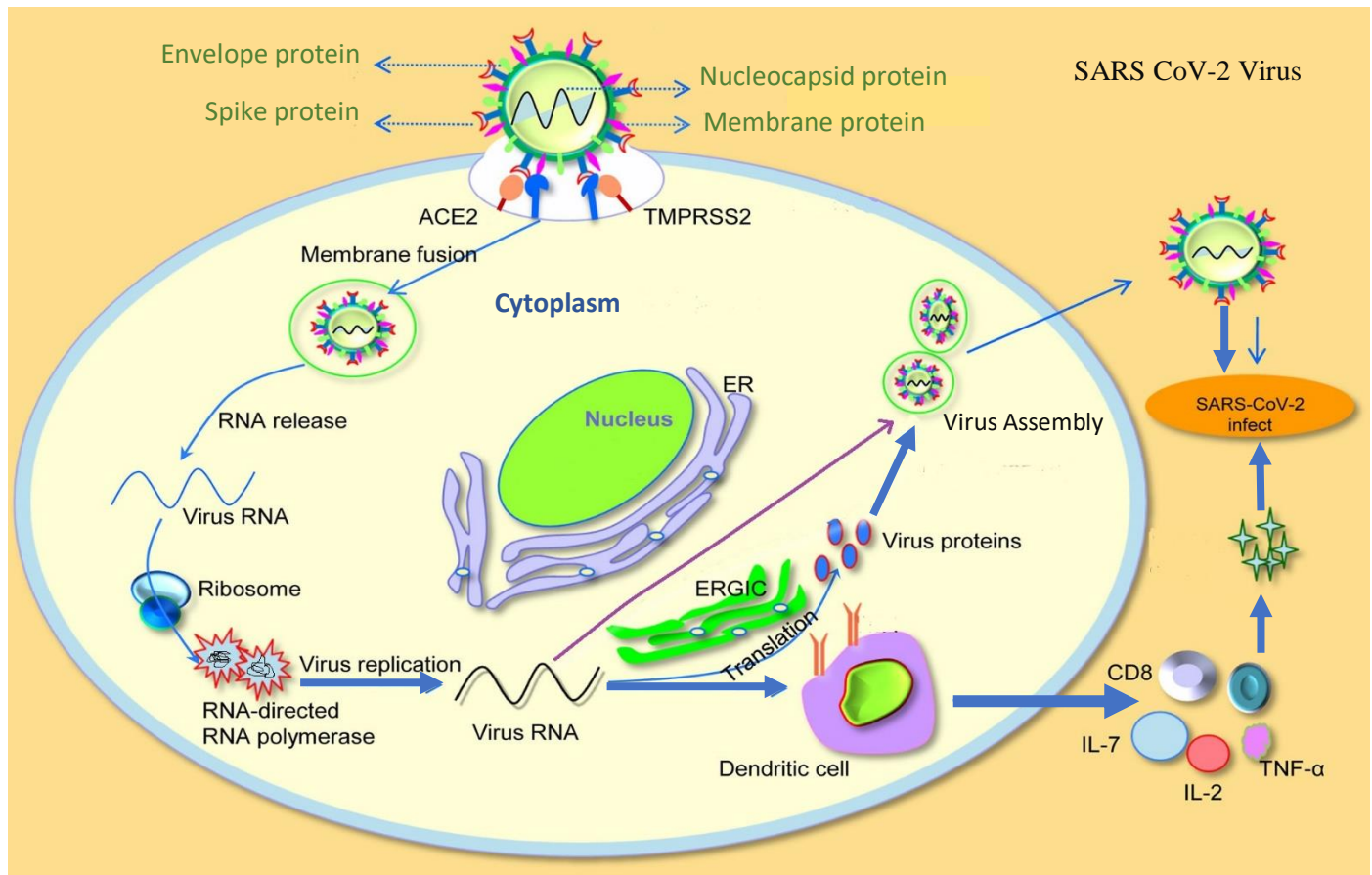


(Figure-1. SARS CoV-2 Virus Structure)

Each of the 29 proteins encoded by the SARS-CoV-2 genome: 16 non-structural, 4 structural, and 9 accessory proteins [19]. The genome organization of  $\beta$ -coronaviruses is exhibited by SARS-CoV-2.

The 14 functional open reading frames (ORFs) in the genome are comprised of two noncoding regions at both ends and multiple regions encoding for structural, accessory, and non-structural proteins (NSPs). 16 NSPs (nsp1–nsp16) that are necessary for viral RNA synthesis are encoded by ORF1a and ORF1b [20]. Four structural proteins are needed for the assembly of the virus: the spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein. A selection benefit is provided by nine accessory proteins in the infected host [21].

## SARS-CoV-2 Virus Cell Entry and Replication



(Figure-2. SARS CoV-2 virus cell entry and Replication)

SARS-CoV may directly bind at the cell surface when appropriate exogenous protease is present. This entry point is thought to be 100–1000 times more effective than the endosomal pathway [22]. One important component of tropism is the presence of proteases in the extracellular environment. As a respiratory pathogen, SARS-CoV has long time recognized as being cleaved by respiratory tract proteases, those belonging to the transmembrane protease/serine subfamily (TMPRSS), TMPRSS2, or HAT (TMPRSS11d) [23]. It is true that SARS-CoV fusion can be induced by both TMPRSS2 and HAT (or TMPRSS11d) [24–27]. When target cells express TMPRSS2, the susceptibility of SARS-CoV S-pseudo typed virions to cathepsin inhibitors is reduced [26, 27]. Although they are less susceptible to neutralizing antibodies, SARS-CoV S-pseudo typed virions generated in cells expressing TMPRSS2 still require endosomal cathepsin for entrance. This effect was ascribed to the supernatant's release of spike fragments, which attract antibodies and could play a significant role in the virus's spread [26]. It has been demonstrated that HAT and TMPRSS2 may process the spike protein differently: HAT cleaves the SARS-CoV S protein primarily at R667, whereas TMPRSS2 cleaves the protein at several locations, most notably in a region close to S2'. The specific locations of the protease cleavage sites are still unknown [24].

## Pathophysiology of Coronavirus Cell Entry Mediated by the Viral Spike Protein

The spike protein is a large type I transmembrane protein that can contain up to 1,400 amino acids for the feline coronavirus (FCoV) and 1,160 amino acids for the avian infectious bronchitis virus (IBV). Furthermore, this protein has 21 to 35 N-glycosylation sites, making it highly glycosylated. On the surface of the virion, spike proteins assemble into trimers to form the distinctive "corona," or crown-like appearance. Every CoV spike protein's ectodomain is organized identically in two domains: the C-terminal S2 domain, which facilitates fusion, and the N-terminal S1 domain, which binds to receptors. The fact that a spike protein is cleaved or not during virions' assembly and exocytosis is a prominent difference amongst coronaviruses. With a few exceptions, the virions of the majority of alpha coronaviruses and the beta coronavirus SARS-CoV comprise an uncleaved spike protein; in contrast, the protein is found to be cleaved between the S1 and S2 domains in some beta- and all gamma coronaviruses, usually by the Golgi-resident host protease furin. It's interesting to note that different strains of the beta coronavirus mouse hepatitis virus (MHV), like MHV-2 and MHV-A59, exhibit distinct cleavage requirements. This has significant effects on their fusogenicity. While the S1 subunit exhibits sequence divergence even within species of the same coronavirus, the S2 subunit is the most conserved region of the protein. N-terminal domain (NTD) and C-terminal domain (CTD) are the two subdomains that make up the S1. Both have the ability to bind a range of proteins and carbohydrates and act as receptor-binding domains (RBDs). A class I fusion protein is the coronavirus spike protein [28]. This class of fusion proteins is characterized by the formation of an  $\alpha$ -helical coiled-coil structure; these proteins contain regions in their C-terminal part that are predicted to form coiled coils and have an  $\alpha$ -helical secondary structure. The class I fusion protein family's archetypal member and one of the best-characterized to date is the influenza hemagglutinin protein (HA) [29].

The MHV receptor was the first coronavirus receptor to be discovered in 1991 [30]. To infect cells, MHV binds to the adhesion molecule known as CEACAM1 (Carcinoembryonic antigen-cell adhesion molecule). Type I transmembrane protein CEACAM1 is a member of the immunoglobulin superfamily. The multifunctional protein CEACAM1 is involved in cell signaling and adhesion, among other processes. N, A1, B, and A2 are the four Ig constant region-like domains found in the CEACAM1 ectodomain. MHV binding involves CEACAM1's N-terminal domain N [31, 32]. CEACAM1 has two allelic forms: CEACAM1a and CEACAM1b. Although both of them are capable of acting as receptors, CEACAM1a's binding is far more effective [31].

## Regenerative Medicine: Concepts and Approaches

The urgency for disruptive technologies continues to be underscored by the rising tide of chronic diseases afflicting an aging global population [33]. By 2020, chronic diseases—in particular cardiovascular diseases, cancer, diabetes, and respiratory conditions—will collectively cause more than 70% of all deaths in the world [34, 35]. Moreover, among people 60 years and older, half suffer from disabilities—most frequently visual and hearing impairments, dementia, or osteoarthritis [36]. The goal of regenerative medicine is to restore damaged tissues and put new organs together, providing next-generation approaches to support long-term wellness and decrease the financial burden of managing chronic diseases [37].

Regenerative medicine is an interdisciplinary field that employs various techniques to replace or expedite damaged or diseased human cells or tissues in order to restore normal tissue function. These strategies include proliferating progenitor cells, stem cells, or tissues; utilizing exosomes and cells as delivery systems for genes, cytokines, or other therapeutic agents as well as inducing the body's own repair mechanisms. A particular type of pneumonia known as COVID-19 pneumonia is characterized by diffuse alveolar damage that leads to severe hypoxemia. Lung dysfunction is therefore the most significant cause of death from COVID-19. Here, we examine RM strategies for treating COVID-19 pneumonia based on what RM has been used to treat lung conditions, trauma, or pneumonia caused by other pathogens up to this point. These techniques include stem cell therapy, progenitor cell transplantation, stem cell-derived exosomes, and microRNA therapy [38].

### 1. Stem Cells Based Therapy

Regenerative medicine's future lies in stem cell-based therapy. Stem cells are those that can undergo mitotic cell division to self-renew and differentiate into a wide variety of specialized cell types. It is highly anticipated that they will be used in toxicity screening, drug development, therapy, and regenerative medicine [39].

stem cells are found in the embryonic, foetal, and adult stages of development. They give rise to differentiated cell types, which are the building blocks of organs and tissues. Throughout the postnatal and adult phases of life, differentiated organs contain tissue-specific stem cells that play a crucial role in the healing process after an organ injury. Three primary features of stem cells are (a) clonality (usually originating from a single cell), (b) potency (ability to differentiate into multiple cell types), and (c) self-renewal (large-scale proliferation). Different types of stem cells may have different qualities. For instance, the ability to self-renew and be potent is a characteristic of embryonic stem cells (ESCs) derived from the blastocyst, whereas adult tissue stem cells have limited capacity for self-renewal due to their limited ability to proliferate and differentiate into only specific tissue types [40]. Stem cells are one of PM's main weapons, but this innovative treatment is still in its infancy when compared to other treatments. In the sections, we will go into more detail about stem cell-based therapy as a precision therapeutic candidate for treating COVID-19 and associated diseases.

- **Multipotent somatic stem cells (MSCs)**

Multipotent somatic stem cells consisting three groups constitute a part of the first generation. With more than 60 years of clinical experience, hematopoietic stem cells (HSCs) comprise the first group [41]. The second group, mesenchymal stem/stromal cells (MSCs) have been found to originate from a variety of tissues, including bone marrow, adipose tissue, the umbilical cord, and others [42]. These cells possess distinct characteristics, including immunomodulation, anti-inflammation, angiogenicity, and anti-apoptosis. They were initially utilized in a clinical setting more than 20 years ago [43]. Autologous stem cells belonging to the first generation are listed as follows: bone marrow (B.M.; HSC and MSC), adipose tissue (AT; MSCs), cord blood (C.B.; HSC), cord tissue (C.T.; HSC and MSC), and second generation induced pluripotent stem cells (iPSCs) [44]. The following section provides an explanation of the cell sources and studies related to COVID-19 disease. Adult stem cells or multipotent somatic stem cells are found in every person's body and have the ability to regenerate and differentiate into any type of cell found in that organ [45]. HSCs and MSCs are the most commonly used stem cell sources among these, with the aim of cell therapy [44].

The most beneficial sources of stem cells for precision medicine are autologous ones. C.B., CT, B.M., and AT have been the pertinent sources of autologous stem cells. The easily accessible waste products C.B. and C.T. are the result of accommodation. HSCs are present in C.B., while MSCs, which are scarce and need to be expanded in vitro before being used, are the main component of C.T. [44]. B.M. is a source of MSC and HSC that is used in numerous preclinical and clinical studies to treat different diseases [46].

With the increasing use of cells, especially stem cell therapy in patient care physicians have numerous ways to support Primary arm. Stem cells can differentiate into a variety of cell types and can acquire characteristics from various sources. Some stem cell researchers have proposed MSC therapy as a potential alternative treatment for this novel coronavirus disease since the initial outbreak of the pandemic [47].

- **Mesenchymal Stem Cells (MSCs)**

It has been demonstrated in numerous cells that mesenchymal stem cells (MSCs) are multipotent stromal cells with the ability to differentiate into a wide range of cell types, such as chondrocytes, osteoblasts, and adipocytes. Another study that used allogenic human MSCs derived from bone marrow to treat ARDS patients showed excellent safety and no adverse events related to the treatment. This therapy lessened lung damage in a model of sheep [48,49]. According to prior research, MSC therapy may stimulate the immune system, stem cells can heal damaged tissue, terminate a cytokine storm, and release mediators that reduce inflammation. Pulmonary fibrosis with SARS-CoV-2 infection may be prevented by the use of MSCs [50].

MSCs have demonstrated good safety and low risk in both experimental and clinical research, including numerous immune-mediated inflammatory diseases [48, 51]. MSCs have been demonstrated in earlier research to lower H5N1 influenza virus in elderly patients with acute lung injury and increase the survival rate of H7N9-infected patients with ARDS who do not experience life-threatening complications [52, 53]. Additionally, MSCs can influence dendritic cells' (DCs') induction of inflammatory cytokine secretion [54, 55]. Ling et al.'s research discovered that lung epithelial cells expressed ACE2, while lung stem cells expressed stage-specific embryonic antigen-1, stem cell antigen-1, cytokeratin-7, and ACE2. Moreover, lung cells infected with SARS-CoV that lacked differentiated stem cells were unable to heal. MSC transplantation might therefore be a workable COVID-19 treatment [56].

- **MSCs Therapy For COVID-19**

Although the COVID-19 pandemic has reached an emergency phase, there were no proven treatments for this infection [57]. The COVID-19 treatment approach depends on supportive care and individualized symptom management due to the lack of effective therapy. Extracorporeal membrane oxygenation is advised for refractory hypoxemia, and oxygen therapy is administered to most patients [58].

Currently available medications for COVID-19 include antiviral, antimalarial, anti-HIV, anti-inflammatory, and monoclonal antibodies. Traditional Chinese medicine has also been used in China and Western nations, as well as medications like remdesivir, chloroquine, lopinavir/ritonavir, and nitazoxanide [59–66]. Numerous investigations on the effects of IL-1, IL-2, IL-6, and TNF- $\alpha$  medications have shown that they can reduce COVID-19 patients' inflammatory responses, offering some guidance on anti-inflammatory treatment for SARS-CoV-2 infection that can lead to better results [67].

Additional clinical trials are necessary to evaluate the newly suggested etoposide-based therapy as a COVID-19 treatment [68]. Numerous medication and vaccine clinical trials are presently being conducted to treat COVID-19.

The second entry receptor for SARS-CoV-2 is CD147 which is a marker of undifferentiated embryonic stem cells. Cells derived from human bone marrow that are specific to certain tissues express its protein. In inflammatory diabetic complications, CD147 inhibition can stop the process [69, 70]. Resident stem cells also known as MSC-like cells, are likely the source of the SARS-CoV-2 infection that can cause pulmonary fibrosis in healthy tissue. Type II pneumocytes play a role in the early stages of pulmonary fibrosis in COVID-19 pneumonia patients. Tissue regeneration and immunosuppression may result from MSC transplantation and anti-CD147 antibodies have been shown to inhibit fibroblasts' normal lung cell differentiation in vitro [71,72]. In the first MSC study, seven patients with COVID-19 pneumonia were given an injection of MSCs by Leng et al. [73]. The patient's clinical symptoms and serum proinflammatory cytokines decreased significantly, and there were no negative side effects. After receiving MSCs, the majority of patients tested negative for SARS-CoV-2 nucleic acid within two weeks. All patients, including 64% of those with improved chest CT scans demonstrated clinical improvement. according to Chen et al. [74]; however, immunomodulation and cardiotoxicity did not significantly improve with MSC therapy.

- **Human Umbilical Cord-Derived MSCs (UC-MSCs)**

Patients with COVID-19 have undergone transplantation of human umbilical cord-derived MSCs (UC-MSCs). An injection of human UC-MSCs was used to treat a female patient with severe COVID-19, and the outcome was good efficacy with no side effects [75]. Twelve COVID-19 patients with severe conditions received UC-MSCs transplantation and reported better clinical outcomes, lower levels of IL-6 and C-reactive protein, and no mortality [76, 77]. No major side effects were reported in a Phase I clinical trial using UC-MSCs for COVID-19, and the lung lesions in four patients with moderate-to-severe disease completely disappeared two weeks after injection [78]. Thirteen patients with severe COVID-19 pneumonia were treated with adipose-tissue-derived MSCs; 70% of the patients showed clinical improvement and a decrease in inflammatory factors [79].

Menstrual blood-derived MSCs were used by Tang et al. [80] to treat severe COVID-19 patients. They observed improvements in SaO<sub>2</sub> and PO<sub>2</sub> as well as the absorption of bilateral pulmonary exudation. Immunity- and matrix-regulatory cells (IMRCs) possess mesenchymal differentiation and self-renewal abilities similar to MSCs. COVID-19 patients recovered and tested negative for the virus after receiving IMRC injections, but many inflammatory cytokines, including TNF- $\alpha$ , M-CSF, IL-3, and IFN- $\alpha$ 2, were suppressed [81]. Prior research has demonstrated that stem cells can heal tissues, trigger the immune system, stop a cytokine storm, and release anti-inflammatory mediators. Therefore, pulmonary fibrosis brought on by an infection with SARS-CoV-2 may be avoided. Because interferon-stimulated genes were expressed by the MSCs, they were resistant to viral infection [82–84]. The features of the studies that are included are given table.



### Characteristics Of Included Stem Cell Studies of Coronavirus Disease 2019

Disease	Treatment	No. of patients	Result	References
COVID-19 pneumonia	MSCs	7	Improve outcome without adverse effects	Leng et al [14], 2020
Severe COVID-19 pneumonia	MSCs	25	all patient gained clinical improvement and 64% gained chest CT scan improvement	Chen et al [52], 2020
Severe COVID-19 pneumonia	UC-MSCs	1	showed remission without side effects.	Liang et al [53], 2020
Severe COVID-19 pneumonia	UC-MSCs	12	The UC-MSCs treatment group had shorter clinical improvement time, reduced CRP and IL-6 levels, and no mortality	Shu et al [55], 2020
Moderate and Severe COVID-19 pneumonia	UC-MSCs	9	No serious adverse events were observed and all the patients recovered and pneumonia were discharged.	Meng et al [56], 2020
Severe COVID-19 pneumonia	AD-MSCs	13	70% of patients had clinical improvement and no adverse effects	
Severe COVID-19 pneumonia	MB-MSCs	2	Bilateral pulmonary exudation had been absorbed and SaO <sub>2</sub> and PO <sub>2</sub> were improved.	Tang et al [58], 2020

(Figure-3. Characteristics of Included Stem Cell Studies of Coronavirus Disease 2019)

#### 2. MSC-Derived Exosomes (MSCs-Ex)

Membrane-bound vesicles (EVs) called exosomes are produced in the endosomal compartment and are essential for cell-cell communication [85]. MSC-derived exosomes (MSCs-Ex) are important therapeutic effectors of MSCs that support tissue regeneration and might be a good substitute for MSCs in cell therapy. They can also be categorized as non-immunogenic because they contain a small number of antigenic components [86]. Several methods have been employed in recent years to deliver exosomes to target tissues in various disease models, as well as some clinical trials [87]. Exosomes contain more than 150 miRNA [88] and 850 proteins [89], which are involved in both pathological and physiological events. Different cytokines and growth factors, including TGF $\beta$ 1, HGF, IL-6, and IL-10, are derived from MSCs and are involved in the regulation of immune responses [90]. MSCs-Ex exhibits therapeutic effects in a variety of conditions, such as wound healing, neurological disorders, kidney diseases, and cardiovascular diseases [87]. Treatment based on MSC-EVs may prevent influenza virus replication and virus-induced lung epithelial cell apoptosis [91]. Moreover, they had the ability to considerably reduce pulmonary inflammation and elevated airway hyper-reactivity (AHR) [92]. Numerous other studies have also supported EVs' ability to treat inflammation and lung injury quickly, effectively, and safely in a clinical setting [93].

EVs may be useful in the management of coronavirus-induced acute respiratory syndrome. High levels of neutralizing antibodies could be induced by exosome-based vaccines containing the Spike (S) proteins of SARS-CoV, as demonstrated by Seraphin K. et al. [94]. One of the four structural proteins of SARS-CoV that facilitates the virus's entry into host cells is the S glycoprotein [95]. As a result, this protein might make a useful target for the creation of a SARS CoV vaccine. Membrane-anchored viral surface protein ectodomains are present in the exosome vaccines. As a result, the exosomes' surface contains multiple copies of the same viral protein, which promotes the B cell receptor's cross-linking. Furthermore, a variety of cellular proteins, including those that aid in the induction of immune responses and neutralizing antibody titers, can be found in exosomes [94]. Consequently, exosomes containing SARS-CoV2 components could be a viable COVID-19 vaccine.

### 3. Natural Killer cells (NK cells)

Innate immune cells such as NK cells and monocytes form the first line of defense against viruses [96]. Due to their ability to identify damage-associated molecular patterns, natural killer cells (NK cells) aid in the removal of malignant or virally-infected cells. Endogenous danger molecules, or DAMPs, are released from cancerous or infected cells and interact with pattern recognition receptors (PRRs) to trigger the innate immune system. To mediate the effector functions of NK cells, receptors involved in various signal transduction pathways are induced to be either inhibited or activated upon transfer of NK cells [97]. The most significant aspect of NK cell characteristics is their cytotoxic effects. The major histocompatibility complex (MHC) expression level of a cell determines the NK cell's affinity for that other cell. Reduced MHC expression in malignant and infected cells directs the transfer of NK cells and their cytotoxic effects to these cells, whereas regular MHC expression prevents NK cells from killing normal cells. Cytokines appear to be essential for NK cells to function properly. Numerous cytokines have been demonstrated to both activate and stimulate natural killer (NK) cells, as well as enable NK cells to secrete cytokines. NK cells are noteworthy for their ability to stimulate interferon production, a sign of efficient antiviral immunity [98].

Consequently, NK cell therapy has been shown to have the potential to treat viral infections and is currently being tested as a treatment for a variety of liquid and solid tumors [99]. NK cell therapy is an appropriate technique for enhancing immune system function in patients with defects in the innate immune response. Future applications across a range of organs and tissues will be made easier by the well-tolerated, generally healthy, and flexible nature of placenta-derived NK cells [100]. When combined with conventional treatment, NK cells may help improve a patient's clinical symptoms when they have pneumonia. To determine whether NK cells are effective in treating COVID-19, more research is required [101].

### Conclusion

To treat COVID-19 disease, several therapies have been made available. One therapy approach that has demonstrated encouraging outcomes in clinical studies is the use of mesenchymal cells. This illness has been effectively treated in a number of locations as a result of the large COVID-19 epidemic and the widespread use of several medications. Thus far, there have been no encouraging outcomes from the usage of these medications, and the illness is still killing a lot of people, with certain nations having mortality rates above 6% as a result. The method outlined in this study suggests that MSCs, which are among the cells that influence the immune system, may be essential in treating this deadly illness. These cells have the potential to greatly enhance crucial circumstances since researchers employ immunosuppressive medications (such as tocilizumab) to help people with COVID-19 symptoms. There have been reports of using these cells in some viral illnesses. The use of these cells to viral illnesses like influenza has also shown outstanding outcomes. These cells and their potential as a treatment for COVID-19 are the subject of several investigations. Even phase 3 research has been advanced in this project. Thus far, the outcomes have met expectations. These pertinent findings should prove to be definitive. More study is required before MSCs may be widely used, even if their use has demonstrated promising results.

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