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Review

Stem cell therapy in COVID-19: Pooled evidence from SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS: A systematic review

Saniya Mahendiratta^{a,1}, Seema Bansal^{b,1}, Phulen Sarma^a, Harish Kumar^a,
Gajendra Choudhary^a, Subodh Kumar^c, Ajay Prakash^a, Rakesh Sehgal^d, Bikash Medhi^{a,*}

^a Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

^b Post Graduate Institute of Medical Education and Research, Chandigarh, India

^c PGIMER, Chandigarh, India

^d Dept. of Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh, India



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ABSTRACT

Background: SARS-CoV-2, which majorly affects the lungs and respiratory tract is thought due to dysregulation of the immune system which causes an immense imbalance of the cytokines. However, till now no standard treatment has been developed in treating the disease. On the other hand, it becomes important to prevent the acute respiratory tract infection due to COVID-19 which is the most dangerous phase leading to increased mortality. Hence this systematic review has been framed by pooling the available data of the use of stem cells in SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS.

Methods: 6 literature databases (PubMed, EMBASE, Scopus, Google Scholar, Clinicaltrials.gov, and Clinical trial registry of India) were searched for relevant studies till 10th August 2020 using keywords stem cells, mesenchymal stem cells, cell therapy, SARS CoV-2, SARS Coronavirus, Coronavirus 2, COVID-19, nCoV-19, Novel Coronavirus, MERS CoV, ARDS, acute respiratory distress syndrome.

Results: The observations of this systematic review suggest capability of MSCs in reducing the systemic inflammation and protecting against SARS-CoV-2 as evidenced by the available clinical data.

Conclusion: MSCs can overcome the clinical challenges currently faced by SARS-CoV-2 infected patients, specifically who are seriously ill and not responding to conventional therapies. Though the available clinical data is motivating, still predicting the therapeutic potential of MSCs will be too early in COVID-19. Hence, further studies in a larger cohort of patients becomes a prerequisite to validate their potential efficacy.

1. Introduction

So far, there are seven types of human coronaviruses which have been documented and it includes beta-genera CoV's and α -genera CoV's. SARS-CoV-2, SARS-CoV and MERS CoV belong to the family of beta coronaviruses and are enveloped, positive-sense, single-stranded, and highly diverse RNA viruses [1]. These 3 viruses unlike other hCoV's make the lower respiratory tract more prone towards infection which results in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [2].

Regarding genomic homology, SARS-CoV-2 genome was 79.5 % homologous to SARS-CoV, but shared only 50 % homology with MERS-CoV [3]. Again, bat SARS-CoV genome was 87–92 % identical to human SARS-CoV [3].

Structurally also different coronaviruses (SARS-CoV-2, SARS-CoV and MERS-CoV) are similar with spike, M and N proteins being major membrane proteins, among which the spike protein plays a major role in the establishment of a host infection [4]. In all these three coronaviruses, the spike protein consists of two subunits (S1 and S2), out of which receptor binding domain (RBD) of S1 subunit which is mainly

* Corresponding author at: Dept. of Pharmacology, Research block B. Postgraduate Institute of Medical Education and Research, Room No: 4044 4th floor, Chandigarh, India.

E-mail addresses: saniya.mahendiratta88@gmail.com (S. Mahendiratta), 2006.seema@gmail.com (S. Bansal), phulen10@gmail.com (P. Sarma), hkumar98@gmail.com (H. Kumar), gajendra809@gmail.com (G. Choudhary), subodhbiotech@gmail.com (S. Kumar), ajayprakashpgi@gmail.com (A. Prakash), sehgalpgi@gmail.com (R. Sehgal), drbikashus@yahoo.com (B. Medhi).

¹ Indicates first author. In our article both Saniya Mahendiratta and Seema Bansal contributed equally. So, both are designated as first author.

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responsible for binding of the virus to host receptors and S2 causes the fusion of the virus with the host membrane [5].

Similarly the entry mechanism of the viruses are similar i.e mediated by binding of the RBD to functional receptors on host cell surface where angiotensin converting enzyme (ACE2) is the primary and dominant host receptor but having higher affinity to SARS-CoV-2 than to SARS-CoV [6]. Again high homology was seen between different structural and non-structural proteins (nucleocapsid also between SARS-CoV and SARS-CoV-2) [7]

Again, from pathophysiologic point of view, all the three viruses are similar to a greater extent with occurrence of cytokine storm and ARDS being the major pathological hallmark in all the cases. However, mortality rate is somewhat higher in case MERS-CoV (38 %) and SARS-CoV (9.6 %) [8] compared to SARS-CoV-2 (2.1 %) [9]

Treatment of COVID-19 depends on the clinical condition of the patient such as; patients with mild disease can be treated for their illness at home and not requiring hospitalization. In case of severe or critically ill patients' hospitalization is required with treatment relating to the condition of the patient. The commonly used therapeutic options for the treatment of COVID-19 ranges from hydroxychloroquine, azithromycin, remdesivir, favipiravir, to immunomodulators e.g. steroid and IL-6 antagonists (tocilizumab, itolizumab), convalescent plasma [10]. Although, these agents showed promising results in *in-vitro* studies, however, clinical results are not robust. Hence, a lot of other attractive options are being evaluated either as drug therapy or as vaccine e.g. SARS-CoV-2 entry inhibitors, Fusion inhibitors, RdRp inhibitors, NSP-15 inhibitors etc [11]. In few refractory cases even lung transplantation is tried and found to be useful (very limited data) [12,13,11].

In this context, considering the similarity at the level of structure and disease pathophysiology, in this current study, we evaluated the role of stem cells in context to three coronaviruses, which can cause serious human disease (SARS-CoV-2, SARS-CoV and MERS-CoV) and their final outcome (ARDS).

Stem cells are known as unspecialized cells having capacity to differentiate in to cells of whole organism (totipotent) or all the three germ layers except the extra-embryonic structures (pluripotent) or specialized into discrete cells of specific cell lineages (multipotent) or differentiating into only one cell type (unipotent) [14]. Studies have suggested the modulating properties of MSCs where they can modify the adaptive and innate immune response with the suppression of T-cells, maturation of dendritic cells, reduction of B-cell activation and proliferation, inhibiting the proliferation and cytotoxicity of NK cells while promoting the generation of regulatory T-cells with the help of soluble factors (paracrine) or juxtacrine mechanism [15]. Stem cell therapy has already shown promise in other viral infections e.g. Human immunodeficiency virus (HIV) [16], hepatitis B virus [17], virus associated ARDS [18], influenza and other coronavirus associated lung injury [19]. Many studies have indicated the role of up-regulation of interferon stimulating genes (ISG) and interferon-induced transmembrane (IFITM) family of proteins in the protective efficacy of interferons against viral disease [20].

These protective mechanisms provide stem cells the properties of rejuvenation and regeneration which makes them capable of reducing the inflammation, decrease the cell death, secretion of cell protective substances, anti-oxidative effects and improving overall immune function. Further, direct evidence suggest the protection against influenza virus (A/H5N1) by the reversal of lung injury [21].

The immune modulating action of stem cells is mediated by TLRs (TLR, mainly TLR3 and TLR4) present on the surface of MSCs. RNA viruses [act as Pathogen-associated molecular pattern (PAMP)] activate these TLRs, which leads to secretion of certain chemokines like MIP-1 α

and MIP-1 β , RANTES, CXCL9, CXCL10, and CXCL11 etc, which leads to an anti-inflammatory response [22]. These kind of responses can be useful in COVID-19 patients as a similar situation of hyperimmune response known as "cytokine storm" has been observed. There has been hypersecretion of pro-inflammatory cytokines which includes IL-2, IL-6, IL-7, G-CSF, IP10, MCP1, MIP1A and TNF α which influences MSCs to release anti-inflammatory molecules (IL-10) with the release of soluble factors like transforming growth factor- β 1 (TGF- β 1) prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), indoleamine-pyrrole 2,3-dioxygenase (IDO), and nitric oxide (NO) [23]. These in turn decrease the proliferation of activated T-cells and NO on the other hand causes cell cycle arrest by repressing the phosphorylation of signal transducers and transcription of STAT-5 in T-cells. Further, IDO secretion by MSCs leads to apoptosis of activated T-cells and converts tryptophan into kynurenine causing suppression of proliferation of effector T-cells [24].

Besides stem cell therapy, the use of exosomes as a cell free approach has been studied as they possess hypoimmunogenic properties and are enclosed in a lipid bilayer. These properties makes the exosomes extremely stable and suitable for them to migrate to the target organ of damage rather accumulating via blood flow. The combinatorial strategy of antiviral drugs along with immunomodulatory, tissue protective and healing potential of stem cells and their exosomes may reduce the severity of the COVID-19 [25].

Although many studies [26,27] have evaluated the effect of stem cell therapy in COVID-19, however, till now no systematic review have addressed this issue. In this regard, we have pooled the evidence of safety and efficacy of stem cell therapy from SARS-CoV-2, SAR-CoV, MERS-CoV and ARDS data.

2. Material and methods

2.1. Methods

A systematic search was conducted in 6 literature databases (PubMed, EMBASE, Scopus, Google Scholar, Clinicaltrials.gov, and Clinical trial registry of India) for relevant studies till 10th August, 2020 using keywords stem cells, mesenchymal stem cells, cell therapy, SARSCoV-2, SARS Coronavirus, Coronavirus 2, COVID-19, nCoV-19, Novel Coronavirus, MERS CoV, ARDS, acute respiratory distress syndrome.

2.2. Inclusion criteria

We included studies (*in-vitro* and pre-clinical *in-vivo* and clinical interventional studies) where stem cell or exosomes were used as therapy to modify the outcome of three human coronavirus that can cause serious human disease (SARS-CoV-2, SARS-CoV and MERS-CoV) and their final outcome (ARDS).

2.3. Exclusion criteria

We excluded studies involving other corona-viruses which do not cause serious human disease (229E, NL63, OC43, and HKU1), *in-silico* studies, and studies including intervention other than stem cell/cardioperes/exosomes.

2.4. Extraction of data and analysis

Title and abstract screening were conducted independently by Saniya Mahendiratta, Seema Bansal, Phulen Sarma and Harish Kumar using pre-defined exclusion and inclusion criteria. Ajay Prakash and

Bikash Medhi were consulted for resolving the differences in opinion. Data extraction and subsequent full-text review was done by Saniya Mahendiratta and Seema Bansal using Cochrane data extraction form. Cross checking of the data retrieved for each article was done by other authors.

3. Results

The systematic search of the databases yielded 456 studies. With the removal of zero duplicate 456 articles were reviewed by abstract and title. With initial screening only, 202 met the inclusion criteria and underwent for full text evaluation. Of these, studies 177 studies were not fulfilling our criteria were removed, and final list include 25 articles (Prisma Chart Fig. 1).

3.1. In-vitro studies

3.1.1. In-vitro studies for SARS-CoV-2, SARS-CoV and MERS-CoV

After deliberate search of 4 databases with appropriate keywords, we couldn't find any relevant data regarding *in-vitro* evaluation of safety or

efficacy of stem cell in COVID-19 or SARS-CoV-2, SARS-CoV and MERS-CoV.

3.1.2. In-vitro studies for Acute respiratory distress syndrome (ARDS) (Table 1)

3.1.2.1. Effect of human umbilical cord Wharton's jelly-derived MSC's (hUC-MSC) secreted factors in Lipopolysaccharide (LPS) induced lung injury. Chen et al. [28] in their study investigated the effects of MSC-conditioned medium (CM) on two cell lines: primary human small airway epithelial cells (SAEC) and human alveolar epithelial A549 cells (AEC). Wound healing assay, modified MTT assay, and trans-well migration assay was performed to evaluate MSC-CM effect on proliferation and migration of SAEC and AEC. The stem cell-CM treated AEC and SAEC cells showed evidence of proliferation and effective wound healing compared to control or LPS group. On further exploring the molecular pathways, they found the involvement of JNK, P38 and ERK MAPKin the protective effect of MSC-CM on cellular proliferation, wound healing and migration in AEC and SAEC.

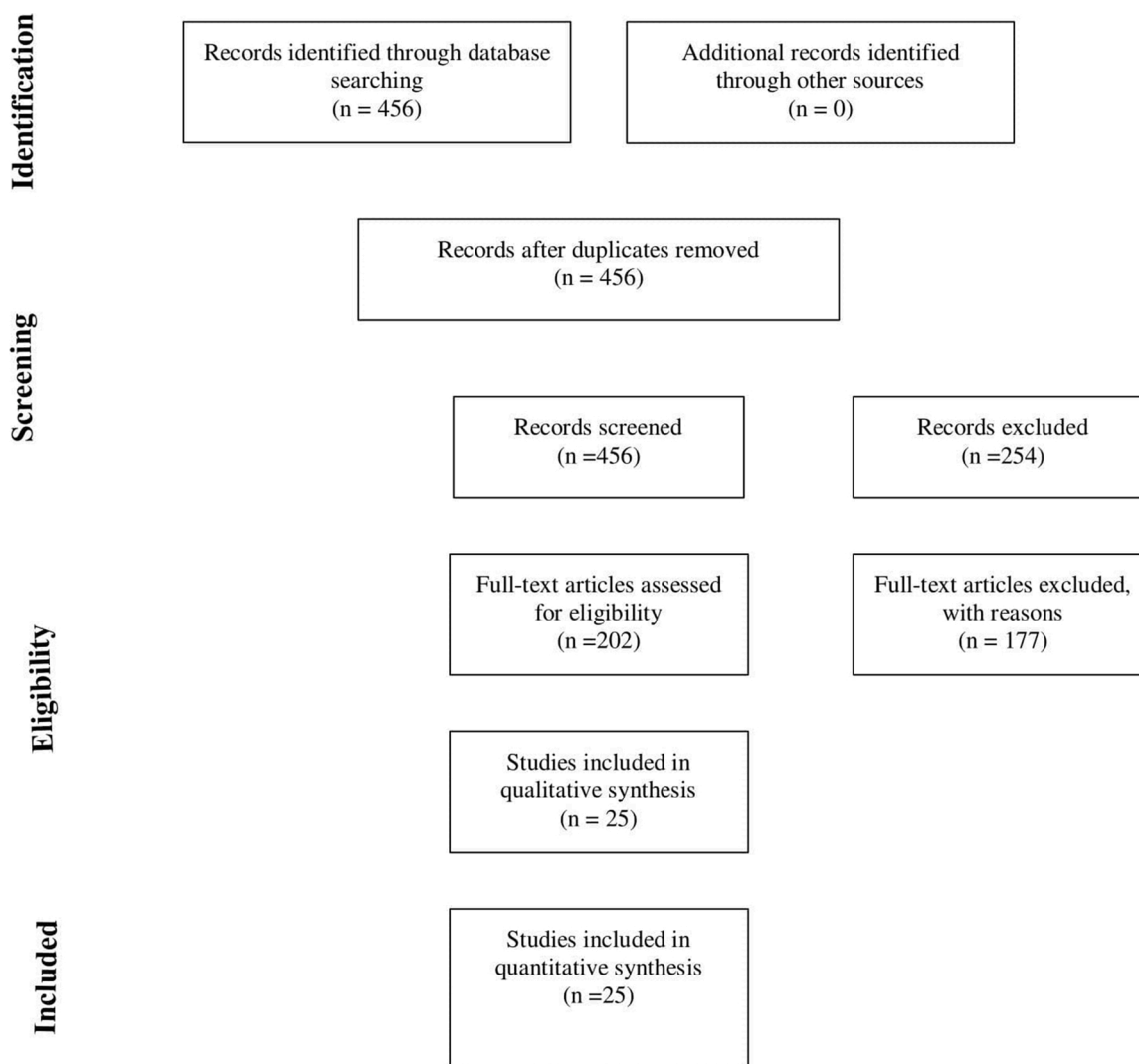


Figure 1: PRISMA chart showing the selection of the studies for systematic review

Fig. 1. Prisma Flow Chart.

Table 1
In-vitro stem cell therapy in Acute Respiratory Distress Syndrome (ARDS).

Author, Year	Aim of the study	Condition	Intervention/ Details of stem cell use	Outcome
Pati et al. 2011 [29]	To study the effects of conditioned media (CM) from MSCs and MSC-PEC co-cultures on Pulmonary endothelial cells permeability.	ALI/ARDS due to Hemorrhagic Shock (HS)	BMMSCs	Inhibition of permeability of PEC. Restoration of VE-Cadherin and B-catenin (chief regulators of vascular integrity and permeability). MSC-PECCM inhibited TNF- α mediated increase in ICAM-1, and VCAM-1 (suggestive of contact-mediated effect) MSC-CM under septic conditions promoted proliferation in A549 cells under septic conditions.
Chen et al. 2015 [28]	To investigate the impact of human umbilical cord Wharton's jelly-derived MSC (hUC-MSC) secreted factors on alveolar epithelial cells under septic conditions	Liposaccharide induced ARDS	hUC-MSC	MSC-CM under septic conditions promoted proliferation in A549 cells under septic conditions. Also caused wound healing and a significant increase in A549 cells
Masterson et al. 2018 [30]	To evaluate the effects of syndecan 2 (CD362)-expressing human mesenchymal stromal cell enhance resolution after ventilator induced lung injury		hMSCs	Conditioned medium from CD362+ human mesenchymal stromal cell attenuated interleukin 1 β -induced nuclear factor- κ B activation in type II alveolar A549 cells. Also rate of wound closure was increased in A549 alveolar epithelial cultures after 24 h of wound injury.
Xiang et al. 2017 [31]	Evaluated the effects of MSC in attenuating the lung inflammation with repairing effect on damaged lung.	LPS-induced lung injury	Menstrual blood-derived stem cells (MenSCs)	Lung injury was attenuated, reduction of inflammation exhibited in the form of decreased levels cytokines. Increased proliferation and decreased apoptosis shown by PCNA (increased expression) and caspase-3 (decreased expression). Also, there was increased protein levels VE-cadherin, β -catenin and PI-3 K and decreased levels p-gsk3 β , p-src and p- β -catenin.
Yi Fong Su et al [33]	Studied the effects of iPSC on the migration of human neutrophils isolated from ARDS patients	LPS-induced lung injury	Induced pluripotent stem cells (iPSC)	Significant decrease in neutrophil migration
Yi Fong Su et al [32]	Evaluated the effects of MSC-CM on the apoptosis of pulmonary neutrophils.	LPS-induced lung injury	MSC-CM	Higher apoptosis was observed when treated with MSC-CM compared to LPS alone

3.1.2.2. Effect of Pulmonary epithelial cells and MSC-PEC conditioning medium on PEC permeability. Pati et al. [29] evaluated the effects of Conditioned Media (CM) isolated from Mesenchymal stem cells (MSC) and MSC-PEC-co-cultures on pulmonary epithelial cells (PEC). They observed their inhibitory activity on the permeability of PEC which was due to the preserved adherens junctions (β -catenin and VE-cadherin). Further, MSC-PEC co-cultures also inhibited adhesion molecule (VCAM-1 and ICAM-1) and leukocyte adhesion expression. This study actually demonstrated the therapeutic potential of MSC in acute lung injury (ALI) caused by Hemorrhagic shock (HS).

3.1.2.3. Effects of CD362+ human mesenchymal stromal cells in modulating the pulmonary functions. Masterson et al. [30] determined the potential of conditioned medium from CD362+ human mesenchymal stromal cells in type II alveolar A549 cells. They performed NF- κ B activation assay, wound healing assay and macrophage phagocytosis assay. It was observed that conditioned medium attenuated interleukin-1 β induced NF- κ B activation and also the rate of wound closure. It was also shown that these effects were significantly more effective compared to heterogeneous human mesenchymal stromal cells.

3.1.2.4. Effects of Menstrual blood-derived stem cells (MenSCs) in LPS induced lung injury. Xiang et al. [31] performed transwell experiments to show the migration ability of MenSCs. Observations showed 17.8 % migration of MenSCs into the lower layer of the membrane from the transwell inserts in LPS group compared to the control group which showed migration in only 9.5 % of cells. For evaluating the effectiveness of MenSCs on apoptosis and cell viability in BEAS-2B cells (human lung epithelial cells), LPS exposure was given to these cells which showed significant reduction in viability and higher rate of apoptosis. This was reversed when treated with MenSCs with reduction in apoptotic rate compared to normal BEAS-2B cells (control).

3.1.2.5. Effects of induced pluripotent stem cells (iPSC) on human neutrophil migration. Yi Fong SU et al. [32] studied the migration of human neutrophils isolated from ARDS patients by treating them with iPSC using transwell migration model. A significant decrease was seen in neutrophil migration induced by LPS when treated with iPSC. Similarly, in their another study [33]. MSC-CM effect on apoptosis of pulmonary neutrophils was studied. These neutrophils were isolated from bronchoalveolar lavage fluid (BALF) samples from mice and cultured with or without LPS and MSC-CM treatment. Higher apoptosis was observed when treated with MSC-CM in comparison to LPS alone.

3.2. In-vivo studies

(Table 2)

3.2.1. In-vivo studies for SARS-CoV-2

A study by Liu et al. [34] demonstrated a novel vaccine platform for treating COVID-19 by SARS-CoV-2 proteins expressing MSCs. They administered MSC-SARS-CoV-2-N cells in C57BL6 mice and observed antibody production in almost all the immunized mice (7/8) after 20 days in which 50 % had strong positive antibody expression. The body weight of the mice remained same or increased with no severe symptoms after the MSC administration. It was also seen that responses were again for Nucleocapsid (N) protein even after transfection with Spike and Membrane proteins of SARS-CoV-2. Further, they performed PCR for N protein in the blood and tissue which demonstrated clearing of MSCs by the immune system. This approach of cell therapy as a vaccine can have one potential risk of uncontrolled proliferation and malignancy if residual cells remains in the body.

3.2.2. In-vivo studies for SARS-CoV and MERS-CoV

After deliberate search of 4 databases with appropriate keywords, we couldn't find any relevant data regarding *in-vivo* evaluation of safety or

efficacy of stem cell in COVID-SARS-CoV and MERS-CoV.

3.2.3. *In-vivo studies for ARDS*

3.2.3.1. *LPS induced acute lung injury*

3.2.3.1.1. *MSC*. Hu et al. [35] studied the effectiveness of MSC in LPS induced lung injury in Sprague Dawley rats. They measured vascular permeability in lungs, performed histopathology and also checked the cytokine levels. Further, they also determined whether expression of hepatocyte growth factor (HGF) in MSC will improve the vascular permeability and lung injury caused by LPS. MSC administration improved the vascular permeability in the lungs with an increase in lung score in histopathological findings specifically with HGF. Additionally, there was a decrease in cytokine levels and rate of apoptosis with an increased expression of VE-cadherin in MSC group expressing HGF compared to acute lung injury (ALI) group. Xiang et al. [31] in his study observed amelioration of lung injury induced by LPS with the administration of MenSCs in C57 mice. They assessed migration, inflammatory responses, proliferation and apoptosis. It was observed that MenSCs were able to migrate and get retained in the injured lungs, attenuating the inflammation with improvement in histopathology. Further, reduced proliferating cell nuclear antigen (PCNA) expression and increased caspase-3 expression was observed indicating proliferative and anti-apoptotic actions of MenSCs compared to LPS group. Chen et al. [36] investigated Heme oxygenase-1 modified MSC (MSC-HO-1) protective effects in LPS induced acute lung injury in Wistar rats. Survival rate and score of lung injury was significantly improved with the administration of MSC-HO-1. There was a reduction in inflammation exhibited by an enhanced production of keratinocyte growth factor, HGF and IL-10 in MSC-HO-1 group compared to LPS group. In a study by Li et al. [37] repairing capacity of MSCs were assessed with down-regulated Hippo-signaling pathway in LPS induced lung injury in C57BL/6 mice. Significant retention of MSCs were seen in lungs, with decreased lung edema and improved lung permeability. There was also decreased inflammation, improved pathological changes with reduced pulmonary fibrosis.

3.2.3.1.2. *Adipose derived stem cell*. Zhang et al. [38] compared the therapeutic effects of Human adipose derived stem cells (hASCs) and mouse derived stem cells (mASCs) in C57BL/6 mice. It was observed that there was an increase in the body weight of the animals in both the groups compared to LPS group but significance in improvement was seen with mASCs. To determine the effects on the integrity of the pulmonary vascular leakage and alveolar-capillary membrane barrier, protein and albumin levels were assessed in bronchoalveolar lavage fluid (BALF) which decreased with the treatment of hASCs and mASCs with much better effect with mASC. Further, there was decreased inflammation and leukocyte migration into the alveoli but mASCs was more potent compared to hASCs in terms of therapeutic effects.

3.2.3.1.3. *Endotoxin induced lung injury:MSC's*. Su et al. [32,33] in his studies assessed the neutrophil apoptosis with the administration of MSC-CMin wild-typeC57BL/6 male mice and also evaluated the activity of induced pluripotent stem cells (iPSCs) in lessening the chemotaxis of neutrophils. In the former study the apoptosis in the BALF neutrophils was enhanced with the reduction in expression of Bcl-xL and Mcl-1. While in the latter study chemotactic responses towards endotoxin were with the reduction of chemokine (C-X-C motif) receptor 2 (CXCR2) expression in mouse peripheral blood neutrophils. Additionally, it was investigated that the effects of the latter study were due to reduced CXCR2 expression and augmented GRK2 activity.

3.2.3.1.4. *E. coli induced lung injury: MSC's*. Lung injury can also be

caused by prolonged pneumonia due to exposure to *E. coli*, which can be treated by MSCs. This has been shown in one of the studies by Devaney et al. [39] where he compared the efficacy of intrathecal and intravenous administration of MSCs along with cryopreserved MSCs and its secretome in Sprague Dawley rats. Results showed reduced severity of pneumonia with improved survival and decreased lung injury. The bacterial load was also decreased with a reduction in inflammation. It was also observed that intrathecal administration was much more effective with higher efficacy of cryopreserved MSC than the secretome. Shalaby et al. [40] in his study demonstrated the anti-oxidant effects of systemic injection of MSC pre and post injury in Balb c mice. It was observed that pulmonary edema was reduced and lung injury was attenuated. Also, anti-oxidant enzyme activities were increased with a reduction of malondialdehyde and myeloperoxidase activity. It was also assessed that the effects were profound when MSC was given before injury compared to post-injection. Masterson et al. evaluated the effects of CD362+ (syndecan-2-positive) human mesenchymal stromal cells in *E. coli* induced lung injury in Sprague Dawley rats. Results showed improvement in arterial oxygenation, lung compliance, also reduction in bacterial load and structural injury in MSC group compared to vehicle.

3.2.3.1.5. *Bleomycin induced lung injury: MSC*. Zhao et al. [41] illustrated therapeutic efficacy of MSC engraftment in lung injury caused by Bleomycin (5 mg/kg) in rats. It was observed that MSC attenuated the lung injury exhibited in the form of decreased hydroxyproline in lungs, laminin and hyaluronan in bronchoalveolar lavage fluid (BALF), which are the markers of fibrosis and lung injury. Even cytokines expression which includes TGF- β 1, PDGF-A, PDGF-B, and IGF-I were reduced significantly thus documenting the favorable effects of MSC engraftment. Wakayama et al. [42] in his study showed amelioration of the lung injury and weight loss by treating the mice with stem cells derived from human exfoliated deciduous teeth (SHEDs) or SHED-derived serum-free conditioned medium (SHEDCM). Even the recovery levels were increased and inflammatory responses were decreased in the treatment group. Kumamoto et al. [43] assessed the effects of minimally cultured BMSCs in female C57BL/6J mice. He observed restoration of the weight loss and increased survival compared to control rats (weight loss recovery of 3/10). Further, anti-fibrotic action was also shown with the downregulation of type I procollagen transcription.

3.3. *Clinical studies*

(Table 3)

3.3.1. *Clinical studies of SARS-CoV-2*

3.3.1.1. *Mesenchymal stem cells*. One of the pilot trials was conducted by Leng et al. [27] in 7 COVID-19 patients using intravenous Mesenchymal Stem cell (MSC) transplantation to assess its therapeutic potential placing 3 severe patients in placebo group. The assessment was done for 14 days after receiving the MSCs which showed no adverse reactions with impressive efficacy outcomes. This was in terms of reduced levels of C-reactive protein (10 fold), increased oxygen saturation (89 %–98 %) with reduction in fever, shortness of breath and pneumonia infiltration and patients testing negative on 13th day after transplantation. Immune profile improved with decrease in pro-inflammatory cytokines and vice-versa for anti-inflammatory cytokines (IL-10) ($p < 0.05$) was seen. Study suggested the absence of ACE2 and TMPRSS2 with high expression of certain trophic factors as the possible immunomodulatory mechanism of MSC.

Table 2*In-vivo* (Preclinical) stem cell therapy in SARS-CoV-2 and Acute Respiratory Distress Syndrome (ARDS).

Author, Year	Aim of the study	Condition	Intervention/ Details of stem cell use	Number of Animals used	Outcome
Liu et al [34]	Vaccine based platform by SARS-CoV-2 proteins expressing MSCs	COVID-19	MSC-SARS-CoV-2-N cells	8 C57BL6 mice	Antibody production was seen in almost all the immunized mice (7/8) after 20 days. Body weight remained same or increased with no severe symptoms. Responses were for Nucleocapsid (N) protein even after transfection with Spike and Membrane proteins of SARS-CoV-2. Limitation: This approach of cell therapy as a vaccine can have one potential risk of uncontrolled proliferation and malignancy if residual cells remains in the body.
Devaney et al. 2015 [39]	Determination of efficacy and mode of action of human MSCs (hMSCs) in acute lung injury	<i>E. coli</i> induced lung injury (ARDS)	Human Mesenchymal stem cells (hMSC's)	48 Sprague Dawley rats	Reduction of <i>E. coli</i> pneumonia, lung injury, bacterial loads in lungs due to suppressed inflammation and improved survival. The effectiveness of intratracheal hMSC administration was equal to intravenous hMSC. Cryopreserved hMSCs were also effective with less efficacy of hMSC secretome. Increased the alveolar concentrations of LL-37
Shalaby et al. 2014 [40]	To assess the effects of MSC in the attenuation of ALI by controlling oxidative stress	<i>E. coli</i> induced lung injury	BMMSCs	Eighty male Balb c mice, in groups of 4 with 20 animals in each group.	Reduced survival rate improved in both pre and post ALI, with higher survival rate in pre-ALI group compared to post ALI. (pre = 19/20 and post = 17/20). Reduced the pulmonary edema, significant reduction of MPO activity and significant rise of anti-oxidant enzyme activities, GSH and TAC levels with reduced MDA levels.
Masterson et al. 2018 [30]	To evaluate the effects of syndecan 2 (CD362)-expressing human mesenchymal stromal cell enhance resolution after lung injury caused by ventilator.	<i>E. coli</i> and ventilator induced lung injury	Human Mesenchymal stem cells (hMSCs)	40 Adult male Sprague Dawley rats (divided into 4 groups and 10 animals in each)	Attenuation of injury by <i>E. coli</i> , improved arterial oxygenation and lung compliance, reduction in bacterial load and decreased structural injury. Also enhanced the resolution after ventilator induced injury with the restoration of arterial oxygenation and lung compliance, resolving lung inflammation and restoring the histologic structure.
Xiang et al. 2017 [31]	Evaluating the effects of MSC in attenuating the lung inflammation and repairing action in damaged lung.	LPS-induced lung injury	MenSCs		Lung injury was attenuated, reduction of inflammation exhibited in the form decreased levels of IL-1 β and increased IL-10. Increased proliferation and decreased apoptosis shown by PCNA (increased expression) and caspase-3 (decreased expression). Also, there was increased protein levels of VE-cadherin, β -catenin and PI-3 K and decreased levels p-gsk3 β , p-src and p- β -catenin.
Chen et al. 2018 [36]	To explore the effects of Heme oxygenase (HO-1-) modified bone-marrow-derived MSCs (MSCs-HO-1)	LPS-induced lung injury	Bone-marrow-derived MSCs	8-week-old Wistar rats (divided into 4 groups: NS, lenti-HO-1-GFP, MSC, and MSC-HO-1)	Survival rate was significantly increased in all the groups compared to NS, and further improved in MSC-HO-1 group. Lung injury and its score was reduced, with decreased counts of neutrophil in BALF and retardation of lung water content. Reduction in TNF- α and IL-1 β levels.
Zhang et al. 2013 [38]	To study the therapeutic effects ASC-based therapy	LPS-induced lung injury	(hASCs) and (mASCs) Adipose-derived stem cells	C57Bl/6 mice	Had anti-inflammatory effects, leukocyte migration into the alveoli was decreased (for example neutrophil). The expression of proinflammatory cytokines suppressed and enhanced anti-inflammatory cytokine (IL-10) levels.
Zhao et al. 2008 [41]	To determine the effect of MSC engraftment in the protection of lungs	Bleomycin induced lung injury	BMMSCs	Adult Sprague-Dawley rats	Alveolar wall thickness, fibroblast number and collagen quantity in the lung interstitium were significantly reduced, most alveoli were intact. Laminin (LN), hyaluronan (HA) and Hydroxyproline content was decreased indicating amelioration of injury in the lung and fibrosis.
Kumamoto et al. 2009 [43]	To test the engraftment of minimally cultured BMMSCs on amelioration of progressive fibrotic lung injury.	Bleomycin induced lung injury	2-h adherent BMMSCs or 9-day cultured BMMSCs	C57BL/6 J mice (6–8 weeks old)	Weight was restored and animals survived (80 % survival in 2-h adherent BMMSCs and 74 % in 9-day cultured BMMSCs). Attenuation of bronchoalveolar lavage (BAL) and neutrophil count. Downregulation of type 1 pro-collagen indicating reduction of inflammation and lung fibrosis.

(continued on next page)

Table 2 (continued)

Author, Year	Aim of the study	Condition	Intervention/ Details of stem cell use	Number of Animals used	Outcome
Wakayama et al. 2015 [42]	To evaluate the use of stem cells derived from human exfoliated deciduous teeth (SHEDs) or SHED-derived serum-free conditioned medium (SHEDCM)	Bleomycin induced lung injury	human exfoliated deciduous teeth (SHEDs)	Adult 7- to 9-week-old C57BL/6 J mice	Improvement in weight loss and survival rate, reduced inflammatory cells and fibrosis. There was suppression of pro-inflammatory cytokines (IL-6, IL-1 β , TNF- α) with the induction of anti-inflammatory M2-like lung macrophages

3.3.1.2. *Mesenchymal stem cells derived from umbilical cord.* Alturi et al. [26] presented the first case of a COVID-19 patient from China aged 65-year old treated with umbilical cord MSC (3 doses each of 50 million 3 days apart allogenic umbilical cord MSC). Similarly Zhang et al. [44] presented the case of 54-year old man intravenously infused with hUC-MSC. In both the cases patients were critical with severe pneumonia, low oxygen saturation, shortness of breath, respiratory failure and multiorgan failure requiring mechanical ventilation and were given simultaneously the standard treatment. Related to above study the efficacy outcome was contributed by immunomodulatory effects with no known adverse or hypersensitivity reactions.

Another study by Liang et al. [45] who presented a case of a SARS-CoV-2 infected critically-ill female aged 65-years. She presented with fatigue and fever and was prescribed antibiotics and phlegm reducing agents as supportive agents. After some time, she complained of chest tightness with glass opacity of lungs on X-Ray and her RT-PCR was covid positive. The patient was treated with anti-viral agents following the diagnosis and treatment guidelines for SARS-CoV-2. The patient condition worsened with acute diarrhea and acute respiratory failure and she was diagnosed as critically ill patient. These results indicated that the current therapy she was receiving was not working properly and hUCMSCs was proposed. After she received the first dose, no adverse effects were observed indicating the tolerability and her vital signs were also improved. After the second administration the T-cell counts normalized and it was observed that initial therapy of α -thymosin when combined with hUCMSCs greatly reduced the inflammation. The patient was relieved of ICU and her vital signs recovered to the normal levels and she tested negative for the virus.

Peng et al. [46] also presented the case of a 66-year old female who had sore throat, cough and fever after coming in contact with COVID-19 patient. She was tested positive for SARS-CoV-2 at day 10 and was considered severe according to guidelines of COVID-19 diagnosis and treatment. Convalescent plasma was given to the patient along with the UC-MSCs and was observed for certain clinical, laboratory, and radiological parameters. It was observed that absolute lymphocyte count was improved after twice administration of convalescent plasma and no infusion or allergic reactions were seen after UC-MSC administration. After some days she tested negative, recovered and discharged from the hospital.

3.3.1.3. *Mesenchymal stem cells derived from Bone Marrow (BMMSCs).* In a prospective non-randomized open-label cohort study by Sengupta et al. [25] utilized exosomes derived from allogenic BMMSCs (ExoFlo). The evaluation was in terms of efficacy and safety in 24 confirmed COVID-19 patients treated with an i.v dose of 15 mL. 83 % survival rate was observed with a recovery rate of 71 % (17/24), stability in 13 % (3/24) and mortality unrelated to treatment was 16 % (4/24). Laboratory investigations showed significant reduction in absolute neutrophil count (p-value <0.001) with alleviated levels of acute phase reactants, C-reactive protein, downregulating cytokine storm and restoring immunity again implying a key action on immune functions. Further RCT's

are required to explore its therapeutic potential.

3.3.1.4. *Cardiosphere derived cells.* Another cell-based therapy (CAP-1002, derived from allogenic cardiospheres) was assessed for its safety and effectiveness by Singh et al. [47]. The assessment was done in 6 critically ill COVID-19 patients (age range of 19–75 years) who were all on ventilatory support with 34 critically ill patients in control group. All patients survived with 4 discharged and 1 still on respiratory support compared to 18 % mortality in control group. Results were well correlated with diminished levels of ferritin and absolute lymphocyte counts, still suggesting the role of cell-based therapies in modifying the immune responses. Cardiosphere derived cells are progenitor cells which have the property of regeneration and hence has been included in this systematic review.

3.3.2. SARS-CoV and MERS-CoV

After deliberate search of 4 databases with appropriate keywords, we couldn't find any relevant data regarding *clinical studies* evaluating the safety or efficacy of stem cell in SARS-CoV and MERS-CoV.

3.3.3. Clinical studies of ARDS

3.3.3.1. *Allogeneic adipose-derived MSCs.* A single-center, double-blind, placebo-controlled, randomized study designed by Zheng et al [48] was done in which adipose-derived MSCs was systemically administered to assess its safety and feasibility in ARDS patients. Twelve patients were recruited with at least 18 years of age as the eligibility criteria and diagnosis was made with a PaO₂/FiO₂ ratio of < 200 within 48 h. Six patients were allocated in MSC group and other 6 in placebo. Single dose of 1 × 10⁶ cells/kg or saline was administered to the patients as a i.v. infusion over 60 min in both the groups with 28 days as the follow-up period. No ADR was reported with the exception of 2 patients (1 had diarrhea and the other had rash on the chest, which resolved in 48 and 24 h). 1 patient died in MSC arm and 2 in placebo group but the deaths were not related to the treatment. In terms of efficacy, oxygenation index was improved significantly from baseline compared to placebo group with no significant difference in improvement in PaO₂/FiO₂ between two groups at all the time points. ARDS biomarker SP-D levels were significantly reduced at day 5 compared to day 0 in MSC group, and similar trend was seen with IL-6 levels but the change was not significant.

3.3.3.2. *Allogeneic bone marrow-derived MSCs.* Wilson et al. [49] performed a multicentre, open-label, dose-escalation, phase 1 clinical trial with 9 ARDS patients to evaluate the safety and tolerability of MSC. Patients were divided into 3 cohorts with 3 in each group based on different doses of MSC. Low dose: (1 million cells/kg), Intermediate dose: (5 million cells/kg) and high dose: (10 million cells/kg PBW). Assessment was based on Lung injury score (LIS) and Sequential Organ Failure assessment (SOFA). Within 60 days of study infusion 2 patients

Table 3
Clinical studies of Stem cell therapy in patients with SARS-CoV-2 and ARDS.

Author Year	Study design	Status	Condition	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome	Remark
Leng et al, 2020 [27]	Pilot study	Completed	COVID-19	18–95 years Total: 7 (1 critically severe, 4 severe, 2 common type)	Mesenchymal Stem cell (MSC)	3 severe type	Primary Outcome: All symptoms (high fever, weakness, breathlessness and low oxygen saturation) disappeared in all the patients 2–4 days after the treatment with no adverse effects. RT-PCR turned negative for nCoV-19 Efficacy outcome: For critically severe patient (decrease in CRP, increase in oxygen saturation, respiratory rate decreased to normal range, Chest CT: showed ground-glass opacity and decreased pneumonia infiltration.	Patient enrolled in this study were COVID-19 positive who had no improvement with standard treatment. Had no history of tumors.
Zhang et al, 2020 [44]	Case report	Completed	COVID-19	Critically ill 54-year old male patient having cough, fever and tightness of chest from 4 days	Umbilical cord Wharton's jelly-derived MSCs (hWJCs)	NA	Efficacy Outcome: Recovery of Shortness of breath, decrease in CRP, increased lymphocyte count, decrease in inflammatory mediators and the patient was discharged. No ADR reported and COVID-19 nucleic acid turned negative after 6 days.	No malignancy And from 3 months the patient should not be included in any other clinical study
Alturi et al, 2020 [26]	Case report	Completed	COVID-19	65y/o with severe pneumonia, respiratory failure and multiorgan failure requiring mechanical ventilation	doses each of 50 million allogeneic umbilical cord stem cells with conventional therapy	NA	Vital signs stabilized, not dependent on ventilator. After the infusion patient was negative for the virus on throat swabs after 2 days.	This was the first coronavirus case treated with umbilical cord cells reported from China.
Liang et al, 2020 [45]	Case report	Completed	COVID-19	65-year-old woman	hUCMSCs administrated intravenously for three times with antibiotics and thymosin α 1	NA	Reduced serum levels of bilirubin, CRP, ALT/AST along with improvement of vital signs. Decreased counts of white blood cells, and neutrophils and increase in lymphocyte count and throat swabs tests reported negative	
Peng et al, 2020 [46]	Case report	Completed	COVID-19	66-year old female	Convalescent plasma along with UC-MSCs		Absolute lymphocyte count was improved after twice administration of convalescent plasma and no infusion or allergic reactions were seen after UC-MSC administration.	
Singh et al, 2020 [47]	Case series	Completed	COVID-19	6 COVID-19 critically ill	Allogeneic cardiosphere-derived cells (CDCs) (CAP-	Contemporaneous control group (n = 34)	No ADR reported. 4 patients improved clinically with the	

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Table 3 (continued)

Author Year	Study design	Status	Condition	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome	Remark
				patients (19–75 years)	1002) along with hydroxychloroquine and tocilizumab		exception of 2 who remained critically ill but stable. 6 (18 %) deaths in control group	
Sengupta et al,2020 [25]	Prospective nonblinded nonrandomized primary safety trial	Completed	COVID-19	24 COVID-19 patients (18–85 years)	Exosomes derived from allogeneic BMMSCs		83 % survival rate, 71 % patients recovered, 13 % remained critically ill but stable and 16 % expired unrelated to treatment. No ADR reported.	Exclusion criteria included pre-existing cardiopulmonary, hematologic diseases, liver and kidney dysfunction, metabolic disorder with irreversible coagulopathy, pregnancy, immunodeficiency secondary to other viruses, or disseminated intravascular coagulation.
Simonson et al [51]	Case reports	Completed	ARDS	40 and 58years old men	MSC		The improvements in both the patients was broad with a decrease in inflammatory markers. Additionally, level of surfactant protein B was increased in bronchial alveolar fluid (BAL) which is an indicator of recovery of alveolar epithelial function. Study drug was well tolerated with 1 patient with diarrhea and other with rash in MSC group (resolved within 48 and 24 h) 1: Death in MSC arm and 2 in control arm (not related to study drug) Improvement in oxygenation index. Significant lowering of SP-D levels at day 5 compared to day 0.	
Zheng et al. 2014 [48]	Single-center, randomized, double-blind, placebo-controlled study.	Completed	ARDS	Total: 12 ARDS: 6	Human adipose derived MSC's	Placebo: 6	Well tolerated 3 patients had serious ADR not related to MSC, out of which 2 patients died. Mean Lung injury score was improved from baseline till day 3 in all 3 groups. Greatest decrease in high dose (high dose 2.9 to 1.6 [–45 %]) and lowest in low dose group 3 to 2.1 [–30 %]) Similar results with SOFA (sequential organ failure assessment) score: (high dose 7 to 3.7 [–48%] and low dose 8 to 7.7 [–4%])	Limitations: Small sample size
Wilson et al. 2015 [49]	Multicentre, open-label, dose-escalation, phase 1 clinical trial.	Completed	ARDS	Total: 9 Divided into 3 groups with 3 patients in each group (according to doses)	Allogeneic BMMSCs		Well tolerated 3 patients had serious ADR not related to MSC, out of which 2 patients died. Mean Lung injury score was improved from baseline till day 3 in all 3 groups. Greatest decrease in high dose (high dose 2.9 to 1.6 [–45 %]) and lowest in low dose group 3 to 2.1 [–30 %]) Similar results with SOFA (sequential organ failure assessment) score: (high dose 7 to 3.7 [–48%] and low dose 8 to 7.7 [–4%])	
Matthay et al.	Double-blind, Randomized, placebo-	Completed	ARDS	Total: 60 MSC: 40	Mesenchymal stem cells	Placebo: 20	Infusion of 20 h caused fatal cardiopulmonary	

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Table 3 (continued)

Author Year	Study design	Status	Condition	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome	Remark
2018 [50]	controlled, phase 2a trial						arrest but death not related to MSC. Mortality at day 28 and 60 was non-significantly higher in MSC group than placebo. Ventilator free and organ failure free days were non-significantly few in MSC group than placebo. Oxygenation index had non-significant reduction in MSC group compared to placebo.	

died out of 9 (mortality rate 22 %). It was noticed that the first death was on day 9 in low dose group, and other was on day 31 with intermediate dose. LIS score improved in all the 3 groups with highest improvement in high dose and lowest improvement in lower dose, similar results were seen with SOFA scores. There was no significant decrease biomarker concentration at baseline, after 6 h and on day 1 and 3.

Another study by Matthay et al. [50] which was a prospective, randomized trial, multicentre, double-blind was performed to assess the safety of MSC in 60 ARDS patients in which 40 were in MSC group and 20 in placebo arm. There was no MSC related hemodynamic or respiratory adverse events, but there was death of 1 patient within 24 h of infusion which was unrelated to MSC. Mortality at day 28 was 12 (30 %) and at day 60 was 15 (38 %) which was higher non-significantly in MSC group compared to placebo (3 (15 %) at day 28 and 5 (25 %) at day 60) with OR of 2.4 (0.5–15.1) (at day 28) and 1.8 (0.5–7.6) (at day 60) but there was a reduction in the oxygenation index which was not significant compared to placebo.

Simonson et al. [51] presented two cases, first of an old man aged 58 years who had hospitalization after the start of cough, high fever and dyspnea. He had history of hypertension and was diagnosed with influenza A H1N1. The other patient aged 40 year man, with no past medical history and was hospitalized because of loss in weight, malaise, gingival hyperplasia, fever and night sweats. Acute Myeloid Leukemia (AML) was diagnosed for which chemotherapy was started. The condition of the patient deteriorated progressively where ARDS was a possible contributing factor according to Berlin criteria. The condition of both the patients worsened even after the conventional and supportive therapy and hence was administered MSCs. The improvements in both the patients was broad with a decrease in inflammatory markers. Additionally, level of surfactant protein B was increased in bronchial alveolar fluid (BAL) which is an indicator of recovery of alveolar epithelial function.

3.3.3.3. Umbilical cord derived mesenchymal stem cells. Chang et al. [52] in his study reported the case of a 59-year old man with a history of pulmonary tuberculosis and being treated with corticosteroids. After developing fever, cough and rhinorrhea, he was hospitalized and further developed progressive bilateral diffuse infiltrations. Finally, he was diagnosed with ARDS and hypoactive delirium because of his ill health. He was administered MSC intrathecally derived from umbilical cord which showed improvement in his laboratory parameters with a slight

reduction in bilateral lung infiltrates. He further experienced 6 generalized tonic-clonic seizures for which he was put on an anti-convulsant. However, the patient could not survive due to repeated pulmonary infections but the study still suggests the possible use of MSCs in an ARDS patient.

3.4. Clinical trials registered

Registered Clinical Trials for the role of stem cell therapy in SARS-CoV-2 infection is shown in Table 4

4. Summary and conclusion

This systematic review yielded several important findings including *in-vitro* data of ARDS where stem cell therapy has been used, derived from various sources have shown increased proliferation and migration in lung cancer cell lines. They even exhibited decreased apoptosis and neutrophil migration. Similarly, *in-vivo*/preclinical data demonstrated the stem cells efficacy in different models of ALI. Results were quite promising as the stem cells demonstrated efficacious results in amelioration of lung fibrosis while decreasing the inflammation and edema. These findings very well correlated with certain case reports and clinical studies in terms of efficacy and safety profile where the capability of stem cell-based therapy to reduce the systemic inflammatory responses have been demonstrated in ARDS patients.

Additionally, these studies have highlighted several different mechanisms highlighting the importance of stem cells in restoration of the lung function. So, this published data of stem cells use in virus induced ARDS indicates a possible role of stem cells-based therapies for COVID-19 infection. Some case reports also discuss the safety and efficacy of stem cells in SARS-CoV-2 specifically in critically ill patients when they become unresponsive to conventional therapy. The benefits which have been noticed from these studies includes decreased inflammation by downregulating the cytokine levels without causing any allergic reactions, hence indicating tolerability to the treatment. Therefore, we believe that the current evidence from *in-vitro*/*in-vivo* and clinical studies suggests a potential of MSCs to be used in the treatment of COVID-19 patients. Although the results of clinical study data are motivating, still it will be too early to forecast potential therapeutic role of MSCs in COVID-19. Hence, large-scale trials of MSC therapy should be conducted to validate their clinical efficacy.

Table 4
List of registered stem cell therapy based clinical trials for COVID-19.

Author, Year	Study design	Status	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome
AlZoubi et al. 2020 [53]	Phase I Interventional	Recruiting	5 Patients positively diagnosed with COVID-19 (18 years and older)	Wharton's Jelly-Mesenchymal stem cell		Primary Outcome: Improvement of clinical symptoms (fever, pneumonia, respiratory distress, sneezing, cough, diarrhea)
Guillory et al. 2020 [54]	Phase 2 multi-center, double-blind, randomized, placebo-control clinical trial	Not yet recruiting	200 (18 years and older)	Autologous Adipose Tissue-Derived MSCs (Celltex-AdMSCs)	Phase 2 Placebo group	Primary Outcome: Safety and Tolerability Incidence of COVID-19 in study and control group
Akram et al. 2020 [55]	Prospective, Randomized Phase 2 Clinical Trial	Recruiting	20 (10 years and older)	MSCs	Phase 2 Placebo Group	Primary Outcome: Overall survival at 30 days post intervention
Q et al. 2020 [56]	Single-center, Prospective, Randomized Clinical Trial	Recruiting	20 (18–65 years old)	Allogeneic Human Dental Pulp Mesenchymal	Placebo group (3 mL of 0.9 % saline)	Primary Outcome: Time to Clinical Improvement
Vanegas et al. 2020 [57]	Phase 2	Recruiting	30 (18–79 years old)	Umbilical cord derived MSCs	Placebo group	Primary Outcome: Clinical deterioration or death
Iglesias et al. 2020 [58]	Pilot Study	Recruiting	10 (18 years and older)	MSCs from umbilical cord allogenic	historical controls treated in INCMNSZ	Primary Outcome: clinical, biochemical, inflammatory and immune changes
Filho et al. 2020 [59]	Phase 2 (Exploratory clinical study)	Recruiting	90 (18 years and older)	NestaCell® MSCs	Matching Placebo	Primary Outcome: change in clinical condition
Cheng et al. 2020 [60]	Phase II, Randomized, Placebo-Controlled, Double-Blinded, Clinical Trial	Enrolling by invitation	100 (Child, Adult, Older Adult)	allogeneic adipose-derived MSCs	Placebo (Saline)	Primary Outcome: Incidence of hospitalization and symptoms associated with COVID-19
Perez et al. 2020 [61]	Pilot phase, open label, non-randomized study	Active but not recruiting	9 (18 years and older)	MSCs derived from Wharton Jelly of Umbilical cords		Primary Outcome: Oxygen Saturation
Gil et al. 2020 [62]	Phase I/II clinical trial	Recruiting	26 (18–80 years old)	Allogenic Adipose Tissue-Derived Mesenchymal	Control: No intervention	Primary Outcome: Safety and efficacy via ADR and survival rate
Cheng et al. 2020 [63]	Phase II, Open Label, Single-Center, Clinical Trial	Enrolling by invitation	56 (Child, Adult, Older Adult)	Autologous adipose-derived MSCs		Primary Outcome: Incidence of hospitalization and symptoms associated with COVID-19
Cheng et al. 2020 [64]	Open, single center, single arm test design	Not yet recruiting	24 (18–75 years old)	Dental pulp MSCs		Primary Outcome: Time of disappearance of ground-glass shadow in the lungs
Shi et al. 2020 [65]	Phase 1 multicentric trial	Recruiting	20	Conventional treatment plus MSCs	Conventional Control Group	Primary Outcome: Evaluation of Pneumonia Improvement and Side-effects
Li et al. 2020 [66]	Phase 1/2 Randomized Controlled Trial	Not yet recruiting	20 (18–75 years)	BMMSCs	Conventional treatment plus placebo	Evaluation of pneumonia improvement and safety assessment
Wang et al. 2020 [67]	Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Trial	Active not recruiting	100 (18–75 years)	Human Umbilical Cord-MSCs	Standard of care plus 3 does of placebo	Evaluation of Pneumonia Improvement
Tarar et al. 2020 [68]	Phase 2 RCT	Recruiting	20 (30–70 years)	Umbilical Cord- MSCs	Treatment will be done for five subjects under Standard of Care	Assessment of Pneumonia and side effects.
Hancharou et al. 2020 [69]	Phase 1/2	Enrolling by invitation	40 (18–70 years)	Allogenic pooled olfactory mucosa-derived mesenchymal	Standard Treatment	Number of patients cured
Liu et al. 2020 [70]	Phase 1/2 RCT	Recruiting	30 (18–75 years)	hMSC's	Conventional treatment and Placebo intravenously	Improvement and recovery time of inflammatory and immune factors
Fujian et al. [71] 2020	Early Phase 1	Active not recruiting	60 (18–70 years old)	Umbilical Cord MSCs with Oseltamivir, hormone and oxygen therapy	oseltamivir, hormones, oxygen therapy, mechanical ventilation and other supportive therapies	Improvement of pulmonary function
Nouri et al. 2020 [72]	Phase 2–3 Clinical Trial	Recruiting	60 18–65 years	MSCs	Conventional therapy and supportive therapy	Evaluation of Pneumonia Improvement and safety assessment
[73]	Prospective Non-Interventional Study	Active, not recruiting	40 3 Months and older	Allogeneic Haematopoietic Stem Cell Transplantation		Comparison of inflammatory/immunological biomarkers
Ricordi et al. 2020 [74]	Phase 1/2 double blinded trial	Recruiting		Umbilical Cord Mesenchymal + Heparin	Heparin + Supportive therapy	Assessment of safety

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Table 4 (continued)

Author, Year	Study design	Status	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome
Thakur et al. 2020 [75]	Randomized, Placebo-Controlled, Double-Blind, Single Center, Phase 2 Trial	Not yet recruiting	24 18 years and older 100 Child, Adult, Older Adult	along with best supportive care allogeneic adipose-derived MSCs	Placebo (Saline)	Detection of the changes from baseline for inflammatory markers, and oxygenation, and reduction in time for a negative PCR test result.
Adas et al. 2020 [76]	Prospective Double Controlled Study	Recruiting	30 (40–60 years)	MSCs	Patients that are on a ventilator and will receive saline injections	Covid-19 infection related symptom improvement.
Itticheria et al. 2020 [77]	Prospective, two-arm, partially masked, single center clinical study	Not yet recruiting	20 18-60 years	Stem cell Educator-Treated Mononuclear cells Apheresis	Conventional treatment of patients with SARS-CoV-2	Patient number who could not complete the SCE therapy
[78]	NA	Withdrawn	0 18–75 years	hUC-MSC	—	—
Liao et al. 2020 [79]	Phase 1 Study	Not yet recruiting	9 18-80 years old	hUC-MSC (BX-U001) + supportive care		Assessment of safety
Juan et al. 2020 [80]	Two-treatment, Randomized, Controlled, Multicenter Clinical Trial	Not yet recruiting	100	Allogeneic and expanded adipose tissue-derived MSCs	Regular respiratory distress treatment	Efficacy and safety assessment
Rosenberger et al. 2020 [81]	Prospective Phase II Study	Not yet recruiting	40 18 and above	MSCs in Inflammation-Resolution Programs of SARS-CoV-2 Induced ARDS	No intervention	Improvement of lung injury score
Qi et al. 2020 [82]	Phase 1 and 2	Recruiting	9 18–70 years	Human Embryonic Stem Cells Derived M cells (CASTem)		Safety and efficacy
Gelinjns et al. 2020 [83]	Randomized Phase 3 clinical trial	Recruiting	300 18 years and older	MSCs (Remestemcel-L)	Placebo	Number of all-cause mortality
Coll et al. 2020 [84]	Prospective, Double-blind, Randomized, Parallel, Placebo-controlled Pilot Clinical Trial	Recruiting	30 18–75 years old	XCEL-UMC-BETA (WJ- MSC)	Placebo	Number of patients who died
Stewart et al. 2020 [85]	Phase 1, open label, dose-escalating and safety trial using a 3 + 3+3 design	Not yet recruiting	9 18 years and older	Mesenchymal Stromal cells		Participant number with Treatment-Related Adverse effects.
Fairbairn et al. 2020 [86]	Phase 1/2 Randomized, Placebo-Controlled Trial	Not yet recruiting	70 18-85 years	ACT-20-MSC	Placebo (MEM- α)	Mortality at day 30
Sender et al. 2020 [[87]]	Phase 1b Randomized, Double-Blind, Placebo-Controlled Study	Not yet recruiting	45 18-80 years	BM-Allo.MSC	Placebo (plasmalyte and human albumin)	Incidence of AEs, mortality and its cause and Number of ventilator-free days
Rave et al. 2020 [88]	Phase I/II Study of Human Placental Hematopoietic stem cells Derived Natural Killer cells	Recruiting	86 18 years and older	CYNK-001		Number and severity of adverse events for Phase 1 and Time to Clearance of SARS-CoV-2 for Phase 2
Hill et al. 2020 [89]	Early Phase 1	Not yet recruiting	30 18 years and older	Mesenchymal Stromal cells		Incidence of unexpected adverse events and Improved oxygen saturations ≥ 93 %
Barbado et al. 2020 [90]	Double Blind, Placebo-controlled, Phase II Trial	Recruiting	24 18 years and older	Allogenic Mesenchymal Stromal cells MSV	Placebo	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation Oxygenation index
Wang et al. 2020 [91]	Phase 2	Recruiting	16 18-80 years	UC-MSCs		
Monsel et al. 2020 [92]	Phase1/2	Recruiting	40 18 years and older	umbilical cord Wharton's jelly-derived mesenchymal stromal cells	NaCl 0.9 %	Efficacy in respiration
[93]	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase II Study	Recruiting	140 40-80 years	allogeneic ex vivo expanded placental mesenchymal-like adherent stromal cells (PLX-PAD)	Placebo solution for injection	Number of ventilator free days
Ting et al. 2020 [94]	Phase 2/3 Study	Recruiting	400 18-89 years old	MultiStem	Placebo intravenous infusion	Ventilator-Free Days. Safety and tolerability
Miller et al. 2020 [95]	Multi-center, Randomized, Sham Controlled, Double-	Not yet recruiting	24 18 years and older	SBI-101 (device containing allogeneic hMSC's + FDA-approved plasmapheresis device)	Sham device containing no MSCs	Safety and tolerability

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Table 4 (continued)

Author, Year	Study design	Status	Population	Intervention/ Details of stem cell use (Stem size)	Control (sample size)	Outcome
Qu et al. 2020 (96)	blind, Ascending-dose Study Pilot Clinical Study	Not yet recruiting	30 18–75 years	Aerosol Inhalation of the Exosomes Derived from Allogenic Adipose Mesenchymal stem cells		Time to clinical improvement and safety

Declaration of Competing Interest

None.

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