



## Mesenchymal stem cells and their derived exosomes for the treatment of COVID-19

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### Abstract

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection typically presents with fever and respiratory symptoms, which can progress to severe respiratory distress syndrome and multiple organ failure. In severe cases, these complications may even lead to death. One of the causes of COVID-19 deaths is the cytokine storm caused by an overactive immune response. Therefore, suppressing the overactive immune response may be an effective strategy for treating COVID-19. Mesenchymal stem cells (MSCs) and their derived exosomes (MSCs-Exo) have potent homing abilities, immunomodulatory functions, regenerative repair, and antifibrotic effects, promising an effective tool in treating COVID-19. In this paper, we review the main mechanisms and potential roles of MSCs and MSCs-Exo in treating COVID-19. We also summarize relevant recent clinical trials, including the source of cells, the dosage and the efficacy, and the clinical value and problems in this field, providing more theoretical references for the clinical use of MSCs and MSCs-Exo in the treatment of COVID-19.

**Key Words:** COVID-19; Cytokine storm; Immunomodulation; Mesenchymal stem cell; Mesenchymal stem cell-derived exosomes

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**Core Tip:** As the coronavirus disease 2019 (COVID-19) pandemic normalizes, developing efficient treatments is critical to reducing the strain on the healthcare system. We summarize the various current treatments for COVID-19 and the mechanisms of damage caused by severe acute respiratory syndrome coronavirus 2. Through the comparison to existing treatments, we find that stem cell therapy has more research value. Mesenchymal stem cells (MSC) and their derived exosomes (MSC-Exo) have homing, immunomodulatory, and tissue repair abilities. They can reduce lung injury and inhibit pulmonary fibrosis. We summarized the clinical trials in recent years, analyzed the safety and effectiveness of MSC and MSC-Exo treatment from various aspects such as mechanism of action and therapeutic effect, and provided substantial theoretical support for their clinical application.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-single-stranded genomic RNA virus[1]. The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 infection spread rapidly worldwide. Droplets mainly transmit COVID-19, and infected individuals can show mild to severe symptoms of respiratory diseases, such as fever, cough, malaise, dyspnea, *etc.* Some infected individuals may have clinical symptoms such as muscle pain, headache, loss of smell or taste, expectoration, diarrhea, *etc.* In severe cases, patients may develop pneumonia and respiratory failure, and even lead to death[2]. Recent findings highlight that multiple COVID-19 infections significantly increase the risks associated with mortality, length of hospital care, and enduring complications in various organ systems during both the immediate and long-term recovery phases[3], underscores the persistent health risk of COVID-19, exacerbated by the lack of comprehensive, effective treatments. However, numerous research institutions believe there is still hope for ending the pandemic. Contemporary therapeutic strategies against COVID-19 predominantly fall into two categories: One includes the host's reaction to infection, encompassing treatment of inflammation, thrombosis, acute respiratory distress syndrome (ARDS), and modulation of the renin-angiotensin-aldosterone system; the other involves direct actions against the virus, including the use of antiviral drugs, recovery plasma, and antibody therapies[4]. In addition, in some countries and communities, traditional herbs and vitamins, among other health supplements, are commonly used to tackle COVID-19[5]. Despite the widespread adoption of these treatment methods, they still have their limitations. Here, we have compared the various treatment approaches for COVID-19 (Table 1). The comparison in Table 1 demonstrates that stem cell therapy shows greater research potential and therapeutic value compared to existing treatment options.

Mesenchymal stem cells (MSCs) are distinguished by their intrinsic capacity for self-renewal and the ability to differentiate in multiple directions. As pluripotent stem cells, they have the potential to slow aging and restore balance to organs affected by trauma, or various pathological conditions[6]. MSCs effectively regulate immune responses in clinical research settings, as demonstrated in both animal models and human clinical trials. The application of MSCs is vital in mitigating hyperactive immune reactions and repairing pathological damage[7]. A significant aspect of the therapeutic mechanism of MSCs involves MSC-derived exosomes (MSCs-Exo), classified as a specific category of paracrine extracellular vesicles[8]. These exosomes encapsulate a range of bioactive molecules, including cytokines, growth factors, signaling lipids, mRNAs, and regulatory microRNAs (miRNAs), essential for intercellular communication and the intercellular transfer of these bioactive elements[9]. MSCs-Exo has similar biological functions with MSCs, such as repairing and regenerating tissues and regulating the immune system, suggesting the feasibility of MSCs and MSCs-Exo in the treatment of acute lung injury as well as their prospective application in the healing of COVID-19[10,11]. This paper reviews the potential mechanisms of MSCs and MSCs-Exo in the treatment of COVID-19, reviews and compares the research progress of different sources of MSCs for the remedy of COVID-19, and looks forward to the safety and effectiveness of MSCs targeting these organs through different delivery pathways, which provides the theoretical basis for the subsequent related therapeutic options.

## PATHOGENESIS OF COVID-19 AND DAMAGE TO VARIOUS ORGANS

An exacerbating factor in the progression of COVID-19 is an overactive immune response, characterized by cytokine release syndrome[12]. Specifically, SARS-CoV-2 infects alveolar epithelial cells by mediating membrane fusion *via* angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serines and induces an immune response accompanied by the accumulation of immunoreactive cells, leading to cytokine storm (CS), resulting in lung tissue damage, repair disruption, and subsequent multi-organ dysfunction[13,14]. ACE2 expression in other organs, such as the kidney, liver, and heart, contributes to respiratory and multi-organ complications in critically ill patients[15]. Histological analyses of patients who died from severe COVID-19 showed that lung lesions, characterized by extensive alveolar epithelial damage and inflammatory cell infiltration, were a consequence of viral infection. These pathological changes

**Table 1 Advantages and disadvantages of existing coronavirus disease 2019 treatment approaches**

Treatment categories	Classification	Application examples	Countries and regions	Advantages	Disadvantages
Targeting the host response	Inflammation	Dexamethasone reduces overreaction of the immune system and lowers inflammation[118]	Widely used globally	Reduces the immune system's overreaction and lowers inflammation, decreasing mortality rates	There are uncertainties and individual variabilities, which may entail potential risks and are constrained to early disease intervention
	Thrombosis	Heparin is used to prevent thrombosis and protect the cardiovascular system[119,120]		Reduces the risk of thrombosis and improves the prognosis of patients	Blood clotting needs to be carefully monitored to reduce the risk of bleeding
	Acute respiratory distress syndrome	Oxygen therapy aids in supporting respiratory function and enhancing oxygenation[121,122]		Improves severe hypoxemia	There are side effects on healthy organs and tissues
	Activation of the renin-angiotensin-aldosterone system	ACE inhibitors alter ACE2 expression or activity[123, 124]		Reduces the viral invasion by SARS-CoV-2, thus improving survival and reducing lung inflammation and injury	There is a potential risk of causing or exacerbating hypotension, hyperkalemia, or kidney damage
	Multi-targeted stem cell therapy	Stem cell therapy promotes the repair of damaged tissue, regulates immune responses, and reduces inflammation [125]		Decreases the inflammatory response, lowers the risk of cytokine storms, and promotes the repair of damaged tissues, thereby improving outcomes in severe cases	Further research is necessary to ascertain the safety, efficacy, optimal timing for administration, and appropriate dosages
Targeting viruses	Blocking viral replication	Artemisia annua, through its direct inhibition of viral RNA polymerase[5]	Madagascar (Africa)	Offers a potential for shorter hospitalization	The use of unproven artemisinin therapy raises concerns about the emergence of drug-resistant malaria. For drugs currently in use, there should also be extensive randomized controlled trials to assess their effectiveness and safety in the population
		The active metabolite of remdesivir reduces genome replication by inhibiting RNA-dependent RNA polymerase[4]	Widely used globally		
	Blocking viral access to host cells	Plasma from convalescent patients containing antibodies against SARS-CoV-2[126-128]  Passive administration of pathogen-specific antibodies has been employed to control viral infections[129-132]	United States, United Kingdom, Germany, China, Brazil, Africa, etc.	Provides immediate immune support and benefits critically ill patients who do not have other appropriate treatment options. Early administration of recombinant monoclonal antibody is effective in preventing hospitalization	However, challenges include high variability in antibody levels and quality, the need to match blood types, and the risk of transmission of other pathogens. The neutralizing activity of recombinant monoclonal antibodies is readily lost as new virus variants emerge
Targeting improves immunity	Nutritional supplement	Vitamin C enhances immunity by stimulating interferon production and lymphocyte proliferation and enhancing neutrophil phagocytosis[133]	Widely used globally	Enhances immunity	Further research is needed to fully understand its safety, efficacy, optimal administration timing, and dosage

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2.

are often associated with intense systemic reactions and can lead to death[16-18].

### Damage mechanisms of SARS-CoV-2

Coronaviruses bind to host receptors, mediating membrane fusion and virus penetration through their S proteins[19]. In the host response to COVID-19 infection, two primary immune mechanisms are involved: Innate immunity, which identifies and neutralizes antigens, and adaptive immunity, activated upon direct antigenic interaction. A foundational aspect of the natural immune response is the detection of pathogenic entities by pathogen-associated molecular patterns. This detection catalyzes the activation of the nuclear factor kappa-B pathway and the interferon (IFN) regulatory factor 3 pathway. Activation of these pathways is critical for the induction of type I and type III IFN expression and for synthesizing pro-inflammatory cytokines and chemokines[20]. An effective immune response, as described above, successfully eliminates the virus and improves the patient's clinical symptoms. However, SARS-CoV-2 evades host immune system surveillance through multiple mechanisms, particularly IFN- and ISG-mediated killing[21]. Studies have shown that SARS-CoV-2 can inhibit the early production of IFN, delaying the immune response at the early stages of

infection. This delayed response allows the virus more time to replicate and spread, exacerbating infection[22]. When the host eventually develops an immune response, the immune system needs to generate a stronger response to clear the virus because of the increased viral load. This excessive immune response may release large amounts of inflammatory factors, including interleukin (IL)-1 $\beta$ , IL-2, IL-6, IL-7, IL-8, IL-17, and granulocyte colony-stimulating factor. The massive release of these inflammatory factors prompts T lymphocytes and monocyte macrophages to migrate from the peripheral blood to the site of infection, which may cause a massive uncontrolled immune response that may eventually lead to CS [23] (Figure 1). The specific immune system also exhibits marked dysregulation in COVID-19, with one of the most striking features being the massive depletion of CD4<sup>+</sup> T and CD8<sup>+</sup> T cells that correlates with the severity of the disease, with activated CD4<sup>+</sup> T cells typically differentiating into type 1 T helper cells, which exhibit antiviral activity through the secretion of cytokines such as IFN- $\gamma$ , and follicular helper T cells, which assist the B cells in forming germinal centers to ensure the long-term maintenance of antibodies in the circulatory system and the persistence of the immune response. In contrast, CD8<sup>+</sup> T cells potentially kill virus-infected target cells directly[24,25]. Research has indicated that individuals suffering from severe COVID-19 cases tend to have elevated concentrations of IL-2, IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and granulocyte-macrophage colony-stimulating factor compared to those with mild to moderate infections[26,27]. In addition, the number of lymphocytes (CD4<sup>+</sup> and CD8<sup>+</sup> cells), especially CD8<sup>+</sup> T cells, continued to decrease substantially in severe patients, but the number of neutrophils increased[28]. Consequently, these results suggest that by closely observing CS dynamics, medical professionals could identify patients at an elevated risk of progressing to severe COVID-19 at an early stage.

### **SARS-CoV-2 causes damage to vital organs**

COVID-19 is an acute infectious disease that can invade various organs, including the respiratory system. The parenchymal area contains diffuse alveolar damage, exudative inflammation, extensive, transparent hyaline membrane formations, and alveolar wall edema[29]. In some studies, autopsies have been performed on patients who died of COVID-19 to detect viral loads in multiple organs throughout the body, including the brain. Quantitative real-time polymerase chain reaction viral nucleic acid assay, electron microscopic observation, and immunohistochemical staining were performed to characterize the spread of the viral infection and the different damages to various organs, and SARS-CoV-2 was detected in the lymph nodes, spleen, heart, liver, gallbladder, kidneys, stomach, and testes[30], providing a direct demonstration that SARS-CoV-2 spreads to all parts of the body and causes different histopathological alterations [31,32]. In addition, ACE2 is a functional receptor of SARS-CoV-2, the “gateway” for viral infection of cells. Single-cell RNA sequencing data analysis revealed a subpopulation of cells with high expression of ACE2 in several human organs and tissues, including the brain, lung, colon, heart, liver, kidney, testis, and placenta[33]. However, in the spleen, thymus, lymph nodes, and bone marrow, immune cells, including B and T lymphocytes and macrophages, uniformly showed an absence of ACE2 expression[34]. Therefore, we will use this as a judgment criterion to distinguish primary and secondary infections of COVID-19, defining the presence of tissues and organs with high expression of ACE2 as primary infection and ACE2 negativity as secondary infection (Tables 2 and 3).

## **MSCS AND MSCS-EXO CAN BE A POTENTIAL TREATMENT FOR COVID-19**

A growing number of studies have reported the reparative role of MSCs and MSCs-Exo in repairing tissue and organ damage, as well as respiratory and pulmonary infections. These studies further affirm that the autologous and allogeneic sources of MSC products achieve optimal therapeutic outcomes across a broad spectrum of clinical diseases related to immunomodulation[35].

### **MSCs**

MSCs were first identified in bone marrow by Fridenshtein[36]. In addition to bone marrow, MSCs are present in various sources, are easy to obtain, isolate, and culture, have high amplification capacity, and remain stable after multiple passages *in vitro*[37]. Belonging to the category of pluripotent stem cells originating from the mesoderm, MSCs possess the capability for multi-directional differentiation. They can transform into various types of tissue cells, including adipose, bone, cartilage, muscle, and neural cells when subjected to specific inducing conditions either *in vivo* or *in vitro* [38]. MSCs also have potent tissue-repairing, anti-inflammatory, and immune-modulating functions. MSCs can be imported into the body through multiple pathways, which is not easy to cause immune rejection[39]. In addition, studies have shown that MSCs derived from different human tissues do not express ACE2, suggesting that MSCs are naturally immune to SARS-CoV-2 and that MSCs with low or no HLA expression are resistant to SARS-CoV-2 infection[40], and that this low-immunogenicity enables them to evade host immune responses, which is an important basis for their therapeutic efficacy. In addition, leukemia inhibitory factor (LIF) released by MSCs can counteract the CS during viral pneumonia. However, its expression cannot counteract the disease's damage[41,42]. To enhance the effectiveness of LIF, “LIFNano” nanotechnology, which can amplify the efficacy of LIF by a factor of 1000, has been developed. This significant increase in efficacy can effectively suppress CS associated with COVID-19[43]. Therefore, MSCs present a viable treatment for COVID-19, offering regulation of the hyperactivated immune response and aiding in the recovery from lung damage.

MSCs are extracted and isolated from diverse tissues, such as bone marrow, adipose tissue, dental structures, amniotic fluid, the umbilical cord, liver, tendons, and heart[44]. Given their derivation from specific stromal vascular fractions of tissues, these MSCs display variability in aspects like gene expression profiles, phenotypic traits, growth dynamics, and their differentiation potential[45-47]. Factors such as the extraction site, as well as the MSCs' quality and quantity,

**Table 2 Coronavirus disease 2019 causes primary pathological changes**

Organ system	Primary change	
Lung tissue	Acute interstitial pneumonia occurs along with diffuse alveolar damage. The lung tissue shows macrophage infiltration, hyaline membrane formation, and alveolar wall edema. Microvascular involvement includes hyaline thrombosis, hemorrhage, vascular endothelial edema, and immune cell infiltration[134]	+
Cardiovascular system	Degeneration and necrosis of some cardiomyocytes, interstitial congestion and oedema, and infiltration by a few monocytes, lymphocytes, and neutrophils are observed. The nucleic acid test for novel coronavirus is occasionally positive. Endothelial cell detachment and endothelial or whole-layer inflammation are present in small blood vessels in significant parts of the body, accompanied by mixed intravascular thrombosis, thromboembolism, and infarction in the corresponding areas. The microvessels of major organs are prone to hyaline thrombosis[135]	+
Liver	The liver is enlarged with dark red hepatocyte degeneration and focal necrosis with neutrophil infiltration; hepatic sinusoids are congested, and lymphocyte and monocyte infiltration and microthrombosis are observed in the confluent area[136]	+
Gallbladder	The gallbladder is highly filled, and the mucosal epithelium is detached[137]	+
Kidney	The renal glomeruli exhibit congestion and occasional segmental fibrinoid necrosis; proteinaceous exudates can be observed within the glomerular lumens. Proximal renal tubular epithelial degeneration, partial necrosis, and desquamation are present, while casts can be found in the distal tubules. The renal interstitium is congested, with microthrombi formation noted[138]	+
Brain	Congestion, oedema, degeneration of some neurons, ischaemic changes and detachment, phagocytosis, and satellite phenomena are found. Infiltration of monocytes and lymphocytes in the perivascular space is observed[139]	
Testicle	Varying degrees of reduction in the number of spermatogenic cells and degeneration of Sertoli and Leydig cells are observed [140]	+
Adrenal gland	Cortical cell degeneration, focal hemorrhage, and necrosis are observed[141]	
Esophageal, gastric, and intestinal mucosal epithelium	There is variable degeneration, necrosis, and detachment observed, accompanied by the infiltration of monocytes and lymphocytes in the lamina propria and submucosa[142,143]	+

+: The nucleic acid test for novel coronavirus was positive.

**Table 3 Coronavirus disease 2019 causes secondary pathological changes**

Organ system	Secondary change	
Spleen	The spleen shrinks. The white marrow is atrophic, with a decreased number of lymphocytes and some cell necrosis; the red marrow is congested and focally hemorrhagic, macrophages are proliferated, and phagocytosis is observed in the spleen; anemic infarcts of the spleen are easily found. Immunohistochemical staining shows decreased spleen CD4+ T and CD8+ T cells[144]	+
Lymph nodes	The lymphocyte count is reduced, and necrosis is found. Immunohistochemical staining shows decreased CD4+ T and CD8+ T cells in the spleen and lymph nodes. Lymph node tissues may be positive for novel coronavirus nucleic acid detection in macrophages[145]	+
Bone marrow	Hematopoietic cells are either hyperplastic or reduced in number, with an increased granulocyte-red ratio[146]	

+: The nucleic acid test for novel coronavirus was positive.

influence the composition of growth factors, cytokines, extracellular vesicles, and secreted bioactive elements in the regenerative context, which in turn plays a critical role in shaping the therapeutic outcomes in clinical settings[48]. Selecting an appropriate MSC source is pivotal for the success of their application in treating various diseases. Here, we compare the advantages and disadvantages of MSC therapy for COVID-19 from different sources (Table 4), we believe that umbilical cord MSCs (UC-MSCs) can be prioritized for COVID-19 treatment, but the exact molecular mechanism of UC-MSCs for COVID-19 treatment still needs to be explored in the future[49].

Although cell therapy has many advantages in treating COVID-19, it faces numerous challenges. First, specific cytokines secreted by MSCs, such as vascular endothelial growth factor (VEGF), may induce tumors. Second, since MSCs are highly sensitive to harsh cellular microenvironments (e.g., inflammation), their survival rate is low after transplantation. In addition, the cells may block small-diameter pulmonary arteries during transplantation. Finally, another challenge for cell therapy is the storage of cells at temperatures as low as -80 °C, which requires special equipment and techniques[50,51]. To address these challenges, increasing evidence suggests that MSCs-Exo may be a novel cell-free therapy[52].

### MSCs-Exo

Exosomes are small vesicles containing complex RNAs and proteins with lipid bilayer membrane structure, which can carry and transfer a wide range of proteins, lipids, and nucleic acids related to their cellular origin, acting as signaling molecules to other cells and thus participating in the important regulation of cellular exercises, influencing the



**Table 4 Comparison of different sources of mesenchymal stem cells for treatment of coronavirus disease 2019**

Types	Advantages	Disadvantages
UC-MSCs	Prevent fibrosis and restore the oxygenation index and down-regulated CS in critically ill COVID-19 hospitalized patients; readily available and rapidly expanded to clinically required numbers without raising ethical issues and with minimal allograft rejection[147,148]	More extensive randomized trials and phase III clinical trials of UC-MSCs are still needed to investigate the exact molecular mechanisms of UC-MSCs in treating COVID-19 patients
BM-MSCs	Inhibit CS[149]	Adverse events such as low cryopreservation survival, cell product heterogeneity, immunogenicity, and thrombus generation, which have been observed with BM-MSCs products, as well as the low number of MSCs in bone marrow aspirates and the invasive nature of the process of obtaining MSCs have also prevented the generalization of BM-MSCs[150-152]
PL-MSCs	Higher amounts of CD106 are expressed because surface markers such as CD106 and CD54 are important for immunizing MSCs through cell-to-cell contact[153]	Differences in autologous or allogeneic preparation protocols and ethical concerns about PL-MSCs[154]
ADSCs	Rich tissue sources and tissue collection methods are simple [155]	Some severe side effects have been shown, such as three cases of vision loss after patients with AMD received bilateral intravitreal injections of autologous adipose tissue-derived stem cells at a stem-cell clinic[156]

ADSCs: Adipose-derived mesenchymal stem cells; AMD: Age-related macular degeneration; BM-MSCs: Bone marrow-derived mesenchymal stem cells; PL-MSCs: Placenta-derived mesenchymal stem cells; UC-MSCs: Umbilical cord mesenchymal stem cells; MSC: Mesenchymal stem cell; COVID-19: Coronavirus disease 2019; CS: Cytokine storm.

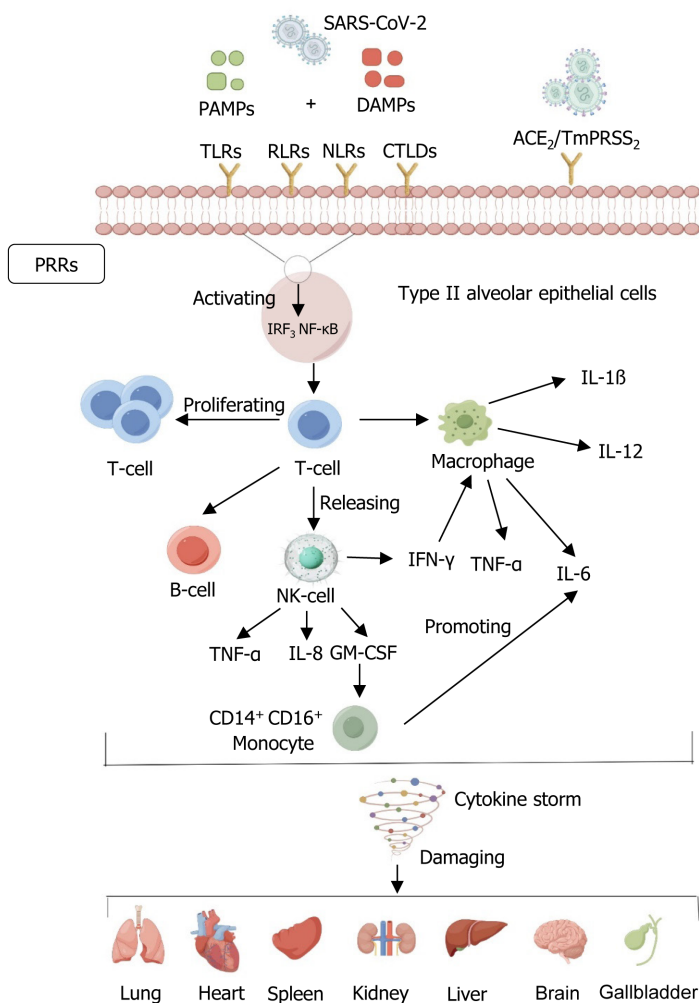
physiological activities of target cells, and mediating biological effects such as inter-cellular signaling and immunomodulation[53]. MSCs-Exo and MSCs share similar functions, including the repair and regeneration of tissues and the regulation of body immunity[54]. Several studies have demonstrated that MSCs-Exo may inhibit CSs and reduce tissue damage conditions, including ARDS, acute lung injury, and fibrosis[55]. MSCs-Exo group had similar therapeutic outcomes and efficacy to MSCs for treating pulmonary fibrosis after COVID-19 and may be a novel therapy for long-term pulmonary sequelae[56]. MSCs-Exo also enhanced macrophage phagocytosis and significantly diminished TNF- $\alpha$  and IL-8 secretion, thereby ameliorating lipopolysaccharide-induced lung injury in mice[57]. Furthermore, many of these MSC-Exos are carriers of miRNAs, which are integral in controlling important cell functions such as cellular proliferation, programmed cell death, and the responses of the host immune system[58,59]. Therefore, MSCs-Exo could serve as optimal carriers for delivering specific antiviral medications in treating COVID-19[60]. However, the widespread use of exosomes faces numerous challenges. With the large variety of MSCs, it is unclear whether there are discrepancies between exosomes of different origins and how much these differences affect the immunomodulatory effects. In addition, these multifaceted challenges include selecting appropriate isolation and purification methods, preparing high-quality, homogeneous, large quantities of exosomes, and optimizing exosome storage conditions[61]. In addition, the issue of efficiently delivering drugs to target cells needs to be addressed. These difficulties must be overcome to utilize the potential of exosomes in COVID-19 treatment fully. MSCs-Exo origin has shown promising applications in various diseases.

## MECHANISMS OF COVID-19 TREATMENT BY MSCS AND MSCS-EXO

As mentioned earlier, the generation of CS caused an uncontrolled immune response in patients, and the subsequent symptoms of ARDS and acute lung injury were the main reasons for the aggravation of COVID-19 patients' conditions and even death. While MSCs and MSCs-Exo have the ability of immune regulation and tissue repair and regeneration, they can be homed to the injury site to alleviate lung injury and inhibit lung fibrosis in the treatment of COVID-19, and have a positive effect on the improvement of the respiratory function and the prognosis of the patients with COVID-19 (Figure 2).

### Homing

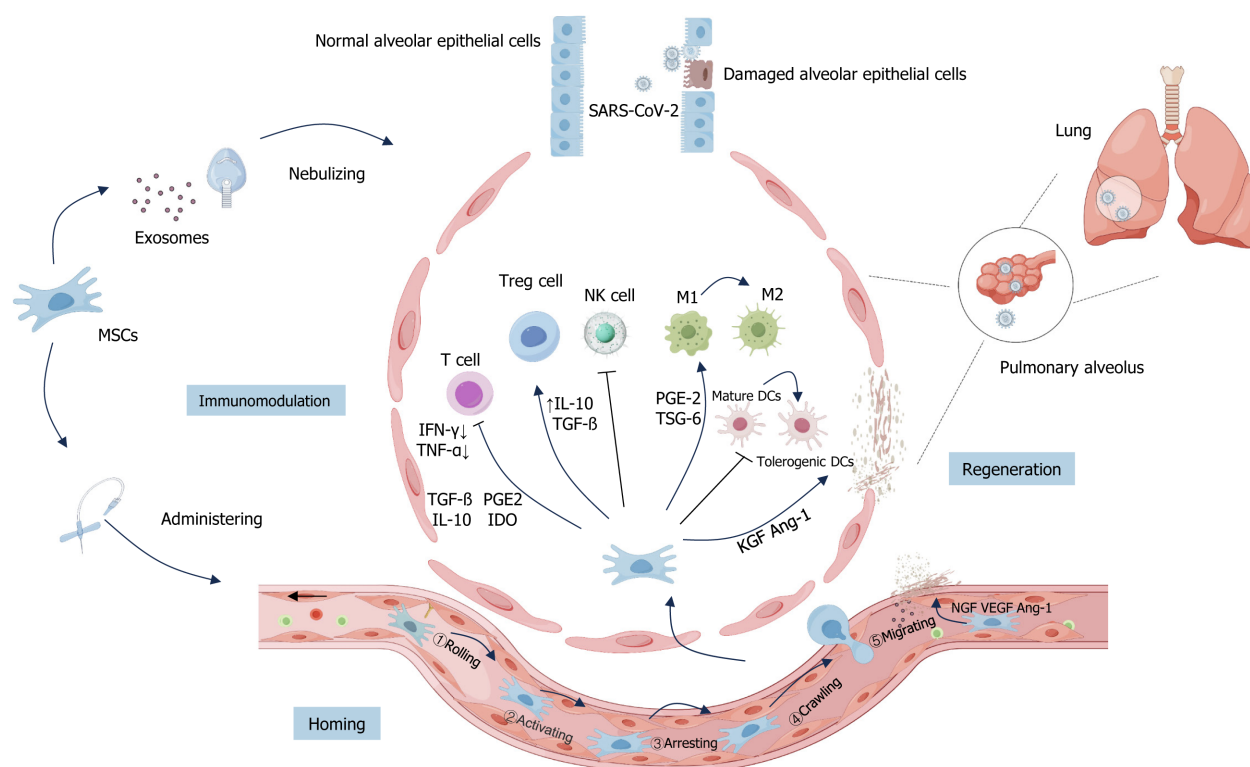
**Homing of MSCs:** The "homing effect" of MSCs allows them to localize to areas of injury due to various causes, which is a prerequisite for the therapeutic action of stem cells[62]. MSCs can be administered *via* systemic routes or directly at specific sites. These two pathways guide the systemic homing and non-systemic homing of MSCs, respectively[63]. In non-systemic homing, MSCs are transplanted locally into damaged tissue, and chemokine gradients guide MSCs to migrate to the injury site accurately. On the other hand, systemic homing involves a more complex biological process, including five key steps: Rolling, activating, arresting, crawling, and migrating. This series of steps enables MSCs to migrate from the blood to distant sites of injury efficiently, which can be accelerated with the help of drugs or may occur through the natural entry of MSCs into the bloodstream. Each step has its unique biological significance, which collectively promotes the efficient transport and localization of MSCs in the body[62]. With this "homing effect", MSCs are delivered to the damaged site and play an active role in repair and regeneration[64].



**Figure 1 Mechanisms of severe acute respiratory syndrome coronavirus 2 damage.** By Figdraw, <https://www.figdraw.com>. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to host receptors, mediates membrane fusion and viral penetration, and predominantly infects type II alveolar epithelial cells expressing angiotensin-converting enzyme 2 receptors in the alveoli. Rapid replication of SARS-CoV-2 after the invasion of the body subsequently triggers a potent immune system response, with heat shock proteins or other damage-associated molecular patterns released by injured lung parenchymal cells, and inhaled pathogen-associated molecular patterns initiating the immune response through the activation of classical pattern recognition receptors, which include not only toll-like receptors, but also multiple lineage-encoded receptors, such as RIG-I like receptor, Nod-like receptors, and C-type lectin-like domains, which further activate interferon regulatory factor 3 and nuclear factor kappa-B pathways and enhance T-cell secretion. Pathogenic T helper cell 1 releases signals to B cells, natural killer (NK) cells, and macrophages, whereas NK cells release tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon (IFN)- $\gamma$ . GM-CSF further activates CD14<sup>+</sup> CD16<sup>+</sup> inflammatory monocytes and enhances the secretion of inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-12, IL-1 $\beta$ ) from alveolar macrophages, thereby further elevating the secretion of inflammatory cytokines, thus further elevating the level of inflammation in damaged lung tissues and causing a cytokine storm that results in multi-organ dysfunction and even failure of the lung, heart, spleen, kidneys, liver, brain, and gall bladder. ACE2: Angiotensin-converting enzyme 2; CTLD: C-type lectin-like domain; DAMPs: Damage associated molecular patterns; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN- $\gamma$ : Interferon- $\gamma$ ; IL: Interleukin; IRF3: Interferon regulatory factor 3; NK cells: Natural killer cells; NF- $\kappa$ B: Nuclear factor kappa-B; NLRs: Nod-like receptors; PAMPs: Pathogen-associated molecular patterns; PRRs: Pattern recognition receptors; RLRs: RIG-I like receptors; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TLRs: Toll-like receptors; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

Kosaric *et al*[65] showed that Ly6Chi cells could not be converted to the Ly6Clo phenotype in injured tissues, resulting in delayed tissue repair. Depletion of Ly6c<sup>+</sup> macrophages can be observed in wounds where bone marrow MSCs (BM-MSCs) appeared through a systemic homing effect after intravenous infusion. This study suggests that MSCs can migrate to the injury site through systemic homing and promote the injury-healing process, providing a theoretical basis for the clinical treatment of COVID-19 with MSCs. In addition, it has been shown that patients with COVID-19 may develop intestinal infections with gastrointestinal symptoms of varying severity, including abdominal pain, diarrhea, constipation, nausea, and heartburn[66]. There have been reports confirming the therapeutic role of MSCs in intestinal injury diseases: Administration of 2, 4, 6-trinitrobenzene sulfonic acid to guinea pigs to induce colitis, followed 3 h later by enema of MSCs, resulted in the non-systematic homing of MSCs to the site of intestinal injury, controlling the development of localized injury and treating COVID-19-induced by multiple mechanisms, such as the promotion of intestinal epithelial regeneration and mucosal repair intestinal infections[67].

**Homing of MSCs-Exo:** In addition, Alvarez-Erviti *et al*[68] concluded that functional small interfering RNAs could be efficiently delivered to the mouse brain by systemic injection of targeted exosomes. This finding implies that MSCs-Exo



**Figure 2 Main mechanisms of mesenchymal stem cells and their derived exosomes for coronavirus disease 2019 treatment.** By Figdraw, <https://www.figdraw.com>. Currently, mesenchymal stem cells (MSCs) and their derived exosomes (MSCs-Exo) used for the treatment of coronavirus disease 2019 (COVID-19) are administered by intravenous infusion or nebulized inhalation. The main mechanisms of MSCs and MSCs-Exo for COVID-19 include: (1) Homing: Non-systemic homing: MSCs are locally transplanted and directed to the site of injury by a chemokine gradient; systemic homing process of MSCs in the inflammatory microenvironment: Rolling; activating; arresting; crawling; migrating; (2) Immunomodulation: Severe acute respiratory syndrome coronavirus 2 invasion into alveoli and other tissues leads to the activation of T cells. At the same time, MSCs coordinate local and systemic innate and adaptive immune responses, promote macrophage polarization from M1 to M2 subtypes, inhibit T cell activation and proliferation, promote the proliferation of regulatory T cells (Tregs), inhibit the killing function of natural killer cells and the maturation of dendritic cell (including mature dendritic cells and tolerogenic dendritic cells). T cells produce interferon (IFN)- $\gamma$  and IFN- $\alpha$ . MSCs may produce anti-inflammatory mediators such as transforming growth factor  $\beta$ , prostaglandin E2 (PGE 2), indoleamine 2,3-dioxygenase, and interleukin-10, which regulate T-cell and Treg-cell-mediated immune responses. On the other hand, MSCs can promote macrophage polarization from the M1 to M2 subtype by secreting PGE 2 and tumor necrosis factor  $\alpha$  stimulated gene 6; and (3) Regenerative repair: Growth factors such as keratinocyte growth factor and angiopoietin-1 (Ang-1) promote the restoration of the alveolar-capillary barrier, while nerve growth factor, vascular endothelial growth factor, and Ang-1 promote neovascularization in healing tissues, activate the coagulation pathway, and promote blood coagulation, which contributes to repair and regeneration. MSC: Mesenchymal stem cell; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; NK cells: Natural killer cells; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; IFN- $\alpha$ : Interferon- $\alpha$ ; TGF- $\beta$ : Transforming growth factor  $\beta$ ; PGE2: Prostaglandin E2; IL: Interleukin; IDO: Indoleamine 2,3-dioxygenase; TSG-6: Tumor necrosis factor  $\alpha$  stimulated gene 6; Ang-1: Angiopoietin-1; DCs: Dendritic cells; KGF: Keratinocyte growth factor; NGF: Nerve growth factor; Tregs: Regulatory T cells; VEGF: Vascular endothelial growth factor.

may also retain the homing properties of MSCs. However, this property of MSCs-Exo has not yet been systematically studied, and deeper exploration is still needed to broaden therapeutic ideas against COVID-19 in the future.

### Immunomodulation

**Immunomodulatory role of MSCs:** MSCs have a bi-directional immunoregulatory mechanism, exerting an immune-boosting effect when the immune response is low and inhibiting the immune response when the immune response is strong. When MSCs migrate towards the injury site, they exert their immunosuppressive properties to inhibit the development of CS, which is achieved through the paracrine pathway of MSCs that releases large amounts of soluble cytokines, growth factors, chemokines, and other mediators or directly interacts with immune cells. Key factors associated with these processes are numerous, including IL-6[69], transforming growth factor  $\beta$  (TGF- $\beta$ )[70], prostaglandin E2[71], indoleamine 2,3-dioxygenase[72] and nitric oxide synthase (iNOS)[73]. Also, MSCs play a critical role in modulating local and systemic immune responses, influencing a range of *in vivo* effector functions[74]. These functions encompass enhancing macrophage polarization, suppressing the activation and proliferation of T-cells, fostering the growth of regulatory T-cells (Tregs), and reducing the cytotoxic activity of natural killer cells, among others [75,76]. Among them, MSCs can promote macrophage polarization from the M1 subtype to the M2 subtype, this process can be mediated by cytokines (e.g., TGF- $\beta$ ) secreted by MSCs[57,77,78]. MSCs can also regulate T cell function in various ways, such as secreting soluble proteins (e.g., programmed death ligand 1) to inhibit the proliferation and activation of CD4<sup>+</sup> T cells and inducing them to be hyporesponsive[79,80].



It was found that MSCs cultured in a serum-free medium significantly inhibited bleomycin-induced lung fibrosis by enhancing the induction of Tregs into the lungs and correcting the dysregulated cytokine balance[81]. In addition, MSCs can regulate the activity and differentiation of immune cells and inhibit immune responses. In a mouse model of acute lung injury, infusion of MSCs reduced the number of M1-type macrophages, inhibited neutrophil chemokine secretion, reduced the enrichment of CD38<sup>+</sup> and CD11b<sup>+</sup> CD38<sup>+</sup> monocyte-derived dendritic cells in the lungs, and inhibited antigen presentation processes[82].

**Immunomodulatory role of MSCs-Exo:** MSCs can also promote macrophage polarization from the M1 subtype to the M2 subtype by secreting miRNA-carrying exosomes (*e.g.*, miR-182)[57,77,78]. On the other hand, MSCs-Exo promotes the proliferation and immunosuppressive capacity of Tregs by up-regulating the inhibitory cytokines IL-10 and TGF- $\beta$ , attenuating the inflammatory response, and decreasing the level of overactive immune response in patients with COVID-19[79,80]. In addition, recently published studies have shown that MSCs-Exo induces M2 polarization in macrophages by down-regulating iNOS and up-regulating arginase 1 antibody[83] to ameliorate the adverse consequences of SARS-CoV-2 infection, which predicts a great potential for the application of MSCs-Exo in immune modulation.

### Regenerative repair and antifibrotic effects

**Regenerative repair and antifibrotic effects of MSCs:** In the context of critical COVID-19 patients, some present with significant alveolar and pulmonary vascular endothelial cell damage, accompanied by varying degrees of pulmonary fibrosis. MSCs promote the repair and regeneration of the damaged alveolar epithelium by secreting multiple cytokines and trophic factors[84,85]. MSCs can restore the function and integrity of damaged alveolar epithelium by secreting paracrine factors such as TGF- $\alpha$ , TGF- $\beta$ , hepatocyte growth factor (HGF), epithelial growth factor, and angiopoietin 1[86]. Gong *et al*[87] demonstrated that MSCs co-cultured with alveolar epithelium *in vitro* could successfully differentiate into type II alveolar epithelial cells and repair the damaged alveolar structure. In addition, the decrease of alveolar permeability to proteins caused by intravenous infusion of MSCs given to ARDS patients may be mediated by the reduction of alveolar epithelial damage, which also provides biological evidence for treating lung injury with MSCs[88].

In addition, MSCs produce various pro-angiogenic factors that activate both extrinsic and intrinsic coagulation pathways, promote blood coagulation, and facilitate neovascularization in healing tissues. The latest clinical findings suggest that pulmonary vascular endothelial cells can also be essential as therapeutic targets during SARS-CoV-2 infection[89]. MSCs can release VEGFs to form neovascularization and improve endothelial function. Several studies have confirmed the ability of skin-derived ABCB5<sup>+</sup> MSCs to activate the pro-angiogenic hypoxia-inducible factor-1 pathway under low oxygen conditions. This activation significantly enhanced the transcription of VEGF by approximately quadrupling its level. Consequently, this upsurge in transcription was observed to substantially boost VEGF protein secretion, effectively contributing to repairing damaged blood vessels[85].

In addition to the damage of alveolar and pulmonary vascular endothelial cells, the lungs of some patients with severe COVID-19 also show different degrees of pulmonary fibrosis symptoms. MSCs can significantly reduce pulmonary fibrosis and improve lung structure and function. It was found that MSCs secreted antifibrotic proteins and improved lung collagen deposition and lung fibrosis scores in mice in a bleomycin-induced lung fibrosis model[90]. The above studies illustrate that MSCs inhibit fibrosis, but whether MSCs can be used in COVID-19-associated pulmonary fibrosis triggered by multiple factors and the specific improvement effect still needs to be verified by more *in vivo* experiments and a more mature clinical evaluation system.

**Regenerative repair and antifibrotic effects of MSCs-Exo:** MSCs-Exo also contributes to the recovery of alveolar epithelial and endothelial cells, maintains vascular barrier integrity, repairs damaged lung tissues, and reduces pulmonary fibrosis. MSCs-Exo contains all the same immunomodulatory and pro-angiogenic factors as MSCs, and the immunomodulation mediated by MSCs-Exo is similar to or even superior to that of MSCs[91]. In addition, highly expressed miR-145 and related proteins within the exosomes also significantly promoted the functional maintenance and regeneration of injured lung tissues, thereby facilitating lung injury repair and providing a more promising therapeutic approach for COVID-19[92]. In an experimental lung fibrosis model, growth factors secreted by MSCs through exosomes, such as HGF, showed anti-fibrotic effects. HGF prevents apoptosis of epithelial cells and shows anti-fibrotic effects in an experimental fibrosis model[93]. Therefore, MSCs-Exo represents a potential novel cell-free therapeutic agent for regenerative repair and antifibrosis in regenerative medicine, and its efficacy needs to be explored in future clinical trials.

### Other possible mechanisms

In addition to the several main mechanisms of action mentioned above for the treatment of COVID-19, there are some other potential mechanisms, such as the antimicrobial effect of MSCs, which also provide new ideas for the treatment of COVID-19. Compared with mild COVID-19 patients, the neutrophil counts in severe patients showed a significant increase at 13-15 d after the onset of the disease, suggesting that severe patients may have a co-infection of bacterial infections and viral infections[94]. Research has demonstrated the vital role of human-derived antimicrobial peptides, integral to the innate immune system, in providing early defense against lung viral infections[95]. MSCs combat pathogenic infections by producing these antimicrobial peptides, a capability that has potential applications in treating severe COVID-19 cases[96]. The antimicrobial actions of MSCs are attributed to the secretion of various cytokines, including LL-37[97], human  $\beta$ -defensin-2 (hBD-2)[98], and lipid carrier protein 2 (Lcn2)[99], among others, and the regulation of immune cell functions. Specifically, MSCs directly eliminate bacteria through LL-37, which interacts with the toll-like receptor-4 signaling pathway, and through Lcn2, which is mediated by hBD-2[98]. MSCs lack phagocytic activity, but when macrophages are reprogrammed from a pro-inflammatory phenotype to an anti-inflammatory phenotype, MSCs stimulate monocyte macrophages to enhance their phagocytosis of bacteria[100] to promote bacterial

infection in critically ill patients' recovery. The antimicrobial effects of MSCs could be utilized as an improved COVID-19 treatment.

### **Multidimensional mechanisms of MSCs and MSCs-Exo in the treatment of COVID-19**

MSCs and MSCs-Exo have multiple roles in treating and repairing COVID-19-induced tissue damage, and there is a close relationship between the mechanisms of homing, immunomodulation, regenerative repair, and anti-fibrotic. The unique homing ability and targeted modifications of MSCs can enhance their ability to promote tissue regeneration[101]. When tissues and organs are damaged, MSCs sense and respond to signaling molecules released from damaged tissues, migrate to these damaged areas, and activate the immune system. Next, damaged cells secrete damage-associated molecular patterns and vigilantes, signaling substances that attract leukocytes such as neutrophils, monocytes, dendritic cells, natural killer cells, and T lymphocytes to the injury site. After successfully eliminating the pathogen, the immune cells shift to an immunosuppressive phenotype that contributes to the production and proliferation of immunosuppressive cells to moderate the ongoing inflammatory response[102]. MSCs can promote the repair and regeneration of damaged tissues by secreting growth factors and extracellular vesicles. MSCs can differentiate into different types of cells, such as osteoblasts, chondrocytes, or adipocytes, to replace the damaged cells, increase the number of new cells, and repair the damaged tissue structure. In addition, MSCs-Exo is one of the key factors released by MSCs and has similar functions to MSCs. For example, MSCs-Exo can also regulate the activity of receptor cells, promote cell self-repair and tissue regeneration, and accelerate wound repair at the injury site[103]. In summary, multiple mechanisms promote the repair of damaged tissues, which makes MSCs and MSCs-Exo promising to be potent tools for treating COVID-19, autoimmune diseases, trauma, and chronic diseases.

## **CURRENT STATUS OF CLINICAL TRIALS OF MSCS AND MSCS-EXO FOR THE TREATMENT OF COVID-19**

Many clinical trials involving MSCs and MSCs-Exo have demonstrated their effectiveness in treating COVID-19 and related complications. As of November 2023, more than 100 registered clinical trials have investigated the use of MSCs and MSCs-Exo for the treatment of COVID-19, and our study covers 20 of the most recent relevant clinical trials in terms of cell source, dosage administered, and therapeutic efficacy (in terms of clinical symptoms, biomarkers, and lung imaging) (Table 5). Meanwhile, we have preliminarily summarized the general criteria for treating COVID-19 by MSCs and MSCs-Exo based on the relevant clinical trials mentioned above, which mainly include the following aspects.

### **Patient selection**

Most of the COVID-19 patients treated with MSCs and MSCs-Exo were moderate to severe, often developed ARDS, and eventually progressed to multiple organ failure. The severity of the disease is not determined by the viral load of SARS-CoV-2 but by the inflammatory response[104]. The abnormal increase in pro-inflammatory and anti-inflammatory cytokines in patients with severe COVID-19 indicates a dysfunction in their immune system, necessitating the treatment with MSCs and MSCs-Exo. COVID-19 patients should meet specific inclusion criteria, including age, underlying diseases, and the patient's immune status, to exclude patients suffering from specific comorbidities or high risk of complications from stem cell therapy. In addition, some studies might choose older patients due to their generally more severe reactions to COVID-19[105].

### **Types of MSCs and MSCs-Exo used in clinical trials**

The collection of MSCs and MSCs-Exo needs to meet ethical and legal requirements and be expanded and prepared in the laboratory to obtain sufficient numbers of cells and exosomes for treatment. In 20 of these clinical trials, 14 used UC-MSCs, 1 used CD362-enriched, umbilical cord-derived MSCs, 1 used placental MSC, 1 used BM-MSCs, 1 used allogenic menstrual blood-derived MSCs, and 2 used MSCs-Exo. These data suggest that UC-MSCs are a significant source for use in clinical trials to treat COVID-19.

### **Therapeutic dose**

The therapeutic dose of MSCs and MSCs-Exo is usually determined based on the patient's body weight and specific clinical conditions. In Table 5, most clinical trials employed a multi-dose (2-3 times) administration approach, with each dose ranging from  $5 \times 10^5$  cells/round to  $2 \times 10^8$  cells/round. In clinical trials involving MSCs-Exo, one study adopted a twice-daily administration (at 8:30 am and 4:00 pm), each session lasting 10 min, while another trial implemented a consecutive 5-d dosing regimen, with each dose ranging from  $1 \times 10^6$  cells/round to  $2 \times 10^8$  cells/round. Given the prevalent administration of doses up to  $2 \times 10^8$  cells/round in current clinical trials, we categorize this as a higher dosage range. Consequently, we delve into the efficacy of high-dose therapy and the potential risks associated with even higher dosages. In the phase 1 trial conducted by Hashemian *et al*[106] focused on treating severe ARDS with MSCs, the findings indicated that administering multiple high-dose (at days 0, 2, and 4,  $2 \times 10^8$  cells/d) intravenous infusions of prenatal allogeneic MSCs was generally safe and well-tolerated.

Notably, although MSCs treatment of COVID-19 showed potential benefits, the increased cell dose may be accompanied by some risks and potential adverse events, such as: (1) Excessive immunosuppression: The use of high doses of MSCs may lead to excessive suppression of the immune system, which may fail to effectively clear the COVID-19 virus, prolonging the period of infection or allowing the virus to recur[107]; (2) Cell transplantation-related reactions:

Table 5 Efficacy of mesenchymal stem cells and their derived exosomes in clinical trials for the treatment of coronavirus disease 2019 patients

No.	Study title	Trial ID	Phase	Indications	Source	Route and time of administration	Dose	Effectiveness of treatment			Number of patients	Ref.
								Clinical symptoms	Cytokine storm biomarkers	Lung image		
1	Effectiveness and safety of normoxic allogenic umbilical cord mesenchymal stem cells administered as adjunctive treatment in patients with severe COVID-19	NCT04333368	Phase 1	Severe COVID-19	NA-UC-MSC	Intravenous infusions, 3 rounds (at days 0, 3, and 6)	$1 \times 10^6$ /kg	Improved the oxygenation index, oxygen saturation	↓ESR, CRP		42	[104]
2	Repair of acute respiratory distress syndrome in COVID-19 by stromal cells (REALIST-COVID Trial): A multicenter, randomized, controlled clinical trial	NCT03042143	Phase 2	Moderate and severe ARDS in COVID-19	ORBCEL-C	Intravenous infusions, 1 round	$400 \times 10^6$ cells	Prolonged duration of ventilation, modulated the peripheral blood transcriptome			60	[157]
3	Human placenta-derived mesenchymal stem cells transplantation in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 (phase I clinical trial): Safety profile assessment	IRCT20200621047859N4	Phase 1	ARDS in COVID-19	PL-MSC	Intravenous infusions, 1 round	$1 \times 10^6$ cells/kg	Not show any adverse events			20	[153]
4	Bone marrow-derived mesenchymal stromal cell therapy in severe COVID-19: Preliminary results of a phase I/II clinical trial	NCT04445454	Phase 1/2	Severe COVID-19	BM-MSC	Intravenous infusions, 3 rounds ( $1, 4 \pm 1, 7 \pm 1$ )	$(1.5-3) \times 10^6$ cells/kg	The higher survival rate in the MSC group at both 28 and 60 d	↓D-dimer		32	[158]
5	Mesenchymal stromal cell therapy for COVID-19-induced ARDS patients: A successful phase I, control-placebo group, clinical trial	IRCT20160809029275N1	Phase 1	ARDS in COVID-19	UC-MSC	Intravenous infusions, 3 rounds (1, 3, 5)	$1 \times 10^6$ cells/kg	Improved the SpO <sub>2</sub> /FiO <sub>2</sub> ratio	↓CRP, IL-6, IFN- $\gamma$ , TNF- $\alpha$ , and IL-17A; ↑TGF- $\beta$ , IL-1 $\beta$ , IL-10		20	[159]
6	Safety of DW-MSC infusion in patients with low clinical risk COVID-19 infection: A randomized, double-blind, placebo-controlled trial	NCT04535856	Phase 1	Low clinical risk COVID-19	UC-MSC	Intravenous infusions, 1 round	High dose: $1 \times 10^8$ cells or low dose: $5 \times 10^7$ cells				9	[160]
7	Safety and long-term improvement of mesenchymal stromal cell infusion in critically	U1111-1254-9819	Phase 1/2	Critical COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 1, 3, and 5)	$5 \times 10^5$ cells/kg/round		↓Ferritin, IL-6, MCP1-CCL2, CRP, D-dimer, and neutrophil levels;	A decrease in the extent of lung damage was observed in the	17	[161]

	COVID-19 patients: A randomized clinical trial								↑TCD3, TCD4, and NK lymphocytes	fourth month		
8	Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: A multicenter randomized double-blind trial	NCT04333368	Phase 2	ARDS in COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 1, 3 ± 1, and 5 ± 1)	1 × 10 <sup>6</sup> cells/kg/round	Significant increase in PaO <sub>2</sub> /FiO <sub>2</sub> ratios			47	[162]
9	Clinical experience on umbilical cord mesenchymal stem cell treatment in 210 severe and critical COVID-19 cases in Turkey		Phase 1	Severe/critical COVID-19	UC-MSC	Intravenous infusions, 1 round	(1-2) × 10 <sup>6</sup> /kg	Significantly lower mortality, improvements in SaO <sub>2</sub>			210	[163]
10	Cell therapy in patients with COVID-19 using Wharton's jelly mesenchymal stem cells: A phase 1 clinical trial	IRCT20190717044241N2	Phase 1	Severe COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 0, 3, and 6)	1.5 × 10 <sup>8</sup> cells/round		↓Ferritin		5	[70]
11	The systematic effect of mesenchymal stem cell therapy in critical COVID-19 patients: A prospective double controlled trial	NCT04392778	Phase 1/2	Critical COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 0, 3, and 6)	3 × 10 <sup>6</sup> cells/kg/round		↓Ferritin, fibrinogen, and CRP		30	[164]
12	Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: A randomized controlled trial	NCT04457609	Phase 1	ARDS in COVID-19	UC-MSC	Intravenous infusions, 1 round	1 × 10 <sup>6</sup> cells/kg/round	Survival rate was 2.5 times higher in the UC-MSC group than in the control group	↓IL-6		40	[165]
13	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	ChiCTR2000029606	Phase 1	Severe and critical COVID-19	Allogenic menstrual blood-derived MSCs	Intravenous infusions, 3 rounds (1, 3, 7)	Total 9 × 10 <sup>7</sup> cells	Significant improvement in dyspnea on days 1, 3, and 5 and significant improvements in SpO <sub>2</sub> and PaO <sub>2</sub>		Improved the lung condition	44	[166]
14	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	NCT04288102	Phase 2	Severe COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 0, 3, and 6)	4 × 10 <sup>7</sup> cells/round			Significant reduction in the proportions of solid component lesion volume	100	[147]
15	Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-	IRCT20200217046526N2	Phase 1	ARDS in COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 0, 2, and 4)	2 × 10 <sup>8</sup> cells/round	Reduced dyspnea and increased SpO <sub>2</sub> within 2-4 d	↓TNF-α, IL-8, and CRP. There is no significant difference between	Reduction in ground-glass opacities or consolidation	11	[106]



	induced ARDS patients: A case series								the two groups ( $P > 0.05$ )			
16	Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial	NCT04355728	Phase 1/2a	ARDS in COVID-19	UC-MSC	Intravenous infusions, 2 rounds (at days 0 and 3)	$(10 \pm 2) \times 10^7$ cells/round	Improved patient survival and a shorter time to recovery	↓GM-CSF, IFN- $\gamma$ , IL-5, IL-6, IL-7, TNF- $\alpha$ , and TNF- $\beta$	24	[167]	
17	Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: A phase 1 clinical trial	NCT04252118	Phase 1	Moderate and severe COVID-19	UC-MSC	Intravenous infusions, 3 rounds (at days 0, 3, and 6)	$3 \times 10^7$ cells/round		↓IL-6, IFN- $\gamma$ , TNF- $\alpha$ , MCP-1, IP-10, IL-22, IL-1RA, IL-18, IL-8, and MIP-1	Complete fading of lung lesions within 2 wk	18	[168]
18	Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells	ChiCTR2000031494	Phase 1	Severe/critical COVID-19	UC-MSC	Intravenous administration, 1 round	$2 \times 10^6$ cells/kg	Improved the weakness, fatigue, shortness of breath, and oxygenation index as early as the third day	↓CRP, IL-6	Shorter lung inflammation absorption	41	[49]
19	Nebulization therapy with umbilical cord mesenchymal stem cell-derived exosomes for COVID-19 pneumonia	ChiCTR2000030261	Phase 1	Moderate COVID-19	MSCs-Exo	Nebulized, twice a day (am 8:30, pm 16:00) for 10 min each	1 million cells/kg predicted body weight		↓CRP, IFN- $\gamma$ , IL-17, ATH 19; ↑NK	Absorption of pulmonary lesions	7	[115]
20	Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: A pilot study	NCT 04276987	Phase 2	Severe COVID-19	HAMSCs-Exo	Nebulized, consecutively 5 d	$2.0 \times 10^8$ nanovesicles		↓CRP, IL-6, lymphocyte counts, and LDH	Massive infiltration and ground-glass opacity disappeared	7	[114]

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HAMSCs-Exo: Human adipose mesenchymal stem cells-derived exosomes; IP-10: Interferon gamma-induced protein 10; LDH: Lactate dehydrogenase; MCP-1: Monocyte chemoattractant protein-1; MCP1-CCL2: Monocyte chemoattractant protein-1/c-c motif chemokine ligand 2; MIP-1: Macrophage inflammatory protein-1; NA-UC-MSC: Normoxic-allogenic umbilical cord mesenchymal stem cell; ORBCEL-C: CD362-enriched, umbilical cord-derived mesenchymal stem cells; COVID-19: Coronavirus disease 2019; NK: Natural killer; IL: Interleukin; IFN- $\gamma$ : Interferon- $\gamma$ ; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; MSCs-Exo: Mesenchymal stem cells derived exosomes; TGF- $\beta$ : Transforming growth factor  $\beta$ ; MSCs: Mesenchymal stem cells; ARDS: Acute respiratory distress syndrome; PL-MSCs: Placenta-derived mesenchymal stem cells.

High doses of MSCs may trigger cell transplantation-related reactions, including fever, headache, nausea, vomiting, or severe anaphylactic reactions[108]; (3) Thrombosis and bleeding risk: High-dose MSCs are associated with an increased risk of thrombosis and bleeding, leading to deep vein thrombosis or bleeding events[109]; (4) Organ damage: High doses of MSCs may trigger inappropriate cell proliferation or differentiation in the body, affecting the function of the kidneys, heart, lungs, or other vital organs[110]; and (5) Risk of neoplasia: High doses of MSCs may increase the risk of neoplasia and involve abnormal proliferation of MSCs or tumor formation[111]. Overall, when deciding on the therapeutic dose, physicians must carefully consider the patient's condition and potential risks and closely monitor the patient's response to ensure the safety and efficacy of the treatment.

## Route of administration

Currently, the treatment of COVID-19 by MSCs and MSCs-Exo mainly includes intravenous injection of MSCs and nebulization of MSCs-Exo. Both methods have their advantages and disadvantages. Intravenous infusion of MSCs is typically used for treating systemic diseases or conditions that require circulation through the bloodstream to various parts of the body, such as certain types of autoimmune diseases, inflammatory diseases, tissue injury repair, and some degenerative diseases[75,112]. MSCs can repair multiple organ damage induced by COVID-19. However, since MSCs are live cells, their infusion can trigger immune system responses in the body, leading to varying degrees of side effects like inflammatory reactions and allergic responses. Additionally, MSCs may not be evenly distributed in the body after infusion. In some instances, specific areas affected by a disease may not receive an adequate concentration of cells, resulting in suboptimal therapeutic effects[113]. Primarily, the application of nebulized MSCs-Exo is targeted toward treating respiratory conditions, including chronic obstructive pulmonary disease, asthma, and pulmonary fibrosis[114]. Exosomes can directly target the lungs and upper respiratory tract through nebulization, offering high therapeutic effectiveness for pulmonary diseases. Some studies have performed MSCs-Exo nebulization in patients with mild and severe COVID-19, which promoted the absorption of lung lesions and shortened the length of hospital stay in patients with mild COVID-19[114,115]. Nebulization is a non-invasive method of administration, usually more acceptable to patients. It is proved that MSCs-Exo can be used as a safe and feasible new approach for the treatment of COVID-19[95,96]. However, nebulized MSCs-Exo is limited to treating respiratory system-related diseases, and the mechanism of action of exosomes may not be as broad as that of MSCs, offering more specificity. In summary, the clinical application should be based on the specific conditions of patients and disease characteristics to choose the appropriate treatment.

## Monitoring

Patients should receive regular medical monitoring during treatment with MSCs and MSCs-Exo, including respiratory status, oxygen saturation, and lung imaging tests. Regular medical monitoring helps to determine the success of the treatment and further treatment as needed. The study demonstrated that after MSC therapy, significant radiological improvements in lung computed tomography (CT) scans were observed in patients, with a notable reduction in pulmonary complications. Some patients showed almost complete resolution of opacities without residual fibrosis 50 d post-treatment. One patient experiencing acute renal failure, pulmonary edema, and bilateral multiple effusions showed a significant reduction in COVID-19-related turbidity post-treatment[106]. Soetjahjo *et al*[104] showed that patients treated with UC-MSCs (normoxic-allogenic-UC-MSC) improved oxygenation index and oxygen saturation on day 22 of treatment. The levels of three key inflammatory markers (procalcitonin, erythrocyte sedimentation rate, and C-reactive protein) were also tracked: C-reactive protein showed a significant reduction in both MSCs and controls after 22 d. Also, this treatment regimen improved oxygenation index and oxygen saturation, contributing to lung healing. Significant improvements were also seen in the levels of biomarkers closely associated with severe and critical COVID-19[104]. A clinical study demonstrated that a mildly ill patient's first chest CT examination revealed an isolated nodule outside the lower lobe of the left lung. The second examination showed a significant reduction in the density and volume of the nodule after MSCs-Exo nebulization treatment, which promoted the absorption of the lung lesion, did not cause acute allergic or secondary allergic reactions, and shortened the hospitalization time[115]. In summary, we believe using MSCs and MSCs-Exo in COVID-19 patients is effective.

## CHALLENGES AND SOLUTIONS

Although MSCs and MSCs-Exo have great potential for the treatment of COVID-19, the controversial nature of using them as emerging agents for clinical therapy remains, such as instability in the quality of different batches of MSCs and MSCs-Exo and uncertainty in predicting effects. In addition, due to the unique properties of MSCs and MSCs-Exo, their manufacturing, transportation, and application processes are significantly different from those of standard drugs. Ensuring rigorous quality control at each stage of these processes is critical to maintaining the integrity and efficacy of these products[97]. Therefore, the Scientific Committee of the International Society for Cellular Therapy emphasized the importance of considering key factors to improve clinical success and gain wider acceptance. Similarly, in China, conducting stem cell trials mandates adherence to the "Guidelines for Quality Control of Stem Cell Preparation and Preclinical Research (for Trial Implementation)" and the "Stem Cell Clinical Research Management Methods". This ensures that MSC therapeutic trials are performed in compliance with international standards.

Meanwhile, scientists are exploring various innovative drug delivery methods to enhance the clinical application of MSCs and MSCs-Exo. Existing methods of delivering MSCs into the body for therapeutic purposes include direct intracellular internalization of nanocarriers and autologous MSC encapsulation in combination with drug administration. However, the complex intracellular environment may degrade the internalized nanocarriers and affect the physiological properties of the cellular carriers. Several studies have constructed a nanoengineering platform based on MSCs, which solved the problem of nanocarriers being degraded by the bio coupling of MSCs and type I collagenase-modified liposomes loaded with Nidanib (MSCs-Lip@NCAF) and adhered to the surface of MSCs through specific biologic ligand-receptor interactions[116]. Autologous MSC-embedded tissue repair coagulant (Tissucol Duo®) has also been feasible, safe, and potentially clinically effective as a prophylactic alternative to prevent prolonged air leakage after pneumonectomy in high-risk patients[117]. In summary, the combination of MSCs piggybacked with corresponding drugs or the use of MSCs themselves as carrier-embedded drugs also has great therapeutic potential. Especially in the face of a more infectious pandemic with faster viral mutation, the number of clinical trials on the safety and efficacy of COVID-19 treatment worldwide is still far from enough, resulting in the exact efficacy and regulatory mechanisms of MSCs and

MSCs-Exo in the clinical treatment of COVID-19 patients with severe illnesses are still in the early stage of exploration. In addition, besides mainly attacking the respiratory tract and lungs, the SARS-CoV-2 virus also affects the heart, kidneys, nervous system, and gastrointestinal tract to varying degrees. To evaluate the safety and effectiveness of MSCs and MSCs-Exo in targeting different organs through various delivery routes, more preclinical and randomized controlled clinical trials are needed. This will help to achieve a better therapeutic effect of MSCs and MSCs-Exo in the treatment of COVID-19 and also provide a more theoretical reference.

## CONCLUSION

With the normalization of the COVID-19 pandemic, developing practical therapeutic approaches is critical to reducing the healthcare system's stresses. The homing, immunomodulation, regenerative repair, and antifibrotic effects of MSCs and MSCs-Exo promote the repair of damaged tissues, making MSCs and MSCs-Exo promising to be a potent therapeutic tool in the treatment of COVID-19. An in-depth understanding of their therapeutic mechanisms and optimization of the application process are crucial, and future studies should focus on improving the safety and efficacy of these therapeutic regimens to make substantial progress in the fight against COVID-19.

## FOOTNOTES

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