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Review article

Therapeutic potential of mesenchymal stem cells in multiple organs affected by COVID-19

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ABSTRACT

Currently, the world has been devastated by an unprecedented pandemic in this century. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the agent of coronavirus disease 2019 (COVID-19), has been causing disorders, dysfunction and morphophysiological alterations in multiple organs as the disease evolves. There is a great scientific community effort to obtain a therapy capable of reaching the multiple affected organs in order to contribute for tissue repair and regeneration. In this regard, mesenchymal stem cells (MSCs) have emerged as potential candidates concerning the promotion of beneficial actions at different stages of COVID-19. MSCs are promising due to the observed therapeutic effects in respiratory preclinical models, as well as in cardiac, vascular, renal and nervous system models. Their immunomodulatory properties and secretion of paracrine mediators, such as cytokines, chemokines, growth factors and extracellular vesicles allow for long range tissue modulation and, particularly, blood-brain barrier crossing. This review focuses on SARS-CoV-2 impact to lungs, kidneys, heart, vasculature and central nervous system while discussing promising MSC's therapeutic mechanisms in each tissue. In addition, MSC's therapeutic effects in high-risk groups for COVID-19, such as obese, diabetic and hypertensive patients are also explored.

1. Introduction

The outbreak of a new coronavirus has changed the global routine. In late December 2019, most of the staff at Huanan Seafood Wholesale Market, Wuhan, China, presented clinical symptoms resembling viral pneumonia [1–3]. The disease rapidly spread among other Chinese provinces and then to other countries. The pathogen causing the novel infectious disease was identified as a coronavirus, initially called 2019 novel Coronavirus (2019-nCoV) and then renamed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses [4]. The new disease was designated as coronavirus disease 2019 (COVID-19) and classified as a pandemic on March 11, 2020, by the World Health Organization [5].

Since treatment is still lacking, researchers around the world have been seeking drugs, vaccines, and other novel therapies. Stem cell therapy has emerged as a potential treatment for the dysfunctions in multiple organs affected by COVID-19. Mesenchymal stem cells (MSCs)

are the most suitable stem cell type due to their immunomodulatory properties, as well as general safety regarding MSC interventions [6]. Their major therapeutic factor is the secretion of paracrine mediators such as cytokines, chemokines, growth factors, and extracellular vesicles, which promote tissue regeneration and repair [7–9].

This article discusses how MSCs therapy could help in the treatment of multiple organs affected by COVID-19.

1.1. The virus

SARS-CoV-2 belongs to the *Coronaviridae* family and is classified as a β -CoV (*Betacoronavirus genus*) [4]. It is the seventh coronavirus capable of infecting humans. However, unlike most of the other coronaviruses, it can cause severe respiratory syndrome, similar to SARS-CoV and MERS-CoV, which caused epidemics in the last two decades [3].

The new coronavirus has a tropism for cells that present human angiotensin-converting enzyme 2 (ACE2), a protein involved in the

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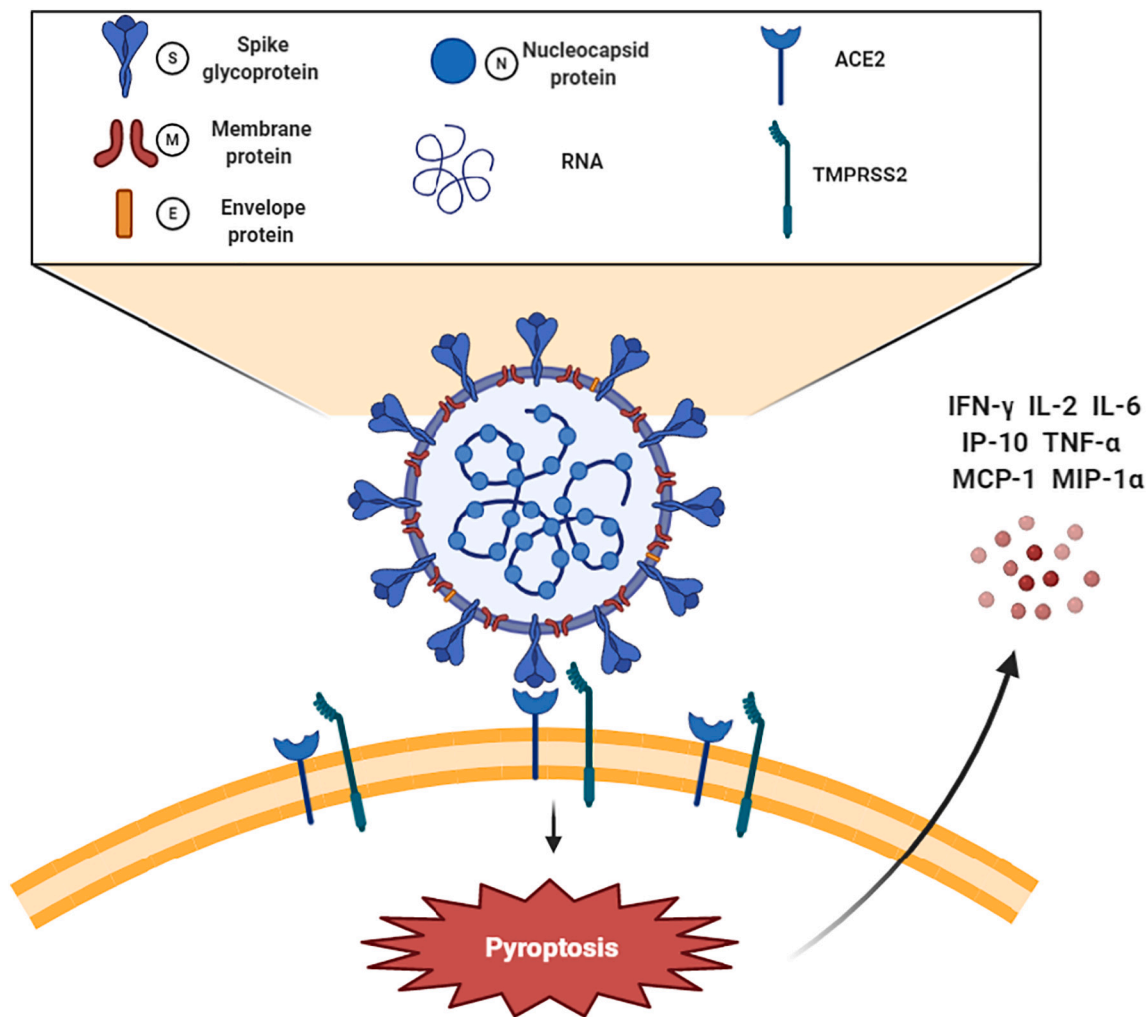


Fig. 1. SARS-CoV-2 structure and infection.

Infection and associated inflammatory triggering by SARS-CoV-2. SARS-CoV-2 virion representation displaying its spike (S) glycoprotein, membrane protein and envelope protein composing the external envelope, while the viral RNA is located internally, surrounded by nucleocapsid protein. During alveolar epithelium infection, SARS-CoV-2' S protein binds to ACE2 receptors and is modified by serine protease TMPRSS2, present on the cell's surface. Then, SARS-CoV-2 infects the cell, triggering cellular damage that progresses to pyroptosis. Cell death releases multiple proinflammatory cytokines, such as IL-2, IL-6, TNF- α and MCP-1, that in dysregulated immune responses may cause persistent tissue inflammation.

ACE2 - angiotensin-converting enzyme 2; IFN- γ - interferon-gamma; IL - interleukin; IP-10 - CXCL10; TNF- α - tumor necrosis factor-alpha; MCP-1 - monocyte chemoattractant protein-1; MIP-1 α - macrophage inflammatory protein.

renin-angiotensin system (RAS) regulation. This receptor is widely expressed in many organs, including the lungs, heart, kidneys and intestine [10–13]. Once the viral RNA is inside the target cell, replication and translation processes begin, assembling new virions that will be released via the secretory pathway [14].

SARS-CoV-2 is transmitted through exposure to droplets or aerosol exhaled by infected individuals or by direct contact with contaminated fomites [15,16]. SARS-CoV-2 enters the human airway and infects type-II pneumocytes and alveolar macrophages as soon as it reaches the alveoli [17,18]. Generally, in viral infections, host cells are expected to identify viral elements through pattern recognition receptors that activate nuclear factor NF- κ B and *interferon* (*IFN*) regulatory factors, inducing the synthesis of type-I antiviral interferons and chemoattractants. In contrast to common respiratory viruses, the new coronavirus evades antiviral effects from type-I interferons, as these proteins are barely produced [19]. Chemokines first attract innate immune cells such as monocytes, dendritic cells, and natural killer (NK) cells, which are responsible for subsequently recruiting lymphocytes, the agents of the adaptive immune system. An effective response from lymphocytes is crucial for a favorable outcome in which CD4⁺ T cells help B cells to

produce neutralizing antibodies against the viral S protein, and help CD8⁺ T cells to exterminate infected cells [12,17].

Otherwise, a dysfunctional immune response may lead to a hyper-inflammatory state, which in turn can progress to a phenomenon known as cytokine storm. In this scenario, the patient's immune system overreacts unloading numerous cytokines such as interleukin-2 (IL-2), IL-6, IP-10 (CXCL10), tumor necrosis factor-alpha (TNF- α), and monocyte chemoattractant protein-1 (MCP-1) into the bloodstream, affecting multiple organs. The cytokine storm is considered the main pathologic mechanism of this viral disease and is strongly associated with critical cases (Fig. 1) [20–22].

COVID-19 is a complex disease that displays a wide spectrum of clinical presentations, ranging from asymptomatic infection to death-threatening cases [23]. The most common clinical symptoms are mild-to-moderate and comprise fever, dry cough, myalgia, fatigue, and dyspnea. Other manifestations include loss of smell and taste and gastrointestinal disorders [21,24–26]. Advanced age, obesity, diabetes, and cardiovascular diseases (CVD) are some of the risk factors that aggravate COVID-19 [3,24,27,28]. Complications associated with severe cases include acute respiratory distress syndrome (ARDS), multiple organ

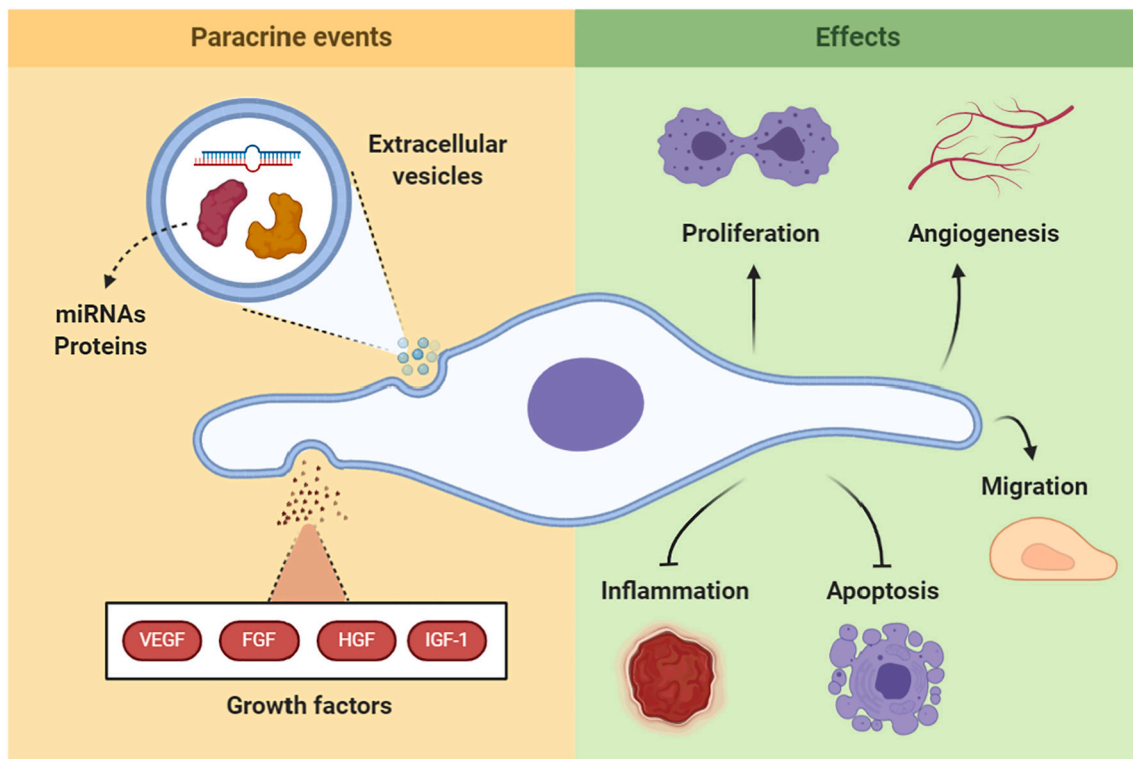


Fig. 2. MSC's therapeutic mechanisms.

MSC's main therapeutic mechanisms. MSC paracrine signaling either through soluble growth factors or through EV carrying multiple molecules, promotes angiogenesis and induces resident tissue cells to survive and proliferate, while inhibiting inflammation progression and cell apoptosis. Direct viral damage to the tissue and dysregulated immune responses are key pathophysiologic mechanisms in multiple organ dysfunctions in COVID-19. Therefore, MSC's ability to induce tissue remodeling may be beneficial to patients with COVID-19, improving recovery and restraining long-term dysfunction.

VEGF – vascular endothelial growth factor; FGF – fibroblast growth factor; HGF – hepatocyte growth factor; IGF-1 – insulin-like growth factor-1.

failure, and disseminated intravascular coagulation [29].

1.2. The cell

MSCs are promising tools in cell therapy due to their multipotent differentiation, immunoregulation and tissue regeneration effects [7,8]. Easy to obtain, MSCs are found in most vascularized tissues such as bone marrow, adipose tissues, umbilical cord, placenta and even menstrual blood, but can also be generated from embryonic stem cells [30–33]. These cells are considered safe, even in allogeneic environment, avoiding immune responses due to their low expression of MHC-I and MHC-II [8,34].

MSCs migrate towards damaged tissue areas, curbing the injury and preserving the tissue. Their therapeutic effects are mainly through paracrine signaling of growth and survival factors, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and insulin-like growth factor-1 (IGF-1), which promote angiogenesis, cell survival and cell proliferation [35,36].

Furthermore, MSCs can directly inhibit the release of proinflammatory cytokines, such as TNF- α and IFN- γ by immunosuppressive responses in the innate and adaptive immune systems [36–38]. For example, MSCs can interact with Th2 lymphocytes, attenuating NK cell responses and inducing changes in M1 macrophages to M2 anti-inflammatory macrophages. MSC's IL-10 production can suppress Th17 lymphocyte expansion through JAK/STAT/SOC3, while TNF- α production is reduced. Through the release of TGF- β , MSCs are one of the key regulators of Treg lymphocyte populations [39].

Extracellular vesicles (EVs) are another MSCs mechanism of action that involves carrying biological messengers into injured sites. EVs comprise microvesicles and exosomes, which contain transcription factors, growth factors, cytokines, mRNAs, and microRNAs (miRNAs), and

are responsible for the angiogenic, anti-inflammatory, and anti-apoptotic effects [40–43]. EVs are nanovesicles measuring 30–150 nm that originate from direct budding of the cell membrane or *via* endosomal secretion. They are composed of cytosolic contents and a lipid bilayer similar to their mother cell [9,44], and therefore, are able to mimic cell interactions between the source and the target [41,45].

Therefore, MSCs and MSC-EVs are considered potential instruments in therapy due to acting simultaneously in crucial mechanisms of tissue damage. Namely through tissue remodeling, by modulating inflammatory cells and signals, enhancing tissue survival, and favoring angiogenesis, while presenting low risk of immunogenicity and tumorigenicity [41]. Thus, MSCs are suitable candidates for cell therapy in COVID-19 (Fig. 2).

2. MSCs-based therapies for multiple organs affected by COVID-19

At first, health care professionals and researchers thought that COVID-19 was simply a respiratory disease. However, many recent findings demonstrate that this infection is more intricate than expected, affecting a myriad of organs, culminating in multiple organ dysfunction [46–48]. SARS-CoV-2 tropism is not limited to the upper and lower respiratory tract. Renal, cardiovascular, nervous, and gastrointestinal systems are also targets given their high expression of ACE2 [49–52]. Single-cell RNA-sequence analysis has identified enriched ACE2 expression in lung type II pneumocytes, enterocytes, stomach epithelial cells, kidney proximal tubules, podocytes, myocardium cells, arterial smooth muscle cells, and pancreatic beta-cells [53,54]. These data indicate that direct viral tissue damage in addition to a dysregulated immune response, is an important pathophysiologic mechanisms of multiple organ dysfunction in COVID-19.

Hereafter, we report on how the SARS-CoV-2 virus damages the lungs, heart, vasculature, kidneys and nervous system; how MSCs act and which mechanisms they adopt on certain injuries, proving their therapeutic potential; how comorbidities such as obesity, diabetes, and hypertension can complicate the infection.

2.1. Lungs

The lungs are the most affected organs by SARS-CoV-2, developing intra-alveolar fibrin with hyaline membrane, including proliferative intra-alveolar and interstitial fibroblasts, bronchopneumonia and necrotizing bronchiolitis in some cases [55,56]. The interaction among the virus, pneumocytes, and alveolar macrophages establishes a cascade of inflammatory events, producing cytokines, chemokines, and stimulating inflammatory cells infiltration [57,58].

Many studies reported that lungs of patients with COVID-19 presented diffuse alveolar damage with inflammatory cell infiltration in the alveolar cavity, including macrophages, monocytes, CD4⁺ T lymphocytes, eosinophils, and neutrophils, along with alveolar wall thickening. In addition, alveolar septum edema exhibited CD68⁺ macrophages, CD20⁺ B cells, CD8⁺ T cells, type II pneumocyte hyperplasia, and interstitial fibrosis, besides inclusions of SARS-CoV-2 in type II pneumocytes [57–63]. Moreover, thrombotic microvascular lesions were observed, apparently mediated by an intense activation and deposition of complement system proteins within the pulmonary septum microvasculature, such as C5b-9, C4d, and MASP2 [58,64]. Some severe cases of infected patients showed lymphocytopenia, depletion of CD4⁺ and CD8⁺ T cells, and neutrophilia, besides massive macrophage and neutrophil infiltrates into the lung tissue [12,60]. Patients with severe disease also presented a panel of increased proinflammatory cytokines and chemokines such as IL-6, IL-8, TNF- α , MCP1, and RANTES, as compared to patients with non-severe disease. Inflammatory cell infiltration exacerbates inflammation and exudation, which promotes alveoli dysfunction and a vicious cycle of continuous cytokine release, leading to cytokine storm. These findings demonstrate that pyroptosis and apoptosis contribute to lung injury, with pyroptosis predominating [12]. Therefore, the therapeutic alternative of MSC use might assist in the improvement of severe lung injury caused by direct infection and immunopathological lesions.

MSC's therapeutic potential has received considerable attention in preclinical settings, with marked therapeutic effects in multiple respiratory diseases, including ARDS, as observed in patients with COVID-19 [65]. MSCs have demonstrated many possible mechanisms for improving ARDS resolution through their anti-inflammatory and anti-apoptotic effects on host cells, reducing lung alveolar epithelium permeability, increasing alveolar fluid clearance, and enhancing host mononuclear cell phagocytic activity [66]. Therefore, MSCs are currently under investigation as a potential therapy for COVID-19.

One of the critical mechanisms implicated in COVID-19 pathology is alveolar edema and infiltration, mainly due to loss of epithelial selective permeability. Therefore, it is crucial to recover alveolar epithelial integrity with concomitant edema resolution [65]. The ability of MSCs to restore alveolar fluid clearance has been noted in *ex vivo* perfused human lungs. Intrabronchial administration of either MSCs or MSC-conditioned media (MSC-CM) in lipopolysaccharide (LPS)-induced ARDS has been shown to reduce lung edema and normalize alveolar fluid clearance [67]. Mouse models also demonstrated diminished apoptosis in airway epithelial cells [68,69]. Moreover, *in vitro*, MSCs or MSC-CM prevented epithelial barrier dysfunction, selective permeability loss, and consequent disruption of fluid transport by restoring epithelial sodium transporters and tight junctions [70,71]. Another mechanism MSCs can improve epithelial integrity and regulation is by transferring healthy mitochondria to epithelial cells, reducing oxidative damage and apoptosis, thus increasing survival in mice [72,73]. Immunomodulation can also be regulated by direct mitochondrial transfer, either to T cells, stimulating T_{reg} phenotype that restricts

inflammatory responses, or to macrophages, promoting enhanced phagocytosis [74,75].

The therapeutic potential of MSCs was assessed in other respiratory viruses. Immediate MSC therapy significantly attenuated H9N2 avian influenza virus-induced acute lung injury and inflammation in mice. They were capable of increasing the survival rate, decreasing lung edema and histological injury, improving gas exchange, and reducing alveolar proinflammatory chemokines and cytokines, such as granulocyte macrophage colony-stimulating factor (GM-CSF), monokine induced by gamma interferon (MIG), IL-1 α , IFN- γ , IL-6, and TNF- α [76]. In an *in vivo* pig model of swine H1N1 influenza, MSC-EVs reduced virus shedding and virus-induced production of proinflammatory cytokines, alleviating histopathological lesions in the lungs. When analyzed *in vitro*, MSC vesicles inhibited H1N1 influenza virus replication and virus-induced apoptosis in lung epithelial cells, mainly through RNA transfer [77]. Similar results were found in an H5N1-infected mouse model treated with MSCs [78]. MSCs have been hypothesized to neutralize free virus particles through the production of antibiotic proteins such as Cathelicidin antimicrobial peptide LL-37 (LL-37), which binds to virus and lung cell binding sites while also stimulating immunosuppression [79,80].

However, MSC effects in virus-induced lung injury appear to be viral strain-specific. H1N1-infected mice administered MSCs, although showing modestly reduced viral load and lower influenza-induced thrombocytosis, did not display any improvements in survival, histopathology, inflammatory profile resolution or prevention [65,81,82]. As the virus induced ARDS model is not yet fully established, with variable viral concentrations in inoculation dose, frequency and timing, MSC's therapeutic effect is still under question in viral scenarios.

Many cytokines and chemokines are involved in MSC's therapeutic capacity in respiratory diseases. Prostaglandin E2 (PGE2) produced by MSCs can drive macrophages from M1 to M2, an anti-inflammatory phenotype, increasing their production of anti-inflammatory cytokine IL-10 [20]. Another key potent anti-inflammatory protein secreted by MSCs is TNF stimulated gene-6 (TSG-6), which can contribute to decreasing inflammatory cytokine and cell counts in bronchoalveolar lavage fluid, while also contributing to fibrosis resolution [83]. Knock-down of TSG-6 expression in MSCs nullified most of these anti-inflammatory effects [84]. TSG-6 is involved in a well-described mechanism by acting on resident macrophages, decreasing TLR2/NF- κ B signaling, and thereby decreasing the secretion of proinflammatory mediators [85,86]. Herpesvirus entry mediator (HVEM) and B- and T-lymphocyte attenuator (BTLA) signaling also seems to be involved in MSC response to ARDS, particularly its immunomodulatory effects. Transplanted lung MSCs expressing HVEM showed improved regulation of inflammatory responses in innate and adaptive immune cells in LPS-induced ARDS model [87].

Moreover, MSC therapy can be beneficial even in indirect COVID-19 injuries. Preclinical studies using ventilator-induced lung injury models in rats showed that treatment with MSCs or MSC-CM decreased bronchoalveolar liquid concentrations of cytokines and inflammatory cells [88,89]. MSCs can also prevent secondary bacterial infections in patients with COVID-19 through their anti-microbial capacity, showing reduced bacterial levels in the alveoli, blood, and spleen in mice as well as in *ex vivo* human lungs [67,90].

Although few studies have investigated MSC therapy in viral-induced ARDS, the collective literature suggests a moderate beneficial effect of MSCs in general ARDS. Therefore, as COVID-19 patients receive mainly support therapy, MSCs are promising therapeutic candidates. Further investigations are necessary, especially regarding MSC timing and frequency of administration, hopefully in the strongest evidence scenario: randomized double-blind clinical trials.

2.2. Blood vessels

Many clinical conditions, including general pneumonia, increase the

risk of venous thromboembolism (VTE); hence, anticoagulants are routinely used as prophylaxis. [91–93]. However, COVID-19 seems to cause more frequent thrombotic disorders or endothelial damage than infections by other respiratory viruses such as SARS-CoV, MERS, and influenza [94]. Preliminary reports suggest that disseminated thrombotic events such as disseminated intravascular coagulation (DIC) occur in patients affected by COVID-19 [95–97]. Two studies from Netherlands and China with severely ill COVID-19 patients demonstrated that, respectively, 31% of 184 had thrombosis with most events being VTE, and that 25% of 81 developed VTE [98,99]. Out of the 1026 patients hospitalized with COVID-19, 40% were considered to be at a high risk of VTE, based on the Padua Prediction Score [100].

A retrospective multicenter study investigating 183 patients found higher levels of D-dimer and fibrin degradation products (~3.5- and ~1.9-fold, respectively) as well as increased prothrombin time (~14%) in COVID-related deaths. Approximately 71.4% of non-survivors vs 0.6% of survivors met the criteria for DIC [96]. Elevations in prothrombin time, D-dimer, and IL-6 levels are associated with a procoagulant profile and poor prognosis in patients with COVID-19 [101]. Furthermore, based on a meta-analysis of 400 severely ill patients, platelet count was inversely correlated with COVID-19 severity [102].

One aspect that still raises questions in COVID-19 is the dissociation between relatively well-preserved lung mechanics and the severity of hypoxemia. Patients with COVID-19 maintain high respiratory system compliance, indicating a well-preserved elastic lung tissue, but display a high shunt fraction, indicating poor gas exchange (*i.e.*, low oxygenated blood leaving the lungs). In physiological settings, endothelial self-regulation due to low oxygen levels takes place to activate vasoconstriction in the alveoli-endothelium which is not properly exchanging gas. However, COVID-19 may dysregulate this mechanism, leading to hyperperfusion of inefficient alveoli causing lower pO_2 , even though the ventilation capacity is only moderately reduced [103,104].

As SARS-CoV-2 is capable of infecting ACE2-expressing cells, direct endothelial cell infection was detected in multiple organs in post-mortem patients with COVID-19, revealing viral endothelial inclusions and a high frequency of congested small lung vessels [105]. Therefore, the direct endothelial lesion pathway may have a central role in the onset of COVID-19 coagulopathy and thrombotic disorders. As risk factors for COVID-19 and thrombotic diseases, such as age [106], obesity [107], diabetes [107], and hypertension [108,109] overlap, vascular damage may be a critical enhancer of disease progression. The World Health Organization (WHO) has already recognized COVID-19-related thrombosis, recommending daily prophylactic low molecular weight heparin or twice daily subcutaneous unfractionated heparin use in severe cases even after hospital discharge [110,111].

Increased research efforts are being made to investigate possible therapeutic strategies aimed to reduce blood clot formation, vascular damage and reverse the inflammatory and procoagulant systemic state caused by COVID-19 [112,113]. MSC's proangiogenic signaling, enhancing endothelial cell survival, and its supportive role in vascular remodeling, make them great therapeutic candidates in endothelial disorders [114–116].

MSCs are potent stabilizers of the vascular endothelium, decreasing endothelial permeability and protecting against inflammatory disruption of barrier function. In *ex vivo* perfused human lungs, MSCs reduced extravascular lung water, improved lung endothelial barrier permeability and restored alveolar fluid clearance in LPS models [83]. Keratinocyte growth factor (KGF) was essential for the beneficial effect of MSCs on alveolar epithelial fluid transport, in part by restoring amiloride-dependent sodium transport [117]. MSCs could protect the endothelial barrier function and regulate inflammation as they secrete VEGF and HGF, contributing to endothelial barrier stabilization in pulmonary capillaries, endothelial cell apoptosis inhibition, endothelial V-cadherin recovery, and proinflammatory factors reduction [66,116].

Epithelium-derived microparticles from pulmonary damage are a potential source of procoagulant mediators in the alveolar space in

patients with ARDS [118]. There is also a positive feedback between coagulation and inflammation, optimizing the response to injury and resulting in a wide range of diseases related to excessive inflammation and/or thrombosis [119]. Regarding the uncontrolled coagulation and thrombotic events due to COVID-19, reports on transfused MSC indicate that they express tissue-factor, a procoagulant, potentially leading to thrombosis and complement activation. There is considerable concern regarding the use of MSCs in clinical trials investigating thrombotic pathologies, as most protocols include transfusion of MSCs to the blood circulation [119]. Since the injection of cells and appropriated solution might elicit coagulatory responses, to the best of our knowledge no clinical trials have been conducted using MSC in thrombogenic settings. However, this behavior is still in question, as MSC could decrease thrombi size in acute pulmonary thromboembolism mice [120,121].

Thus, we can speculate that MSC therapy could modulate inflammation in the endothelial cell microenvironment and regulate endothelial permeability during COVID-19, preventing dysfunction. Synergistically, continuing the WHO-recommended treatment with anticoagulants, MSCs could directly inhibit endothelium apoptosis, acting as a potent regulator of vascular remodeling and recuperating blood flow control. In fact, the simultaneous use of both strategies seems to inhibit procoagulant events related to MSC transfusion. [122].

2.3. Heart

Several studies have shown that CVD predisposes patients to severe COVID-19 conditions, increasing the probability of mortality [24,95,97,99]. However, the effects of SARS-CoV-2 specifically in the heart are not well known. COVID-19 patients without previous history of CVD displayed cardiovascular manifestations, such as increased protein levels of cardiac troponin, myoglobin, creatine kinase and NT-proBNP, in addition to clinical symptoms, in particular chest pressure, suggesting myocarditis involvement [96,98,100–103]. Even small increases in troponin I levels (0.03–0.09 ng/mL) were significantly associated with death [123]. Myocardial injury occurs in ~25% of hospitalized patients and is associated with a greater need for mechanical ventilator support and higher hospital mortality [124].

One proposed cardiac pathophysiological mechanism is through direct myocardial injury, as SARS-CoV-2 seems to have the capacity to infect cardiomyocytes, pericytes and fibroblasts *via* the ACE2 pathway [125]. Furthermore, systemic cytokine-mediated injury, inflammatory cells infiltration, cardiac hypoxemia, coronary plaque rupture with acute myocardial infarction and adrenergic stress are other mechanisms implicated in COVID-19 cardiac pathology [124]. Post-mortem endomyocardial biopsy from COVID-19 positive patients found hypertrophied cardiomyocytes along with inflammatory infiltrates, focal edema, interstitial hyperplasia, fibrosis, degeneration, necrosis and signs of lymphocytic myocarditis [126].

Evidence suggesting that SARS-CoV-2 can cause myocardial lesions are corroborated by the structural similarity of the virus to SARS-CoV-1 (virus responsible for the 2002–2004 SARS epidemic) [103,127]. Both were found to be dependent on ACE-2 receptors for targeting and infecting human cells, and also to cause excessive cytokine responses, hypoxia and impaired left ventricular performance [64,94,96,105,106].

Previous studies indicated that SARS-CoV-1 infection, promotes ACE-2 dysregulation, arresting the cardioprotective effects of angiotensin 1–7 and leading to the synthesis of TNF- α [128,129]. Moreover, the activation of Smad signaling pathway triggers TGF- β signaling, which develops myocardium interstitial fibrosis [128,130].

To the best of our knowledge, no published study described the action of MSCs specifically in the heart of patients with COVID-19. Therefore, our review discusses the role and effectiveness of MSCs and MSC-EVs therapy based on similar cardiovascular manifestations.

Multiple studies reported the use of MSCs as beneficial for myocardial restoration [115,116,131–133]. In a model of Coxsackievirus B3-induced myocarditis in mice, MSCs exhibited a cardioprotective role

by inhibiting the expression of NOD2, ASC, caspase-1, IL-1 β , IL-18 and NLRP3 inflammasome in the left ventricle, which recovered myocardial contractility and fibrosis. They also reduced apoptosis, oxidative stress, intracellular viral particles production and TNF- α mRNA expression, while activated cardiac mononuclear cells and the IFN- γ protective pathway [114,134].

MSCs have also demonstrated beneficial effects in models of acute myocardial infarction. MSCs were able to reduce infarct size, preserve systolic and diastolic cardiac performance and activate resident cardiac stem cells, promoting its proliferation, migration and angiogenic capacity, which ultimately led to reduced fibrosis [66,83]. These results validate the cardioprotective, proangiogenic, and prosurvival effects of MSCs in the heart *via* immune system and tissue repair modulation [83,117,135,136].

Clinical trials involving the therapeutic use of MSCs in cardiac pathologies are still in very early phases. General safety has been demonstrated using mixed methodologies and MSCs source [137]. The main challenges encompass MSC's low tissue retention and survival after transplantation. However, initial results suggest that MSCs improved left ventricular function, questionnaire-assessed symptoms and quality of life, although more robust investigation is necessary [137].

Taken together, these data demonstrate the promising therapeutic potential of MSCs for various cardiovascular complications. Based on SARS-CoV-2 pathophysiology in the heart and the similarity observed in CVD, mainly in myocarditis, MSC therapy could constitute a potential treatment for COVID-19 related heart alterations.

2.4. Kidneys

SARS-CoV-2 has also tropism for the kidneys, with preference for renal proximal tubule epithelial cells and glomerular cells. These cell types are enriched with ACE2, TMPRSS2, and cathepsin L (CTSL), a facilitator of SARS-CoV-2 infection [49,53,138,139]. Therefore, this set of proteins forms a key point that allows viral entry, replication, and immune response establishment, thereby promoting acute kidney injury [49,140,141]. Studies have shown viral particles in the peritubular space, renal tubular epithelial cytoplasm, podocytes, glomerular capillaries, and a lower proportion in distal tubule epithelium, where ACE2 is known to be expressed [50,105]. These findings show that SARS-CoV-2 can directly infect renal epithelia, promoting acute renal injury in patients with COVID-19 [50,142]. Recent research described major renal morphological changes in COVID-19 postmortem individuals, such as acute proximal tubular injury with loss of brush border, vacuolar degeneration, tubular lumen dilation, necrotic regions, and epithelium detachment with a bare tubular basement membrane [50,143]. Tubular atrophy, mild interstitial fibrosis, Bowman's capsule rupture with global collapse of glomerular capillaries, podocytes vacuolization, and glomerular basement membrane retraction were also observed [50,143,144]. In addition, patients with COVID-19 showed renal dysfunction leading to increased levels of creatinine, urea, uric acid, proteinuria, hematuria, and inflammatory markers [12,50,143–145].

Although SARS-CoV-2 viral particles can promote renal injury by direct infection, some studies reported that the virus was not present in podocytes and tubules. It is suggested that the host inflammatory response to coronavirus is exacerbated, causing cytokines such as interferons to damage cells [143,144]. A study showed lymphocyte infiltration, high levels of complement system proteins, and macrophage infiltration in tubulointerstitial regions, in which proinflammatory cytokines derived from macrophages led to tubular injury, enhancing SARS-CoV-2 cytotoxic effect [146]. Virus-induced inflammatory mediators cause indirect effects such as hypoxia, shock and rhabdomyolysis, damaging kidney tissues [145]. Besides, high levels of these inflammatory substances are responsible for rapid multiorgan failure and death [12].

MSCs are being extensively studied for their therapeutic potential to

treat renal injury [147]. MSCs were able to reduce tubular cell apoptosis, inflammatory infiltrate, and interstitial fibrosis in rats with unilateral ureteral obstruction (UUO). Different mechanisms are controlled by the paracrine effect of MSCs in remodeling fibrosis. They inhibit trans-differentiation of activated myofibroblasts through TGF β /Smad2/3 signaling pathway, reduce mesangial cell proliferation through PI3K/Akt and MAPK signaling and induce high expression levels of MMP2 and MMP9 [12]. MSCs are able to reduce TGF- β , which has a key role in fibrogenesis because it stimulates ECM protein synthesis, fibroblast proliferation, and stress fiber synthesis, while decreases matrix degradation and promotes epithelial-mesenchymal transition of tubular cells [148,149]. MSC and MSC-CM improved tubulointerstitial fibrosis, decreased TGF- β expression, prevented degeneration of ZO-1 (a tight junction protein) in tubular epithelial cells, reduced mesangial expansion and suppressed excessive tubule dilatation in mice with diabetic nephropathy [150]. In addition, Li et al. reported that umbilical cord-derived MSCs promoted urine microalbumin improvement, glomerular hypertrophy repair, glomerular basement membrane thickening, fibrotic alteration, and podocyte process effacement, also in kidneys of mice with diabetic nephropathy [12]. These data show that MSCs have great potential to improve tubulointerstitial fibrosis by different mechanisms in the kidneys of patients with COVID-19.

MSC also have the ability to promote anti-inflammatory outcomes at long distances through their direct and indirect paracrine effects. In mice with ischemic or reperfusion acute kidney injury (AKI), intravenously infused MSCs are incorporated into the lungs and secrete soluble factors into bloodstream that improve kidney injury and ischemic renal repair by suppressing inflammatory reactions [151]. Recent evidence has shown that a combination of exosomes with soluble factors secreted by MSCs contribute to anti-inflammatory response, repair, and regeneration of renal tissues. The miRNAs transported by MSC exosomes are involved in tubular epithelium protection and regeneration [150]. In a mice model of aristolochic acid-induced nephropathy, MSC EVs reduced creatinine and urea levels, tubular necrosis, and interstitial fibrosis, while also reduced profibrotic genes expression (e.g., α SMA, Col 1a1, and TGF- β) and cellular activity of fibroblasts, pericytes, and myofibroblasts. In addition, they reduced inflammatory cells, promoted renal cell proliferation, and reduced apoptosis [149]. MSC-EV's miRNAs were transferred to host cells, altering their genetic expression, inhibiting inflammatory and profibrotic pathways [149]. miRNAs are also involved in tubular epithelium protection and regeneration [150]. These data show that MSC EVs have antifibrotic and anti-inflammatory properties, attenuating the innate immune response and favoring renal regeneration.

The renoprotective feature of MSCs is attributed to their unique ability to modulate the inflammatory immune response. MSCs promoted accelerated M2-polarized macrophage infiltration, trophic factors secretion, tubular epithelium proliferation, renal function improvement and IL-6 and TNF α reduction in mice with rhabdomyolysis-induced AKI [152]. Other studies also reported that MSCs promoted an increased expression of IL-10 and IL-4 mRNA, decreased expression of IL-1 β and TNF- α mRNA, and decreased inflammatory cells infiltration, reduced a proinflammatory (Th1) environment, and increased anti-inflammatory effects (Th2) [147,153,154].

MSC transplantation into the renal subcapsular region of rats with podocyte injury induced by puromycin promoted blood pressure reduction and decreased proteinuria, albuminuria, and serum creatinine. Renal regenerative and reparative effects of MSCs are also related to restoration of Wilms' tumor suppressor 1 (WT1) and VEGF expression and improvement of podocytes' functional and structural integrity, including proteins such as nephrin and podocin (slit diaphragm), synaptopodin, and podocalyxin (cytoskeletal proteins) [154]. Marrow mononuclear cell fraction, that includes MSC and other progenitor cells, can also promote renal tissue restoration [155].

Clinical trials with MSC administration in patients with AKI or sepsis-associated AKI, chronic kidney disease or diabetic nephropathy has been

limited to a small number of early phase clinical trials. Overall, MSC demonstrated good safety and tolerability, however only modest alterations in plasma cytokine profiles were observed, without a clear signal of improved outcome for MSC-treated patients [156–158].

Beyond MSC's paracrine effect, mitochondrial transfer also plays a role in kidney injury regeneration and repair. Bone marrow-derived MSCs transferred mitochondria to proximal tubular epithelial cells of mice with diabetic nephropathy *in vivo* [150]. These embedded mitochondria suppressed apoptosis, regulated mitochondrial factors such as Bcl-2, Bax, and PGC-1 α , inhibited reactive oxygen species (ROS) production, recovered transporter expression such as megalin and SGLT2, and repaired tubular structures [159]. Therefore, it was shown that MSCs have several mechanisms that promote renal regeneration and repair, thus unraveling the very promising therapeutic potential for patients affected by COVID-19.

2.5. Central nervous system

Several patients with COVID-19 have reported neurological events such as headache, dizziness, hypogeusia, and hyposmia [12,160]. In a systematic review of 554 patients who tested positive for COVID-19, the average prevalence of headaches was approximately 8% and dizziness was 7%–9.4% [63,161–163]. There are also many reports of cases that manifested more severe neurological symptoms, such as acute cerebrovascular diseases (acute ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage and subarachnoid hemorrhage), meningitis or encephalitis, acute hemorrhagic necrotizing encephalopathy, acute Guillain-Barré syndrome, hypopsia, and neuralgia [160,164,165]. In a large retrospective cohort study comparing 1916 COVID-19 patients and 1486 influenza patients adjusted for age, sex, and race, the likelihood of stroke was almost 8-fold higher for COVID-19 (odds ratio 7.6) [166].

The mechanisms underlying neural manifestations in COVID-19 are probably multifactorial: viral, immune, hypoxia, and hypercoagulability. Direct damage to the brain caused by SARS-CoV-2 is still under debate. Some authors have suggested direct brain infection as endothelial cells, arterial smooth muscle cells, glial cells, and neurons express ACE2 receptors in the brain [54,167]. In a preprint, SARS-CoV-2 was capable of infecting human brain organoids and the brain of mice overexpressing human ACE2 *in vivo* [168]. In another preprint, all 6 patients autopsies displaying affected brain tissues exhibited foci of SARS-CoV-2 infection and replication, particularly in astrocytes. *In vitro*, astrocyte infection changed energy metabolism, altered key proteins and metabolites ultimately reducing neuronal viability [169]. On the other hand, although autopsies showed SARS-CoV-2 could be detected in the brains of 21 (53%) of 40 examined patients, they were not associated with the severity of neuropathological changes, which were mainly attributed to mild neuroinflammatory or hypoxic changes [170,171]. To the best of our knowledge, no conclusive proof of direct neural infection has been demonstrated in live humans, as most studies did not find SARS-CoV-2 RNA in cerebrospinal fluid (CSF) or brain samples [172–178].

Cerebrovascular alterations such as large-vessel ischemic strokes and cerebral venous thrombosis are consequences of the procoagulant vascular state induced by COVID-19 [179]. Meanwhile, inflammatory cytokine storm provoked by SARS-CoV-2 infection may damage the blood-brain or blood-CSF barriers, oligodendrocytes and neurons [3]. The most common histopathologic findings in autopsies were astrogliosis, ischaemic lesions, neuronal degeneration and activated microglia in the brainstem [126,171].

Several studies have demonstrated positive results of MSC therapy in other neurological diseases, as they have high regenerative capacity and immunoregulatory function. In neurological complications (neurodegenerative diseases or neural inflammation), the main obstacle to treatment is the blood-brain barrier, which many drugs cannot cross to reach the target organ [45,180]. However, MSC EVs can overcome this barrier and solve the problem. Thus, from work already published, and

where it is possible to parallel neurological manifestations to those caused by SARS-CoV-2, the performance and effectiveness of MSC and MSC-EVs are discussed.

Inflammatory conditions in the central nervous system (CNS) are involved in the pathogenesis of acute and chronic neurodegenerative diseases, such as brain and spinal cord trauma, and stroke [181]. In inflammatory responses, microglia are activated, leading to neurotoxic and proinflammatory factors release, including cytokines, ROS, NO, and eicosanoids that can damage neurons and glial cells [181,182]. There is also the activation and recruitment of neutrophils and monocyte-derived macrophages into the bloodstream, further inducing neurodegeneration [183]. Sun et al. demonstrated that therapy with umbilical cord-derived MSC-EVs helped to recover spinal cord injury by reducing levels of IFN- γ , IL-6, TNF- α , and MIP-1 α in mice [182]. Another study using MPTP-induced mouse model, which kills dopamine-producing neurons, reported that bone marrow-derived MSCs decreased proinflammatory cytokines, suppressed microglia activation, recovered blood-brain barrier integrity and prevented neuronal death by releasing TGF- β 1. As a result, MSCs promote neuroprotective effect against cytotoxicity [184].

MSC and MSC-EVs also release neurotrophic factors, rescuing neuromotor activity in spinal cord injury [185,186]. A study that evaluated MSC-EV therapy following stroke in mice found that the treatment helped to improve peripheral immune responses, alleviating the quality and quantity of immunosuppression [187]. MSCs were observed to promote neurovascular recovery and plasticity in other studies that performed the same analysis in rats [187,188]. Recently, using a stroke model Xin et al. reported that MSC-EVs carry miR-133b, which is suggested to be the main component involved in improving cerebral recovery in stroke. MSCs could increase miR-133b levels in ischemic brain tissues, promoting an increase in neuron growth [187,188]. Thus, MSCs have important neuromodulatory capacity that can be used therapeutically.

In clinical trials utilizing MSC for spinal cord injury, stroke or traumatic brain injury side effects related to the procedure noted, although none of them were followed with sequelae. Transplantation of MSCs resulted in neurologic improvement in the majority of clinical trials, with superior performance in motor function, sensory level and daily living activities [189]. MSCs have great potential to improve patient symptoms and quality of life, whereas traditional medicine offers no efficient treatment.

The research presented here demonstrates the promising therapeutic potential of MSC and MSC-EVs in the treatment of various neurological complications. Although far from ideal, those models illustrate the potential benefits MSC may have on the neurological pathology of COVID-19, in different time points of the disease progression.

2.6. Risk groups for COVID-19: obesity, diabetes and hypertension

The main groups at risk of developing severe COVID-19 are elderly and obese individuals, who often have related comorbidities such as hypertension and type 2 diabetes (T2D) [190–192]. The Centers for Disease Control and Prevention (CDC) reported that the majority of patients hospitalized with COVID-19 in march 2020 were elderly (≥ 65 years) and among them, most of those who were obese experienced complications [193–195]. Simonnet et al. [196] showed a high prevalence of mechanical ventilation support as Body Mass Index (BMI) increased, being greatest in patients with obesity (BMI > 35), independent of age, diabetes, and hypertension [196]. Overweight or severely obese patients with COVID-19 had elevated metabolic damage linked to pneumonia aggravation, with higher prevalence of mechanical ventilation, and death [190,194].

The enhanced pathophysiology observed in individuals with obesity and COVID-19 is not clear, but probably is multi-factorial, ranging from complement system hyperactivation, chronic inflammation and comorbidities progression [191,197]. There is a consensus that obesity

negatively affects the immune response. In particular, inflammatory responses are triggered and develop to a constant low-grade systemic inflammation directly impacting the whole body [197]. This complex cellular event involves hyperplasia and hypertrophy of white adipose tissue cells and a macrophage profile switch to a proinflammatory state, that triggers the release of proinflammatory cytokines, such as TNF- α and IL-6. IL-6 is positively correlated to COVID-19 aggressiveness and is one of the main markers of lung injury [198,199]. Furthermore, weight excess is largely known to be positively associated with multiple respiratory diseases, such as asthma, obstructive sleep apnea syndrome, acute lung injury, and ARDS, even after adjusting for other risk factors [191].

Over time, this low-grade inflammation contributes to the development of insulin resistance and progression to T2D [198,200–202]. Individuals with T2D also have impaired immune system responses with altered activities of macrophages, NK cells, and neutrophils. In this scenario, lymphocytes induce production of proinflammatory cytokines due to impaired T_{reg} function [203]. In a cohort study, patients with COVID-19 that had well-controlled levels of glycemia showed controlled COVID-19 symptoms, while T2D patients showed higher levels of neutrophils and IL-6 cytokines [204]. Higher levels of proinflammatory cytokines, D-dimers, and a lower rate of survival were also associated with patients that had T2D and COVID-19 in another study [205]. Hyperglycaemia, regardless of diabetes status, was independently correlated to increased disease severity and mortality in 11,312 hospital patients with COVID [206].

The proinflammatory state seen in obesity can also contribute to the development of hypertension [207,208]. In multiple studies, hypertension was associated with poor COVID-19 outcome, including ARDS, need for intensive care unit, disease progression and mortality [24,209–211].

These data highlight the urgent need to develop therapies designed for potential high-risk COVID-19 patients [212]. The chronic proinflammatory state and impaired immunity typically found in patients with obesity, T2D and hypertension make it even more complex to design strategies aiming to treat COVID-19 based on controlling inflammation and preventing cytokine storm. In this regard MSC therapy may be a strategy to counteract COVID-19 especially in high-risk patients.

MSC therapy has positive metabolic and trophic effects in obesity models. In a preclinical systematic review, MSCs demonstrated strong positive effect in obese mice, improving glucose metabolism homeostasis, lipid profiles, non-alcoholic fatty liver disease and systemic inflammation [213]. Obese mice that received MSCs showed reduced liver fat deposition, IL-6 expression, blood glucose levels and increased glucose tolerance [214]. MSCs and MSC-CM have also presented a recovery effect on obesity-related cardiac alterations, reducing fibrosis, improving arrhythmias and exercise capacity [215].

In the T2D context, MSC transplantation has shown improvement in reversing peripheral insulin resistance and relieving β -cell destruction through paracrine activity [216–219]. Moreover, in hypertension disease, MSC's effects can reduce arterial pressure and induce a decrease in cardiac hypertrophy while also stimulating vascular recovery through secretion of VEGF, IGF, and HGF [220,221]. MSC could also improve systolic blood pressure in renovascular and salt-sensitive hypertension in mice [222,223]. Therefore, although safety must still be thoroughly validated, MSC-based therapy might be appropriate to patients with COVID-19 who have obesity and co-morbidities, as MSC has broad potential therapeutic benefits.

2.7. Challenges

Currently, there are 308 clinical trials registered to assess the therapeutic potential of MSCs for clinical use in patients affected with COVID-19 [224]. Most of these clinical trials use bone marrow or umbilical cord as sources of MSCs, which are intravenously administered. These studies are in phases I and II, evaluating safety and efficacy,

Table 1
COVID-19 multi organ pathology and MSC's potential therapeutic mechanisms.

Organs	SARS-CoV-2 pathogenesis	MSC therapeutic potential
Lungs	Cytokine storm	Immunomodulation \rightarrow paracrine signaling (PGE2, TSG-6, HVEM-BTLA)
	Diffuse alveolar injury Hyaline membrane formation Exudate and cell infiltration inside alveoli Possible secondary infection Progressive loss of function	\downarrow viral load - LL37 protein \downarrow epithelial cells apoptosis \uparrow alveolar fluid clearance and angiogenesis \downarrow histological injury \downarrow pulmonary fibrosis (TGF- β 1)
Heart	Pulmonary fibrosis	Alveolar epithelial integrity recovery
	\uparrow cardiac troponin \uparrow myoglobin \uparrow creatinine kinase \uparrow NT-proBNP ACE-2 dysregulation \downarrow angiotensin 1–7 \uparrow TNF α Myocarditis/microvascular injury/ microthrombocardiomyopathy Hypoxia Arrhythmias	\uparrow myocardial contractility \downarrow apoptosis \downarrow oxidative stress \downarrow TNF- α mRNA Activate resident cardiac stem cells Preserve cardiac function
Blood vessels	Acute cardiac injury with cardiomyopathy, ventricular arrhythmias, and hemodynamic instability Myocardium fibrosis	\downarrow infarct size \downarrow fibrosis
	Endothelial cell infection Hyperperfusion of inefficient alveoli Procoagulant profile: \uparrow D-dimer	\uparrow KGF \uparrow VEGF \uparrow HGF \downarrow endothelial cell apoptosis \downarrow lung endothelial barrier permeability \uparrow angiogenesis Preserves endothelial barrier function
Kidneys	\uparrow fibrin degradation \uparrow IL-6 \uparrow thrombotic disorders	
	\uparrow COVID severity = \downarrow platelet Directly infect renal epithelia Tubular injury Necrotic lesions	\downarrow tubular cell apoptosis \downarrow inflammatory infiltrate \downarrow TGF- β tissue remodeling \downarrow fibrosis
Central nervous system	Epithelium detachment	\uparrow podocytes function and integrity
	Bowman's capsule rupture Renal dysfunction	Nephroprotective effects Regeneration of renal tubular cells through MSC-derived Evs
Central nervous system	Interstitial fibrosis Direct damage (?)	\downarrow IFN- γ \downarrow IL-6 \downarrow TNF α \downarrow MIP-1 α
	Glial cell hyperplasia Acute ischemic stroke/cerebral venous sinus thrombosis/cerebral hemorrhage Ischaemic lesions Neuron degeneration	\downarrow microglia activation \uparrow blood-brain barrier integrity \uparrow angiogenesis \downarrow neurocytotoxicity \uparrow miR-133b \uparrow neurovascular recovery and plasticity

PGE2 - prostaglandin E₂; TSG-6 -TNF-stimulated gene-6; HVEM - Herpesvirus entry mediator; BTLA - B- and T-lymphocyte attenuator; LL-37 - cathelicidin antimicrobial peptides LL-37; TGF- β - transforming growth factor-beta; IFN- γ - interferon-gamma; IL-6 - interleukin 6; TNF- α - tumor necrosis factor-alpha; MIP-1 α - macrophage inflammatory protein; KGF - keratinocyte growth factor; VEGF - vascular endothelial growth factor; HGF - hepatocyte growth factor.

mainly in patients with exacerbated inflammatory responses. As the therapy is innovative, there is a need for caution when administering cells into patients. In preclinical trials, MSCs are quite efficient, but advanced clinical trials have fallen short of expectations. Clinical trials involving the use of MSC in patients with COVID-19 although presented partial improvement of outcome, have received critics regarding loose definitions and limited data availability [225,226]. Some aspects such as dose standardization, frequency of MSC doses and treatment timing, as

defining the optimal stage of COVID-19 at which the cells should be injected, still need to be clarified. Also, the possibility of thromboembolism must always be taken into account [119]. It is important to recognize that in future investigations, patients need to be followed-up, not only in the short term, but also in the long term to detect undesirable adverse effects. Besides, long-haulers, long-COVID or post-acute COVID patients, in which variable symptoms can linger for months, might benefit from MSCs treatment, but clearer definition of post-COVID sequelae as well as solid evidence for MSC's effect in this context is still lacking [227].

In this review article, we summarized the reported evidence of MSCs potential benefits in multiple organs and systems affected by COVID-19 (Table 1). Collectively, MSCs 1) provide an anti-inflammatory environment via different mechanisms, decreasing cytokine, chemokine, and inflammatory cell infiltration; 2) improve pathological resolution, promoting tissue remodeling and reducing fibrosis; and 3) restore organ function, recovering the expression of proteins involved in cell structures in the lungs, kidneys, cardiovascular system, nervous system, and also in hypertensive, obesity, and diabetes models. Thus, MSCs are a very promising treatment strategy for patients with COVID-19, although some challenges will need to be addressed during translational research.

Conflicts of interest

The authors declare no potential conflicts of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

CRediT authorship contribution statement

G.P.C. and A.A.T. were responsible for Conceptualization; G.P.C., A.A., A.L.F., M.A.R., G.P.O. and Y.M.A.A. for Data Curation and Writing the Original Draft; M.A.R. handled Data Visualization; G.P.C., K.R.S., E.A.C.C., A.C.S., S.N.C., L.C. and A.A.T. were responsible for Review & Editing; E.A.C.C., A.C.S., S.N.C., L.C. and A.A.T. were responsible for Supervision and Funding Acquisition.

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Glossary

ACE2 - Angiotensin-converting enzyme 2:

AKI - Acute kidney injury:

ARDS - Acute respiratory distress syndrome:

BMI - Body mass index:

CDC - Centers for Disease Control and Prevention:

CNS - Central nervous system:

CSF - cerebrospinal fluid:

CTSL - Cathepsin L:

CVD - Cardiovascular diseases:

DIC - Disseminated intravascular coagulation:

EV - Extracellular vesicles:

FGF - Fibroblast growth factor:

GM-CSF - Granulocyte macrophage colony-stimulating factor:

hACE2 mice - Transgenic mice expressing human ACE2:

HGF - Hepatocyte growth factor:

IFN - Interferon:

IGF - Insulin growth factor-1:

IL-2 - Interleukin-2:

KGF - Keratinocyte growth factor:

MCP-1 - Monocyte chemoattractant protein-1:

MIG - Monokine induced by interferon-gamma:

MIP-1 α - Macrophage inflammatory protein:

MiRNA - microRNA:

MSC - Mesenchymal stem cells:

NK - Natural killer cells:

PDGF-DD - Platelet-derived growth factor-DD:

PGE2 - Prostaglandin E₂:

RAS - Renin-angiotensin system:

RBD - Receptor-binding domain:

ROS - reactive oxygen species:

SARS-CoV-2 - Severe acute respiratory syndrome-coronavirus 2:

TGF- β - Transforming Growth Factor-beta:

TNF- α - Tumor necrosis factor-alpha:

TSG-6 - TNF-stimulated gene-6:

UOO - Unilateral ureteral obstruction:

VEGF - Vascular endothelial growth factor:

VTE - Venous thromboembolism:

WT1 - Wilms' tumor suppressor 1:

HVEM - Herpesvirus entry mediator:

BTLA - B- and T-lymphocyte attenuator:

LL-37 - Cathelicidin antimicrobial peptides LL-37:

T2D - Type 2 Diabetes:

S protein - SARS-CoV-2 Spike protein:

MSC-CM - Conditioned-media: