

# Current Clinical Application of Mesenchymal Stem Cells in the Treatment of Severe COVID-19 Patients: Review

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**Abstract:** Coronavirus-2019 disease is a newly diagnosed infectious disease, which is caused by the severe acute respiratory syndrome corona virus-2. It spreads quickly and has become a major public health problem throughout the world. When the viral structural spike protein binds to the angiotensin-converting enzyme-2 receptor of the host cell membrane, the virus enters into host cells. The virus primarily affects lung epithelial cells or other target cells that express angiotensin-converting enzyme-2 receptors in COVID-19 patients. Chemokines released by the host cells stimulate the recruitment of different immune cells. A cytokine storm occurs when a high amount of pro-inflammatory cytokines are produced as a result of the accumulation of immune cells. In COVID-19 patients, cytokine storms are the leading cause of severe acute respiratory distress syndrome. Mesenchymal stem cells are multipotent and self-renewing adult stem cells, which are obtained from a variety of tissues including bone marrow, adipose tissue, Warthon's jelly tissue, and amniotic fluid. Mesenchymal stem cells primarily exert their important therapeutic effects through 2 mechanisms: immunoregulatory effects and differentiation capacity. Mesenchymal stem cells can release several cytokines via paracrine mechanism or by direct interaction with white blood cells such as natural killer cells, T-lymphocytes, B-lymphocytes, natural killer cells, and macrophages, resulting in immune system regulation. Mesenchymal stem cells may help to restore the lung microenvironment, preserve alveolar epithelial cells, prevent lung fibrosis, and treat pulmonary dysfunction that is caused by COVID-19 associated pneumonia. Mesenchymal stem cells therapy may suppress aggressive inflammatory reactions and increase endogenous restoration by improving the pulmonary microenvironment. Furthermore, clinical evidence suggests that intravenous injection of mesenchymal stem cells may radically reduce lung tissue damage in COVID-19 patients. With the advancement of research involving mesenchymal stem cells for the treatment of COVID-19, mesenchymal stem cells therapy may be the main strategy for reducing the recent pandemic.

**Keywords:** mesenchymal stem cell, COVID-19, clinical trial, stem cell therapy, acute respiratory distress syndrome

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## Introduction

Coronavirus-2019 disease (COVID-19) is a newly diagnosed infectious disease, which is caused by the severe acute respiratory syndrome corona virus-2. It spread quickly and has become a major public health problem throughout the world.<sup>1</sup> When numerous cases of severe respiratory illnesses were reported in the Wuhan city, Hubei province, China, by the end of 2019, it signaled the start of the main challenge for a human being. Previously, the cases were misdiagnosed as usual flu



and assumed to be caused by the common seasonal influenza virus. In the beginning, it was difficult to make an accurate prognosis of the illness, but it was simultaneously identified as a virus-borne disease. Because of the virus's increasing severity over the next few days, it was declared novel on January 1.<sup>2</sup> The infectious agent was recently diagnosed as a novel coronavirus known as severe acute respiratory distress syndrome coronavirus-2, and this kind of pneumonia was named COVID-19.<sup>3</sup> Then, the number of COVID-19 patients and death has risen dramatically throughout the world.<sup>4</sup>

Currently, mesenchymal stem cells have been identified as one of the main possible therapeutic approaches used for the treatment of COVID-19 patients. Mesenchymal stem cells fight the infection of the virus because of the presence of specific cytokines. These characteristics are present in mesenchymal stem cells in the inherent niche prior to their division process occurred.<sup>5</sup> Nowadays, there is a large scarcity of antiviral agents that can be used to treat COVID-19 diseases. Even though symptomatic treatment and supportive management are recommended for severe COVID-19 patients, those with advanced age and co-morbidities like diabetes mellitus and chronic heart disease are still at high risk for bad outcomes. Thus, developing an appropriate and effective mesenchymal stem cells therapeutic approach for patients with severe COVID-19 infection, which is characterized by severe acute respiratory impairment, is critical.<sup>6</sup> It was shown those mesenchymal stem cells and their derivatives; for example, exosomes significantly reduce the inflammation of the lung and its pathological damage caused by various types of lung injuries.<sup>7,8</sup> Mesenchymal stem cell-derived exosomes contain a variety of proteins and ribonucleic acids (RNAs) which have therapeutic effects on damaged tissues such as regenerative, anti-inflammatory, pro-angiogenic, immunomodulatory, and anti-fibrotic properties.<sup>9-11</sup> Based on this evidence, we hoped to describe the potential therapeutic use of mesenchymal stem cells in the treatments of COVID-19 diseases in this review. We reviewed different clinical trials to get useful information to researchers in the field of stem cell-based therapy because there is disagreement in mesenchymal stem cells therapy to manage COVID-19. We also discussed the aspects of these therapeutic benefits of mesenchymal stem cells in this study, which considered the proposed approach to improve patients' immunological responses to COVID-19 using mesenchymal stem cells.

## Pathophysiological Features of COVID-19

Coronaviruses are encased, sphere-shaped, or pleomorphic viruses with the longest single-strand positive-sense RNA genome among RNA viruses.<sup>12</sup> They are members of a large virus family and it is the main cause of the common cold and other complications like the Middle East respiratory syndrome and severe acute respiratory syndrome.<sup>13,14</sup> Prior to the current pandemic, 6 kinds of coronavirus species were identified to cause respiratory illness.<sup>15</sup> There are 4 kinds of coronaviruses: NL63, human coronaviruses 229E, HKU1, and OC43, which typically infect merely the upper respiratory tract and cause only minor symptoms,<sup>16</sup> but the other three coronaviruses; namely severe acute respiratory syndrome coronavirus, middle east respiratory syndrome coronavirus, and the newly discovered severe acute respiratory syndrome coronavirus-2, can infect the lower respiratory tract and results in lethal pneumonia.

Coronavirus infection is mediated by a trimeric spike glycoprotein found on the viral cell membrane. The spike proteins of coronavirus are class I fusion proteins, which are similar to the envelope of other viruses such as human immunodeficiency virus (HIV) or hemagglutinin of influenza species.<sup>17</sup> The virus contains four types' structural proteins; namely spike proteins, envelope, membrane, and nucleocapsid proteins. The nucleocapsid proteins hold the RNA genome, and the spike, envelope, and membrane proteins together to form the viral envelope.<sup>18</sup> When the viral structural spike protein binds to the angiotensin-converting enzyme-2 receptor of the host cell membrane, the virus enters into host cells. In the host cell, transmembrane protease serine-2 promotes viral uptake by cleaving angiotensin-converting enzyme-2 receptor and activating the severe acute respiratory syndrome coronavirus-2 spike protein, which mediates coronavirus entry into host cells. The spike protein conformation changes after docking, allowing the virus to enter the endosomal pathway. Subsequently, inside the cell, the virus was uncoated and translated into viral components. Once the virus structural proteins are formed, nucleocapsids are assembled in the cytoplasm of host cells and after that bud into the lumen of the endoplasmic reticulum. The structural proteins of the virus are then exocytotically released from the infected cell.<sup>19</sup> Severe acute respiratory syndrome coronavirus-2 spreads primarily through airway droplets and, possibly but not definitively, through the orofecal pathway. During

an infection, the normal latency period is approximately four to five days prior to the symptom appears,<sup>20</sup> but, 97.5% of the symptoms appear in 11.5 days.<sup>21</sup> According to hospital results, patients with COVID-19 diseases was presented with complaints of fever, cough, muscle pain, joint pain, shortness of breathing, diarrhea, headache, and bloody sputum.<sup>22–24</sup> The viral load peaks in five to six days after the onset of symptoms.<sup>25</sup> Patients with COVID-19 infections develop severe acute respiratory distress syndrome between 8 to 9 days of symptom onset along with strong inflammatory responses, hyaline membrane formation, and lung fibrosis.<sup>25,26</sup> Thus, the host cell immune responses are primarily responsible for disease severity. Acute respiratory diseases syndrome caused by severe acute respiratory syndrome coronavirus-2 is characterized by the difficulty of breathing, hypoxemia, and respiratory system failure which is responsible for death in seventy percent of severe COVID-19 patients. Besides, inflammatory cytokine storm caused by the immune response is the leading cause of death, followed by a viral infection and other secondary infections.<sup>27</sup> The interaction of COVID-19 infection and immune cells results in aggressive inflammatory responses and an increased risk of multi-organ failure. Several pro-inflammatory cytokines and other inflammatory mediators such as interleukin-2, interleukin-10, interleukin-7, interleukin-6, interleukin-1 $\beta$ , Interferon- $\gamma$ , interferon- $\alpha$ , monocyte chemoattractant protein-1, and induced protein-10 are significantly increased in COVID-19 infected patients, causing multi-organ dysfunction.<sup>28–30</sup> Increased levels of cytokines and chemokines attract different white blood cells, particularly T lymphocytes and monocytes from the circulation into infected tissue.<sup>31,32</sup> The entrance of white blood cells into lung tissue and the influx of lymphocytes into the respiratory system may be related to the increased neutrophil to lymphocyte ratio, high T helper cell to T regulatory cell ratio, and low lymphocyte level, which are present in about eighty percent of patients.<sup>20</sup> Moreover, the severe acute respiratory syndrome coronavirus-2 can induce damage and death of cells and tissues as a result of the viral life cycle.<sup>33</sup> As confirmed in patients with COVID-19, the replication of the virus in respiratory epithelial cells can cause pyroptosis with vascular leak.<sup>33,34</sup> Pyroptosis is an inflammatory kind of planned cell death that may be triggered by cytopathic viruses and initiates an immune response.<sup>34</sup> The cytokine storm, besides the lesion on lung cells, triggers immune responses; thus, an increasing effort is needed to the

regeneration of injured cells and the blocking or modulation of inflammatory responses.

## Mesenchymal Stem Cell Therapy

Scientists have become increasingly interested in mesenchymal stem cell therapies in a wide range of biomedical sciences over the last few decades because of their immunomodulatory effects, antiviral effects, and paracrine properties, which include the secretion of extracellular vesicle, regulatory mi-RNA, and many biologically active proteins. Mesenchymal stem cells are multipotent and self-renewing adult stem cells, which are obtained from a variety of tissues including bone marrow, adipose tissue, Wharton's jelly tissue, and amniotic fluid. They can differentiate into a wide range of cells, including chondrocytes, osteocytes, neural cells, myocytes, and skin cells.<sup>22</sup> Nowadays, stem cell-based therapy, particularly mesenchymal stem cell therapy, has emerged as a potential therapeutic field, with several opportunities to cure fatal diseases.<sup>35</sup> Although there are significant advancements in the field of mesenchymal stem cell-based therapy, the major limitations of this therapeutic approach remain immunogenicity, inadequate cell source, and ethical concerns. So, mesenchymal stem cells have drawn attention because of their potential source, an increased proliferation rate, ease of invasive procedure as well free of ethical issues. When compared to other treatments, mesenchymal stem cells therapy has several advantages,<sup>36</sup> which include the following: a) mesenchymal stem cells are easily available and are obtained from various tissues such as bone marrow and adipose tissues b) mesenchymal stem cells are multipotent stem cells: c) They can easily spread out to clinical volume in the proper time: d) They can be stored for future therapeutic use: e) So far clinical trials of mesenchymal cells do not reveal any unfavorable reactions to allogeneic mesenchymal stem cells: f) suitability and efficacy of mesenchymal stem cells have been known in many clinical trials.<sup>36</sup> For a variety of reasons, the bone marrow-derived mesenchymal stromal cell appears to be attractive as highly successful treatment options of acute respiratory distress syndrome.<sup>37</sup> Umbilical cord mesenchymal stem cells have exhibited important immunoregulation and tissue fixing properties with low immunogenicity. Because of this, they are an excellent choice for allogeneic adoptive transfer therapy. It has the potential to treat the H5N1 infection-induced acute lung injury, which revealed a similar inflammatory cytokine profile with COVID-19.<sup>38,39</sup> Umbilical cord stem cells can be available easily

and extracted noninvasively but for bone marrow and fat mesenchymal stem cells, an invasive procedure is needed.<sup>37</sup> As previously stated, COVID-19 virus may cause an aggressive inflammatory reaction in the body. The immune system produces an excess amount of inflammatory factors in COVID-19 patients, leading to a cytokine storm, which includes a high production of immune cells and cytokines.<sup>40</sup> This is the start of the mesenchymal stem cells therapy concept to treat COVID-19 patients. Mesenchymal stem cell therapy may prevent the storm release of cytokines via the immune system and promote endogenous repair due to the regenerative properties of the stem cells. Following intravenous injection, a portion of the mesenchymal stem cells entraps in the lung tissue, which is frequently remembered as a limitation in systemic infusion. However, in this case, these mesenchymal stem cells could help to restore the lung microenvironment, preserve alveolar epithelial cells, prevent lung fibrosis, and treat pulmonary dysfunction and COVID-19 associated pneumonia.<sup>41</sup> Mesenchymal stem cells can be obtained from various adult tissues, especially in bone marrow tissue, blood, adipose tissues as well as placental tissue, umbilical cord tissue, amniotic fluid, and then can be stored for future potential applications. Mesenchymal stem cells primarily exert their important therapeutic effects through 2 mechanisms: immunomodulatory effects and differentiation capacity. Mesenchymal stem cells can release several cytokines via paracrine mechanism or by direct interaction with white blood cells such as natural killer cells, T-lymphocytes, B-lymphocytes, natural killer cells, and macrophages, resulting in immune system regulation. Mesenchymal stem cells therapy may suppress aggressive inflammatory reactions and increase endogenous restoration by improving the microenvironment of cells.<sup>42</sup> Higher anti-inflammatory features of mesenchymal stem cells are the primary reason for improving the health of COVID-19 patients after the provision of intravenous mesenchymal stem cell therapy. Moreover, direct cell to cell mitochondrial transmission from mesenchymal stem cells to alveolar epithelial cells and immune cells has been described as a useful mechanism.<sup>43,44</sup>

## Mesenchymal Stem Cells in Coronavirus Disease

In China, one hospital team analyzed the data of one hundred nine patients diagnosed with acute respiratory distress

syndrome and found that acute respiratory distress syndrome progressed more rapidly than other respiratory diseases and that principle of management was too hard. COVID-19 patients with acute respiratory distress syndrome had a high overall mortality rate. As the acute respiratory distress syndrome increased to moderate or severe levels, the mortality rate reaches to up to seventy percent. Since stem cells are resistant to tissue injury, promote tissue regeneration, and have immunomodulatory effects, studies in the field of stem cells by scientists all over the world are bringing good news for the treatment of COVID-19 associated pneumonia.<sup>45</sup> Mesenchymal stem cells therapy increased survival rate and reduced pulmonary edema and tissue injury in the H9N2-infected mouse model as compared to the control group. Mesenchymal stem cells enhanced gas exchange and decreased several chemokines and cytokines such as granulocyte-macrophage colony-stimulating factors, interleukin-1 $\alpha$ , interferon- $\gamma$ , interleukin-6, and tumor necrosis factor- $\alpha$ .<sup>46</sup> Interestingly, mesenchymal stem cells were found to be successful in the treatment of the H1N1 infected pig model, as well as the mesenchymal stem cells treatment group had reduced viral shedding during airway swabs and decreases viral replication in the lower respiratory tracts. After mesenchymal stem cell treatment, the virus-activated production of inflammatory cytokines such as tumor necrosis factor- $\alpha$  was inhibited.<sup>47</sup> Taking into consideration the positive outcomes in different respiratory virus-associated pneumonia patients; mesenchymal stem cells are likely to be effective against the COVID-19 virus, particularly by decreasing the risk of cytokine storms that result in acute respiratory distress syndrome and multi-organ dysfunction in critically ill patients. Research conducted in China, in seven COVID-19-induced pneumonia cases, including aged patients; found that mesenchymal stem cells treatment improved the health of all patients within 14 days of treatment. Only two days after receiving mesenchymal stem cells injections, the patient's pulmonary function and symptoms improved. Immune cells that secrete inflammatory cytokines such as T-helper cells, CD8+ T-lymphocytes, and natural killer cells are disappeared in one week. The level of a pro-inflammatory cytokine such as tumor necrosis factor- $\alpha$  was significantly reduced, implying that mesenchymal stem cells are effective in treating severe acute respiratory distress syndrome.<sup>41</sup> One study in China announced the therapeutic application of mesenchymal stem cells to treat critically ill patients. Furthermore, nine clinical trials of mesenchymal stem cells for the treatment of acute



respiratory distress syndrome were registered. The importance and possible mechanism of mesenchymal stem cells in the treatment of COVID-19-induced severe acute respiratory distress syndrome have been demonstrated.<sup>48</sup> Because effective treatment is lacking and immunological therapies are inadequate mesenchymal stem cells due to their potent immunoregulatory capacity may be important in preventing cytokine storm and decreasing mortality and morbidity rate of COVID-19 patients.<sup>37</sup> Moreover, previous studies indicated that mesenchymal stem cells therapy suppresses the aggressive inflammatory response of the immune cells and initiates endogenous tissue repair by improving the pulmonary microenvironment. But, further studies in larger communities are still required to validate mesenchymal stem cells treatment.<sup>49</sup>

## The Possible Therapeutic Mechanisms of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Patients

Though several attempts have been made to know the curative effects of mesenchymal stem cells in acute respiratory distress syndrome, the mode of action has not been determined. Studying the specific mechanism of mesenchymal stem cells in the treatment of acute respiratory distress syndrome is critical for mesenchymal stem cell-based cell therapy. In the beginning, mesenchymal stem cells were believed to form niches for the proliferation of red bone marrow stem cells, which were very important for cultures. *In vivo* differentiation and transformation of mesenchymal stem cells into bone cells, cartilage cells, fat cells, and even muscle cells have also been studied. As a result, mesenchymal stem cells are grafted at the damaged tissue and help to repair the injury. Despite the use of refined research techniques, the effectiveness of mesenchymal stem cells engraftment remains unsatisfactory. In damage lung models, the engraftment rates were very low.<sup>50,51</sup> Thus, research has concentrated on mesenchymal stem cells' capability to secrete various paracrine factors like immunomodulatory factors, angiogenic factors, antiapoptotic factors, and cell migration factors. These factors encourage the migration and homing of mesenchymal stem cells into damaged tissue for regeneration. Besides, another pathway has been confirmed, and it has been indicated that mesenchymal stem cells interact with host tissue in a variety of ways, including

mitochondrial transfer and direct cell-to-cell interactions. The therapeutic effects of mesenchymal stem cells are primarily reliant on paracrine mechanisms.<sup>52</sup> Severe acute respiratory syndrome corona virus-2 affects lung alveolar epithelial cells or other target cells that express angiotensin-converting enzyme-2 in COVID-19 patients. Chemokines released by type-2 alveolar epithelial cells stimulate the recruitment of inflammatory cells such as neutrophils, monocytes, and T lymphocytes. Then, the accumulation of immune cells in turn results in the production of a high amount of pro-inflammatory cytokines, called cytokine storm. In patients with COVID-19 diseases, cytokine storms are the most common cause of acute respiratory distress syndrome.<sup>52</sup> Cytokine production was also seen in many critically ill patients.<sup>40</sup> The primary function of mesenchymal stem cells during COVID-19 disease treatment is anti-inflammatory effect.<sup>1</sup> Mesenchymal stem cells can significantly decrease the production of proinflammatory cytokines, which might reduce the cytokine storm caused by severe acute respiratory syndrome corona virus-2, and enhance the secretion of interleukin-10, which can decrease neutrophil inflow and aggregation in the lower respiratory tract as well as decrease the production of tumor necrosis factor- $\alpha$ .<sup>53</sup> Keratinocyte growth factor produced via mesenchymal stem cells may decrease tissue damage and promote proliferation and restoration of lung epithelial cells through rising surface-active substances, matrix metalloproteinase-9, interleukin-1Ra, granulocyte-macrophage colony-stimulating factor, and other factors.<sup>54</sup> Based on the most recent study, pulmonary epithelial cells, as a therapeutic target site in COVID-19 diseases, play important roles in the course of COVID-19 infection.<sup>55</sup> Mesenchymal stem cells may produce vascular endothelial growth factors and hepatocyte growth factors. These factors help to restore pulmonary capillary permeability and maintain lung endothelial barrier function. Mesenchymal stem cells control inflammation and protect the pulmonary endothelial barrier by inhibiting pulmonary vascular endothelial cell apoptosis, increasing vascular endothelial cadherin recovery, and decreasing pro-inflammatory factors.<sup>56</sup> Because the COVID-19 virus primarily affects the lower respiratory tracts,<sup>57</sup> the distribution of mesenchymal stem cells in peripheral blood after the intravenous injection is primarily concentrated in the lungs,<sup>58</sup> implying that mesenchymal stem cells are a potential therapeutic choice for COVID-19 pneumonia cases.

## Effects of Mesenchymal Stem Cells in the Treatment of COVID-19 Patients: Findings from Current Clinical Trials

Until now, many clinical studies have been documented for the treatment of COVID-19 patients. Majorities of them are in the process of being completed, with only a few having completed their work and present their findings to the scientific community. The findings are encouraging, and no adverse reaction has been reported during the treatment period. For instance, one study revealed that intravenous injection of umbilical cord-derived mesenchymal stem cells into the aged woman significantly improved the sign and symptoms of COVID-19 disease. Besides, no adverse reactions were seen due to the aforementioned intervention.<sup>44</sup> In three-month follow-up data, intravenous administration of human umbilical cord mesenchymal stem cells increased partial pulmonary function and enhanced health-related quality of life. This indicated that human umbilical cord mesenchymal stem cells are relatively safe and effective for the treatment of patients with severe COVID-19.<sup>59</sup> Another study performed in seven COVID-19-induced pneumonia patients showed that a few doses of mesenchymal stem cells injections lead to increase levels of oxygen saturation, the number of inflammatory markers, and pulmonary tissue regeneration, since chest radiography showed improvement primarily on the ninth day of mesenchymal stem cell treatment. Furthermore, as previously stated, COVID-19 can enter cells via angiotensin-converting enzyme-2 receptors found on a wide range of host cells, including lung type-2 alveolar and capillary endothelial cells. Initially, mesenchymal stem cells were angiotensin-converting enzyme-2 receptors negative. Also, in the follow-up period, using the RNA sequence survey to identify 12,500 transplanted mesenchymal stem cells, it was shown that the cells have not capable of differentiation and remained angiotensin-converting enzyme-2 receptors negative and therefore assumed free from COVID-19.<sup>41</sup> Another clinical study involving twenty-four COVID-19 patients with acute respiratory distress syndrome symptoms indicated that intravenous injection of umbilical cord mesenchymal stem cells with a three-day interval significantly improved the signs and symptoms of patients.<sup>60</sup> Similarly, intravenous injection of a single dose of bone marrow-derived mesenchymal stem cells in sixty patients with moderate to severe acute respiratory

distress syndrome revealed that the mesenchymal stem cells were well-tolerated, and a dramatic decrement of C-reactive protein, interleukin-6, and interleukin-8 levels was seen.<sup>61</sup> The level of C-reactive protein is directly related to inflammation levels; as well factors such as sex, age, and physical condition may not affect its concentration.<sup>62</sup> When comparing the serum profiles of COVID-19 patients with various disease severity, it was discovered that CRP level is a good predictor of disease severity. C-reactive protein levels are directly related to the diameter of pulmonary lesions and severity of presentation in the early stages of COVID-19 disease progression.<sup>63</sup> Many studies found that treatment by mesenchymal stem cells may reduce the level of C-reactive protein as well as inflammatory cytokines and chemokines such as interleukin-6 and tumor necrosis factor- $\alpha$ .<sup>41,64,65</sup>

Another study has also been discovered that severe acute respiratory syndrome coronavirus-2 may damage liver cells by increasing the levels of aminotransferase enzymes and causing liver dysfunction.<sup>65</sup> Liver tissue damage is a common complication of COVID-19 diseases, as it was observed in severe acute respiratory syndrome coronavirus patients. According to previous research, over sixty percent of patients had liver damage, and hepatic biopsy specimens revealing viral nucleic acid and tissue injury.<sup>66</sup> Many researchers have found that mesenchymal stem cells may well differentiate in vitro along the hepatogenic lineage, suggesting that they may be useful in improving liver injuries and regenerating liver tissue via various mechanisms. For instance, in one study using bone marrow-derived mesenchymal stem cells, the findings demonstrated that mesenchymal stem cell therapy dramatically inhibited reactive oxygen species and improved hepatic damage.<sup>67</sup> The findings of the previous studies<sup>68,69</sup> also revealed diminish in the number of liver enzymes following mesenchymal stem cells injection were due to the anti-inflammatory and immunoregulatory characteristics of these cells. Furthermore, many clinical trials have reported kidney involvement, mostly because of acute renal injury, and affect over 70% of COVID-19 patients.<sup>70,71</sup> In this disease, the kidney is the second most commonly damaged organ next to the lung and followed by the heart and liver.<sup>72</sup> According to Cheng et al, elevated serum creatinine and blood urea nitrogen levels were observed in the majority of hospitalized COVID-19 patients.<sup>73</sup> Several studies have shown that applying in vitro expanded mesenchymal stem cells prevent acute kidney injury and increase renal tissue repair.

Interestingly, intravenous injection of mesenchymal stem cells has moved to renal tubules, glomerular capillaries, interstitial tissues, and peritubular capillaries in acute and chronic kidney injury models.<sup>74,75</sup> In several studies, the levels of serum creatinine, blood urea nitrogen, and other renal parameters returned to normal after mesenchymal stem cells intravenous infusion, indicating that these cells have beneficial therapeutic effects in the restoration of renal tissue and the reduction of inflammation within it.<sup>76</sup>

Previous studies indicated that the rate of progression to critical illness and death was significantly decreased in the human umbilical cord mesenchymal stem cell treatment group, compared to patients in the control group. Additionally, the time to clinical improvement in the treatment group was shorter as compared to the control group. So, intravenous human umbilical cord mesenchymal stem cells infusion is a safe and effective alternative treatment for seriously ill COVID-19 patients.<sup>65</sup> Another study confirmed that patients with severe COVID-19 diseases were treated by human umbilical cord Wharton's jelly-derived mesenchymal stem cells from healthy donor people. Thus, the lung function and the clinical sign and symptoms of a patient with severe COVID-19 induced pneumonia were radically improved after stem cell infusion, and the patient becomes recovered and was discharged within seven days of treatment. Following the treatment, the level of lymphocyte count was elevated, whereas the levels of inflammatory cytokines are decreased dramatically. Therefore, intravenous transplantation of human umbilical cord Wharton's jelly-derived mesenchymal stem cells was found to be a suitable and valuable treatment option for severe COVID-19 pneumonia patients, particularly for those in critical condition.<sup>68</sup> Another study involved in eighteen COVID-19 admitted patients showed that intravenous injection of umbilical cord mesenchymal stem cells was safe and effective for patients with moderate to severe COVID-19 diseases.<sup>77</sup>

## Conclusion

Acute respiratory distress syndrome is a serious acute respiratory disease characterized by a high mortality rate. Although several studies were performed, there is recently no specific support for the treatment of acute respiratory distress syndrome. Mesenchymal stem cell-based therapy is the main strategy for the management of acute respiratory distress syndrome because mesenchymal stem cells have potential therapeutic effects like enhancing alveolar epithelial and capillary endothelial

tissue regeneration, removal of pulmonary tissue fluid and microorganisms, and anti-inflammatory and antiapoptotic effects. In some acute respiratory distress syndrome patients, the suitability and potential efficacy of mesenchymal stem cells was confirmed. Clinical evidence suggests that intravenous injection of mesenchymal stem cells can significantly reduce lung tissue damage in patients with COVID-19 diseases. Therefore, mesenchymal stem cell therapy can be a key strategy for reducing the recent epidemic, with the advancement of research involving mesenchymal stem cells for the treatment of patients. Mesenchymal stem cells have a complex mechanism of action. The main mechanisms of action include paracrine mechanisms, extracellular vesicles, and direct cell to cell contact with metastatic cell contents. Despite some advancement, there is no sufficient clinical evidence to show the effectiveness of mesenchymal stem cells in the treatment of acute respiratory distress syndrome. It has been confirmed that severe acute respiratory syndrome coronavirus-2 infection causes an excessive and prolonged inflammatory reaction in some patients, resulting in hyper inflammation known as cytokine storm. Here, cytokine storm inhibition by immunosuppressive is critical in COVID-19 patients, especially those with severe disease. Previous studies indicate that mesenchymal stem cells can significantly inhibit this aggressive inflammatory process, repair tissues, and thus improve recovery via their anti-inflammatory and immunoregulatory effects. Many clinical trials performed in the field of stem cell therapy have documented significant findings, with no adverse reactions being reported in any of them. More studies with a higher sample size are still required in this field.

## Disclosure

The author declared no conflicts of interest for this work.

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