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A Narrative Review on the Management of Severe COVID-19 Infection Using Stem Cell-based therapies with a Focus on the Registered Clinical Trials

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Abstract

The emergence of SARS-CoV-2 has led to a concerning global pandemic. The severity of COVID-19 symptoms may be enhanced due to underlying medical conditions. Several studies demonstrated severe COVID-19 infection can lead to innate and adaptive immune dysregulation, cytokine storms as well and the formation of fibromyxoid exudate in the respiratory alveolar, ultimately resulting in pulmonary fibrosis and ARDS as the leading cause of mortality and morbidity. Currently, there is a widespread global endeavor in finding efficient drugs or vaccines to manage COVID-19. Although some FDA-approved treatments have been introduced for COVID-19, alternative therapies might decrease the mortality rates. Various sources of pluripotent and mesenchymal stem cells as cell-based therapies have been applied on moderate to severe COVID-19 patients with acute respiratory distress syndrome, leading to positive results. Cell-based therapies by modulating the cytokine cascades and cellular apoptosis can probably inhibit tissue remodeling and subsequent end-organ damage. The present review aims to discuss the advantages of stem cell-based therapies in the treatment of COVID-19 patients and the possible challenges associated with their application.

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Abbreviations

- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.
- COVID-19: Coronavirus Disease 2019.
- ARDS: Acute respiratory distress syndrome.
- FDA: United States Food and Drug Administration.
- SPO2: Oxygen Saturation
- PaO2: Partial pressure of oxygen.
- FiO2: Fraction of inspired oxygen.
- MOF: Multiple organ failure.
- IFN-β1: Interferon-β1.
- MSCs: Mesenchymal stem cells.
- hiPSCs: Human-induced pluripotent stem cells.
- ECMO: Extra-corporeal membrane oxygenation.
- DPSC: Dental pulp stem cells.
- ADMSCs: Adipose-derived mesenchymal stem cells.
- BM-MSC: Bone marrow-derived mesenchymal stem cell.
- hP-MSC: Human placenta-derived mesenchymal stem cell.
- WJ-MSC: Wharton’s jelly-derived mesenchymal stem cells.
- hPBSCs: Human peripheral blood-derived stem cells.
- hUC-MSCs: Human umbilical cord-derived mesenchymal stem cells.
- ALI: Acute lung injury.
- MenSCs secretome: Menstrual blood-derived mesenchymal stem cells secretome.
- NHPBSCs: Non-hematopoietic peripheral blood stem cells.
- UCMSCs: Umbilical cord-derived mesenchymal stem cells.

- iNKT cells: Invariant natural killer T cells.
- GVHD: Graft versus host disease.
- VCAM-1: Vascular cell adhesion molecule-1.
- MMP-1: Matrix metalloproteinase-1.
- TGF-β1: Transforming growth factor- β1.
- CCL2:C-C motif chemokine ligand-2
- CXCL12: C-X-C motif chemokine-12
- IL-6: Interleukin-6.
- IL-18: Interleukin-18.
- hWJ-MSC-S: Human Wharton's Jelly Mesenchymal Stem Cells Secretome.
- BW: Body weight.
- ESCs: Embryonic stem cells.
- KLF4: Krupple-like factor 4.
- c-Myc: cellular-Myc.
- BMP4: Bone morphogenetic protein 4.
- NKX2.1: NK2 homeobox 1.
- EGF: Epidermal growth factor.
- bFGF: Basic fibroblast growth factor.
- MAPK: Mitogen-activated protein kinase.
- RA: Retinoic acid.
- KGF1: Keratinocyte growth factor 1.
- WNT: Wingless-related integration site.
- FGF10: Fibroblast growth factor 10.
- 3D-HLO: Three-dimensional human lung organoid.
- PLG: Poly lactide-co-glycolide.
- PCL: Polycaprolactone.
- ACE2: Angiotensin convertase enzyme 2.
- AAT: Alpha-1-antitrypsin.
- CXC4: Chemokine receptor 4.
- CXC7: Chemokine receptor 7.
- DCs: Dendritic cells.
- IL-10: Interleukin 10.
- PCR: Polymerase chain reaction.
- PB plasma/SCs: Peripheral Blood Stem Cells and Plasma stem cells.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to beta-coronaviruses from the Coronaviridae family [1], which recently caused the Coronavirus Disease 2019 (COVID-19) pandemic as a global emergency[2][3]. The coronaviruses have four genera: alpha-, beta-, gamma-, and delta-coronaviruses. Alpha-/beta-coronaviruses are responsible for infections in mammalian species, gamma-coronavirus in avian species, and delta-coronavirus in both avian species and mammals [4]. Viral pneumonia resulting from the COVID-19 outbreak was first reported in December 2019 [5]. Helical nucleocapsid protein (N) surrounding the lipid envelopes packs the viral genome[6]. The SARS-CoV-2 binding proteins are characterized by clove-shape spikes called ‘corona’. The binding proteins consist of the host cell receptor-binding subunit (S1) and the host cell membrane-fusion subunits (S2). The aforementioned virus attaches to the human host cell receptors, to penetrate the host cell and integrate its genome with that of the host cell to ultimately replicate [7]. Despite the high rate of mutation in RNA viruses, SARS-CoV-2 as an RNA virus, has lower mutation rates due to genome-encoded exonuclease; hence, the SARS-CoV-2 has higher adaptivity, leading to more effective human-to-human transmission [8].

The SARS-CoV-2 infection can cause various symptoms as depicted in Figure 1. The severity of SARS-CoV-2 infection is categorized by symptoms and laboratory findings. A severe case of COVID-19 is characterized by the presence of respiratory distress, oxygen saturation (SPO2) lower than 93%, and partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio less than 300 mmHg [9]. COVID-19 can lead to severe complications such as multiple organ failure (MOF). Respiratory failure and MOF is the leading cause of mortality in these population [10][11][12].

Although there are comprehensive evaluations on different United States Food and Drug Administration (FDA)-approved therapeutic agents, including hydroxychloroquine, convalescent plasma, interferon-β1 (IFN-β1), lopinavir/ritonavir, and remdesivir in the COVID-19 treatment; still, there are controversies about their efficacy and safety [13][14]. Several biomaterial-produced agents are studied to strengthen or assist the anti-viral effects of other therapeutic agents, such as silver nanoparticles, and two tetradentate dibasic chelating Schiff base iron Ⅲ [15][16].

The destructive nature, dangerous complications, and adverse impact on the world economy highlight the necessity of finding a novel and efficient candidate to manage this disease [17], reduce the mortality rate, and achieve better recovery, especially in moderate to severe cases [18]. There has been a growing interest in the use of induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) in the treatment of COVID-19 [19][20][21]. Human-induced pluripotent stem cells (hiPSCs) which are derived from somatic cells, have been identified as a suitable source for cell therapy, particularly in the context of infectious diseases, compared to other types of stem cells [22]. Additionally, the anti-inflammatory and immunomodulatory properties of MSCs make them an attractive option for treating COVID-19 [23][24][25].

Accordingly, because of limited data available on the clinical applications of stem cells to manage COVID-19, the present review aims to discuss the advantages and beneficial effects of stem cells, including hiPSCs and MSCs, in the treatment of this infectious disease and the challenges as may arise as a result in this context.

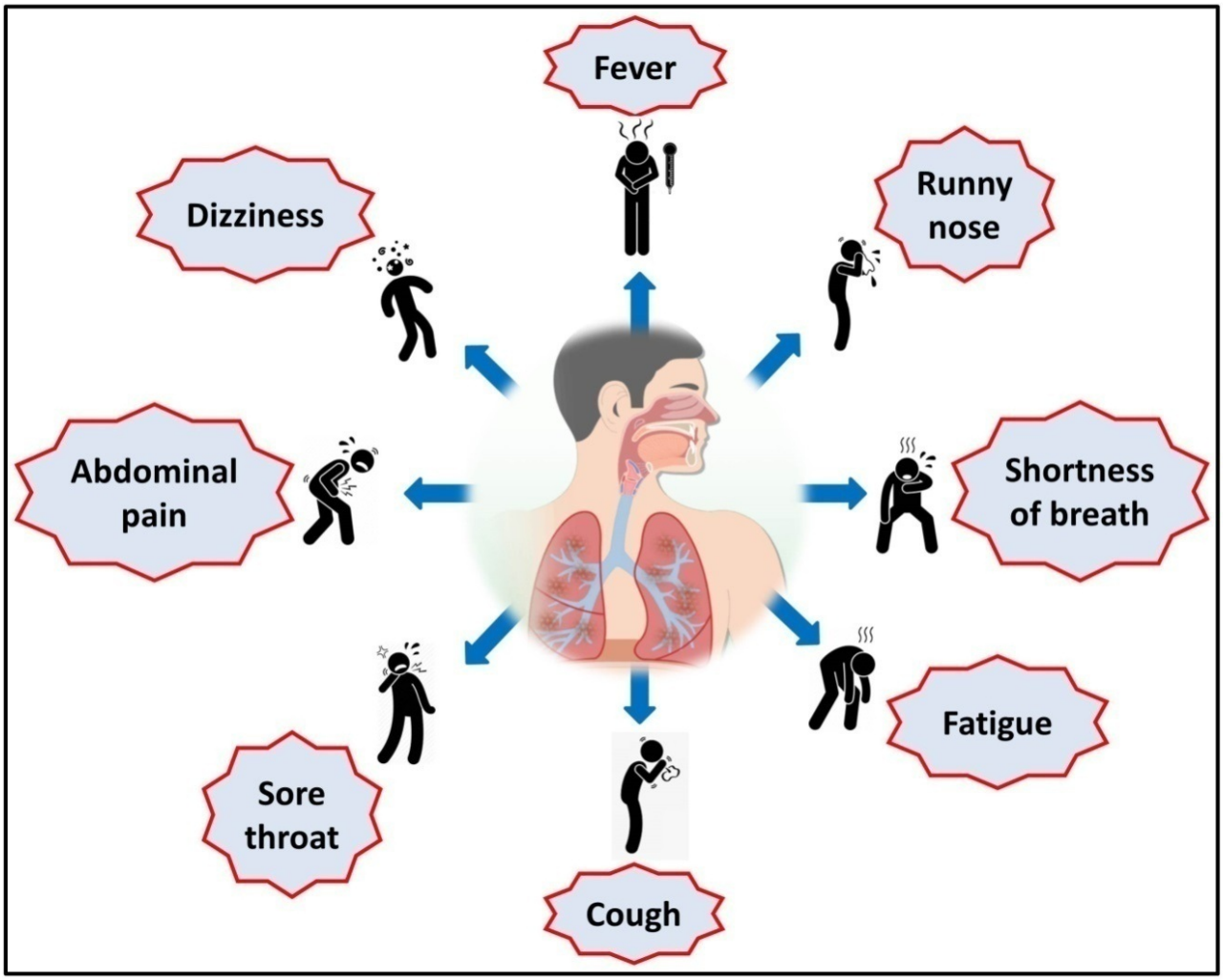

Figure 1. The symptoms of SARS-CoV-2 infection in human beings

2. Rationale for stem cell-based therapies in COVID-19

Regenerative medicine and Tissue engineering are cell-based therapeutic approaches in which the injured tissues and organs are regenerated or replaced using stem cells via cell-loaded and 3-D constructs or platforms [26]. The capability of regulating inflammatory reactions, and enhancing tissue repair, and regeneration are stem cells features [27]. Several retrospective studies demonstrated that patients who died of COVID-19 had higher serum concentrations of inflammatory markers such as interleukin-6 (IL-6) [28][29][30]. The cytokine storm syndrome characterized by the hypersecretion of inflammatory cytokines; is responsible for acute cardiac damage, renal failure, acute respiratory distress syndrome (ARDS), air exchange dysfunction, pulmonary edema, and increasing mortality rates in COVID-19 [9][30]. Effective therapeutic options are lacking in the cases of severe SARS-CoV-2 infection to ameliorate the respiratory complications and hyperinflammatory syndrome. Current care management in severe cases of COVID-19 pneumonia such as anti-viral drugs, extracorporeal membrane oxygenation (ECMO), and ventilator-assisted oxygenation cannot reverse the formation of fibromyxoid exudate in respiratory alveolars and subsequent alveolar fibrosis [30][31]. Despite effective therapy, acute respiratory distress syndrome (ARDS) is the leading cause of mortality and morbidity in severe SARS-CoV-2 infection. An

in vitro study evaluating the characteristics of SARS-CoV-2-exposed induced pluripotent stem cells (iPSCs) demonstrated that the exposed stem cells formed a fibroblast-like phenotype and lost their pluripotent [32]. Several studies depicted that the MSCs application in ARDS models can decrease the alveolar fluid accumulation by repairing and protecting alveolar epithelial and endothelial cells, decreasing endothelial and epithelial permeability, and ultimately ameliorating the alveolar fibrosis [30][33][34]. Some of the therapeutic potentials of stem cell-based therapies in COVID-19 pneumonia are the ability to balance immune responses as well as regulate cytokine storm, the recovery of the lung microenvironment, the protection of alveolar epithelial cells, and the alteration of lung dysfunction. Therefore, stem cell-based therapies can be used as an alternative therapy in cases of moderate to severe COVID-19 infection [35]. MSC could be an appropriate candidate to modulate the complications created by SARS-CoV-2 because of its anti-inflammatory and immunomodulatory effects [36]. Determining the type and source of stem cells for therapeutic applications is of great importance in terms of efficacy and safety in the COVID-19 treatment [37].

Limited multinational well-designed studies have been performed to evaluate precise involved mechanisms of stem cell-based therapies in patients with ARDS or SARS-CoV-2 induced pneumonia. Various studies have faced daunting challenges and limitations in evaluating and interpreting the efficacy of different pharmacological agents in COVID-19 management, such as drug side effects, insignificant suppression of viral loads as the primary outcomes, co-treatments and drug delivery routes, temporary comorbidities, no gender considerations, no placebo-control arm, and small cohort sizes. Stem cell-based therapies could be an alternative route in finding treatment strategies [38][39][40]. Figure 2 depicts an overview of various sources of stem cell application in COVID-19 infection.

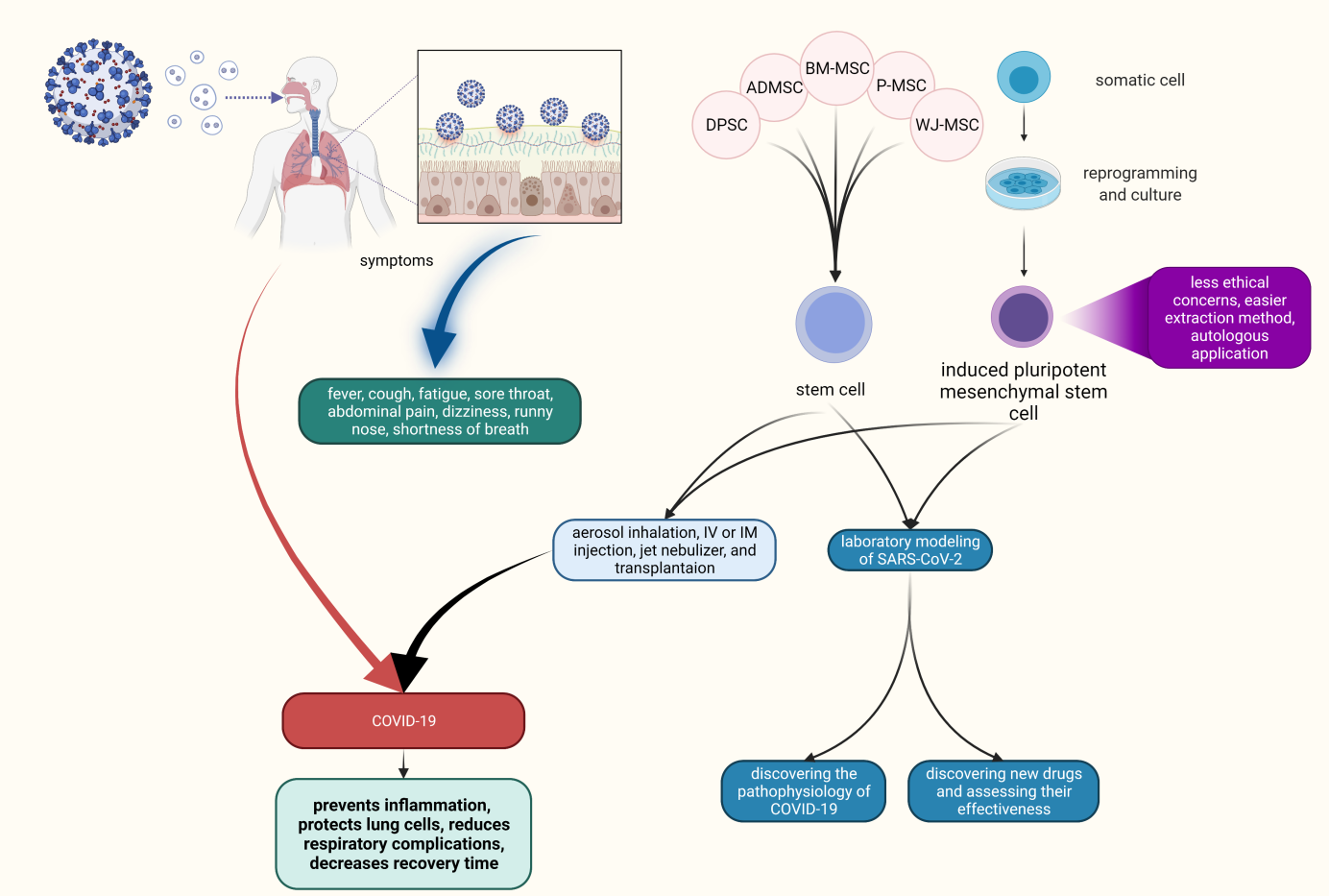

Figure 2. An overview of the application of the various stem cells in the modeling and treatment of COVID-19. Abbreviations: DPSC, dental pulp stem cells; ADMSC, adipose-derived mesenchymal stem cells; BM-MSC, bone marrow-derived mesenchymal stem cell; P-MSC, placenta-derived mesenchymal stem cell; WJ-MSC, Wharton's jelly-derived mesenchymal stem cells; IV, intravenous; IM, intramuscular.

3. Recent stem cell-based studies in the treatment of COVID-19

Many countries such as the United States and China have conducted clinical trials to evaluate the safety and efficacy of stem cell products in treating moderate to severe cases of COVID-19 (Table 1, Table 2). In the conducted clinical trials, stem cells and their products were applied as interventional arms, as shown in Table 1 and Table 2, respectively. There were variable reports of cell doses and protocols. In 27 out of 57 clinical trials, the number of cells used in the interventional arms was based on the patient's weight, whereas in other trials, the number of applied cells was regardless of the patient's weight. Different types of stem cells are being applied as an interventional arm, ranging from embryonic stem cells to mesenchymal stem cells.

Beneficial therapeutic effects of mesenchymal stem cells in the treatment of COVID-19 are being evaluated by many clinical trials, most of which are injected intravenously, except for 6 clinical trials in which the administration of MSCs and MSC-derived exosomes have been suggested through the inhalation route [6]. Among several clinical trials evaluating the safety and efficacy of stem cell therapy in COVID-19, four completed trials suggested improvements in clinical outcomes

without increasing adverse events (Table 1). The completed trials referenced as NCT04473170, NCT04355728, and NCT04491240 respectively using non-hematopoietic peripheral blood stem cells (NHPBSCs), umbilical cord-derived mesenchymal stem cells (UCMSCs) and MSCs exosomes demonstrated improving clinical outcomes without increasing adverse effects. A study referenced as NCT05019287 depicted that MenSCs secretome could be beneficial in reversing hypoxia and reducing the COVID-19 infection mortality rates. The outcome of conducted clinical trials is categorized into primary and secondary outcomes. The evaluated outcomes through the conducted clinical trials are assessment of pulmonary index, Sequential organ failure score, inflammatory markers level, presence and frequency of adverse events, vital signs, clinical symptoms, short-term and long-term mortality rates, duration of ventilator-free days, hospitalization duration and assessment of radiologic improvement such as disappearing time of ground glass opacity.

Table 1. Summary of registered clinical trials using stem cell therapy for COVID-19 disease

No.	Clinical trial identifier	country	Study design	Study phase	Current status	Source of stem cell	Route of delivery	Number of doses	Single-dose concentration (cells)	Dose intervals	Estimated enrollment
1	NCT04313322	Jordan	single-arm, open-label	phase 1	unknown (previously: recruiting)	WJ-MSCs	IV	3	1* 10 e6 /Kg	3 d	5
2	NCT04473170	United Arab Emirates	double arm, open label	phase 1/phase 2	completed	NHPBSCs	jet nebulization	2	2.2* 10 e6	1 d	146
3	NCT04428801	Not mentioned	double arm, double masking	phase 2	not yet recruiting	ADMSCs	IV	3	2* 10 e8	3 d	200
4	NCT04444271	Pakistan	double arm, open label	phase 2	recruiting	BMSCs	not mentioned	2	2* 10 e6 /Kg	7 d	20
5	NCT04336254	China	double arm, triple masking	phase 1/phase 2	recruiting	hDPSCs	IV	3	3* 10 e7	3 d	20
6	NCT0471378	Turkey	triple arm, open-label	not applicable	completed	MSCs	IV	3	1* 10 e6 /Kg	2 d	21
7	NCT04302519	China	single-arm, open-label	early phase 1	unknown (previously: not yet recruiting)	DPMSCs	IV	3	1* 10 e6 /Kg	4 d	24
8	NCT04429763	Colombia	double arm, double masking	phase 2	not yet recruiting	UCMSCs	IV	1	1* 10 e6 /Kg	no intervals	30
9	NCT04486001	USA	single-arm, open-label	phase 1	recruiting	ADMSCs	IV	1	not mentioned	no intervals	20
10	NCT04315987	Brazil	double arm, quadruple	phase 2	unknown (previously: not yet	MSCs	IV	4	2* 10 e7	2 d	90

			masking		recruiting)						
11	NCT04416139	Mexico	double arm, open-label	phase 2	recruiting	MSCs	IV	1	1* 10 e6 /Kg	no intervals	10
12	NCT05017298	not mentioned	double arm, quadruple masking	phase 2	not yet recruiting	ADMSCs	IV	3	2* 10 e8	3 d	30
13	NCT04456361	Mexico	single-arm, open-label	early phase 1	active, not yet recruiting	WJ-MSCs	IV	1	1* 10 e8	no intervals	9
14	NCT04437823	Pakistan	double arm, open label	phase 2	recruiting	UCMSCs	IV	3	0.5 * 10 e6 /Kg	2 d	20
15	NCT04371601	China	double arm, open-label	early phase 1	active, not yet recruiting	UCMSCs	IV	4	1* 10 e6 /Kg	1 d	60
16	NCT04611256	Mexico	double arm, open-label	phase 1	recruiting	ADMSCs	IV	2	1* 10 e6 /Kg	2 d	20
17	NCT04252118	China	double arm, open-label	phase 1	recruiting	UCMSCs	IV	3	3* 10 e7	3 d	20
18	NCT04346368	China	double arm, a single masking	phase 1/phase 2	not yet recruiting	BMSCs	IV	1	1* 10 e6 /Kg	no intervals	20
19	NCT04273646	China	double arm, open-label	not applicable	not yet recruiting	UCMSCs	IV	4	0.5 * 10 e6 /Kg	2 d	48
20	NCT04366323	Spain	double arm, open-label	phase 1/phase 2	active, not yet recruiting	ADMSCs	not mentioned	2	8* 10 e8	not mentioned	26
21	NCT04625738	France	double arm, quadruple masking	phase 2	completed	WJ-MSCs	IV	3	first dose: 1* 10 e6 /Kg (maximum: 80 * 10 e6), other doses: 0.5* 10 e6 /Kg (maximum: 40 * 10 e6)	2-3 d	30
22	NCT04905836	USA	double arm, quadruple masking	phase 2	recruiting	ADMSCs	IV	3	3* 10 e7	2 d	60
23	NCT04992247	not mentioned	double arm, quadruple masking	phase 2	not yet recruiting	ADMSCs	IV	3	1.5* 10 e7	2 d	60
			double								

24	NCT04457609	Indonesia	arm, triple masking	phase 1	recruiting	UCMSCs	IV	1	1* 10 e6 /Kg	no intervals	40
25	NCT04527224	not mentioned	single-arm, open-label	phase 1/phase 2	not yet recruiting	ADMSCs	not mentioned	not mentioned	not mentioned	not mentioned	10
26	NCT05132972	Indonesia	double arm, quadruple masking	phase 2/ phase 3	recruiting	UCMSCs	IV	3	1* 10 e6 /Kg	3 d	42
27	NCT04494386	USA	triple arm, triple masking	phase 1/phase 2	recruiting	UCMSCs	IV	1 or 2	1* 10 e8	2 d	60
28	NCT04339660	China	double arm, triple masking	phase 1/phase 2	recruiting	UCMSCs	IV	1 or 2	1* 10 e6 /Kg	1 w	30
29	NCT04490486	USA	double arm, double masking	phase 1	not yet recruiting	UCMSCs	IV	2	1* 10 e8	3 d	21
30	NCT04355728	USA	double arm, triple masking	phase 1/phase 2	completed	UCMSCs	IV	2	1* 10 e8	2 d	24
31	NCT04392778	Turkey	triple arm, quadruple masking	phase 1/phase 2	completed	MSCs	IV	3	3* 10 e6 /Kg	3 d	30
32	NCT04565665	USA	triple arm, open-label	phase 1/phase 2	recruiting	UCMSCs	IV	1 or 2	not mentioned	6 d	70
33	NCT4888949	Japan	double arm, quadruple masking	phase 2	recruiting	ADMSCs	IV	4	1* 10 e8	1 w	20
34	NCT04522986	Japan	single arm, open label	phase 1	completed	ADMSCs	IV	4	1* 10 e8	1 w	6
35	NCT04461925	Ukraine	double arm, open-label	phase 1/phase 2	recruiting	PMMSCs	IV	3	1* 10 e6 /Kg	3 d	30
36	NCT4535856	Indonesia	triple arm, quadruple masking	phase 1	completed	MSCs	IV	1	one arm (low dose group): 5* 10 e7, the other arm (high dose group): 10* 10 e7	no intervals	9
37	NCT04903327	Brazil	double arm, quadruple making	phase 2	recruiting	MSCs	IV	3	3* 10 e7	2 d	100
38	NCT04390152	Colombia	double arm, quadruple masking	phase 1/phase 2	recruiting	WJ-MSCs	IV	2	5* 10 e7	not mentioned	40
39	NCT04629105	USA	quadruple arm, double	phase 1	recruiting	MSCs	IV	3	1* 10 e8	not mentioned	70

			masking								
40	NCT04397796	USA	double arm, quadruple masking	Phase 1	active, not yet recruiting	BMSCs	IV	not mentioned	not mentioned	not mentioned	45
41	NCT04452097	not mentioned	pentad arm, open-label	phase 1/phase 2	not yet recruiting	UCMSCs	IV	1	one arm (low dose group): 0.5* 10 e6 /Kg, the other arm (medium-dose group): 1* 10 e6 /Kg, the other arm (high dose group): 1.5* 10 e6 /Kg	no intervals	39
42	NCT04492501	Pakistan	quadruple arm, open-label	not applicable	completed	BMSCs	IV	1	2* 10 e6 /Kg	no intervals	600
43	NCT04780685	USA	double arm, quadruple masking	phase 2	recruiting	hMSCs	IV	2	not mentioned	2 d	40
44	NCT04331613	China	single-arm, open-label	phase 1/phase 2	unknown (previously: recruiting)	ESCs	IV	1	for dose escalation (3* 10 e6 /Kg, 5* 10 e6 /Kg or 10* 10 e6 /Kg)	no intervals	9
45	NCT04345601	USA	double arm, open label	phase 1/phase 2	recruiting	MSCs*	IV	2	1* 10 e8 /Kg	3 to 5 d	66
46	NCT04390139	Spain	double arm, quadruple masking	phase 1/phase 2	recruiting	WJ-MSCs	IV	2	1* 10 e6 /Kg	2 d	30
47	NCT04447833	Sweden	single arm, open label	phase 1	active, not yet recruiting	BMSCs	IV	1	(3 patients): 1* 10 e6 /Kg, (number of patients): 2* 10 e6 /Kg	no intervals	7
48	NCT04398303	not mentioned	triple arm, double masking	phase 1/phase 2	not yet recruiting	UCMSCs	IV	1	one arm (UCMSCs): 1* 10 e6 /Kg, the other arm (only conditioned medium): 100 ml	no intervals	70
49	NCT04400032	Canada	triple arm, open label	phase 1/phase 2	completed	UCMSCs	IV	3	one arm: 2.5* 10 e7, the other arm: 5* 10 e7, another arm: 9* 10 e7	1 d	15
50	NCT04467047	not mentioned	single arm, open label	phase 1	not yet recruiting	MSCs*	IV	1	1* 10 e6 /Kg	no intervals	10
51	NCT03042143	United Kingdom	double arm, quadruple masking	phase 1/phase 2	active, not yet recruiting	UCMSCs	IV	1	4* 10 e8	no intervals	120
52	NCT04269525	China	single arm, open label	phase 2	recruiting	UCMSCs	IV	4	9.9* 10 e7	2 d	16

53	NCT04367077	USA	double arm, quadruple masking	phase 2/phase 3	recruiting	BMAPCs	IV	1	not mentioned	no intervals	400
54	NCT04333368	France	double arm, triple masking	phase 1/phase 2	completed	UCMSCs	IV	3	1* 10 e6 /Kg	2 d	47
55	NCT04371393	USA	double arm, triple masking	phase 3	active, not yet recruiting	MSCs	IV	2	2* 10 e6 /Kg	4 d	223
56	NCT04466098	USA	double arm, triple masking	phase 2	active, not yet recruiting	MSCs	IV	3	3* 10 e8	2 d	9
57	NCT04524962	USA	single-arm, open label	phase 1/phase 2	recruiting	MSCs RNA-engineered	not mentioned	1	not mentioned	no intervals	30

Abbreviations. No., Number; WJ-MSCs, Warton's jelly derived mesenchymal stem cells; IV, intravenous; RT-PCR, reverse transcriptase-polymerase chain reaction; NHPBSCs, non-hematopoietic peripheral blood stem cells; SC, stem cell; ADMSCs, adipose-derived mesenchymal stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; hDPSCs, human dental pulp-derived mesenchymal stem cells; MSCs, mesenchymal stem cells; USA, United States of America; DPMSCs, dental pulp derived mesenchymal stem cells; UCMSCs, umbilical cord-derived mesenchymal stem cells; MenSCs, menstrual blood-derived mesenchymal stem cells; hMSCs, human mesenchymal stem cells; ESCs, embryonic stem cells; BMAPCs, bone marrow-derived adult progenitor cells; hEKT-Rex-239, human embryonic kidney T-Rex-239 stem cells; Evs, extracellular vesicles; PMMSCs, placenta-derived multipotent mesenchymal stromal cells.

Table 2. Summary of registered clinical trials using stem cell secretome therapy for COVID-19 disease

No.	Clinical trial identifier	Country	Study design	Study phase	Current status	Source secretome	Route of delivery	Number of doses	Single dose concentration (cells/ Evs)	Dose intervals	Estimated enrollment
1	NCT04602442	Russia	triple arm, double masking	phase 2	enrolling by invitation	MSCs exosomes	inhalation	20	0.5 - 2 * 10 e10 / 3ml solution	Q 12 hrs. for 10 d	90
2	NCT04491240	Russia	triple arm, double masking	phase 1/phase 2	completed	MSCs exosomes	inhalation	20	0.5 - 2 * 10 e10 / 3ml solution	Q 12 hrs. for 10 d	30
3	NCT04798716	USA	quadruple arm, double masking	phase 1/phase 2	not yet recruiting	MSCs exosomes	IV	3	one arm (3 doses, respectively): 2* 10 e9, 4* 10 e9, 8* 10 e9 /ml, the other arm (3 doses, respectively): 8* 10 e9, 4* 10 e9, 8* 10 e9 /ml	1 d	55
4	NCT04276987	China	single-arm, open-label	phase 1	completed	MSCs exosomes	nebulization	5	2* 10 e8 Nano vesicles/ 3 ml	1 d	24
5	NCT05216562	Indonesia	double arm, triple masking	phase 2/phase 3	recruiting	MSCs exosomes	IV	2	not mentioned	6 d	60
6	NCT04969172	Israel	double arm, double masking	phase 2	active, not yet recruiting	hEK-T-Rex-239 exosomes overexpressing CD42	inhalation	5	diluted exosomes / 4 ml NS	Q 24 hrs. for 5 d	155
7	NCT04366063	Iran	triple arm, open label	phase 2/phase 3	recruiting	MSCs + MSCs Evs	IV	one arm: 2 doses of MSCs, the other arm: 2 doses of MSCs + 2 doses of MSCs Evs	one arm: 1* 10 e8 MSCs, the other arm: 1* 10 e8 MSCs + 2 doses of MSCs Evs (not mentioned Evs numbers)	2 d	60
8	NCT04493242	USA	triple arm, triple masking	phase 2	completed	BMSCs Evs	IV	1	one arm: 10 ml / 90 ml NS (8* 10 e11), the other arm: 15 ml / 85 ml NS (1.2* 10 e12)	no intervals	120
9	NCT05125562	USA	triple arm, triple masking	phase 2	not yet recruiting	BMSCs Evs	IV	1	one arm: 10 ml / 90 ml NS (7* 10 e11), the other arm: 15 ml / 85 ml NS (10.5* 10 e11)	no intervals	30
10	NCT04753476	Indonesia	double arm, open-label	phase 2	recruiting	hypoxic MSCs secretome	IV	3	1 ml	1 d (every 12 hrs.)	48
11	NCT05019287	Iran	double arm, double masking	phase 1/phase 2	completed	MenSCs secretome	IV	5	5 ml	1 d	29
12	NCT05122234	Indonesia	double arm, a single masking	phase 3	completed	MSC secretome	IV	1	15 ml / 100 ml NS	no intervals	40

Abbreviations. No., Number; IV, intravenous; RT-PCR, reverse transcriptase-polymerase chain reaction; SC, stem cell; BMSCs, bone marrow-derived mesenchymal stem cells; MSCs, mesenchymal stem cells; MenSCs, menstrual blood-derived mesenchymal stem cells; Evs, extracellular vesicles; the USA, United States of America.

A study referenced as NCT04473170 evaluated the safety and efficacy of nebulized human peripheral blood-derived stem cells (hPBSCs) in treating symptomatic COVID-19-infected patients, and three nebulization methods were assessed. Among nebulization methods, compressor nebulizers preserve the viability of delivered cells without significant loss in their count and morphologic changes. The mentioned study depicted significant improvements in clinical outcomes of the treated group with hPBSCs. In addition, there was no significant difference in adverse effects between the control and hPBSCs treated groups [41][42].

Another study referenced as NCT04355728 investigated the safety and efficacy of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) in treating severe complications of acute lung injury (ALI) and ARDS, completed the phase 1/phase 2 trial on 24 patients. The mentioned clinical trial demonstrated that hUC-MSCs treatment would not increase the adverse events [43]. A completed clinical trial referenced as NCT04491240 investigating the safety and efficacy of two types of inhaled MSCs exosomes in treating severe hospitalized patients with COVID-19 completed the phase 1/phase 2 trials on 30 patients; reported any severe adverse events in MSCs exosomes treating groups [44].

A completed clinical trial referenced as NCT05019287 assessing the safety and efficacy of menstrual blood-derived mesenchymal stem cells secretome (MenSCs secretome) infusion in treating severe hospitalized patients with COVID-19, completed the phase 1/phase 2 trial on 29 patients; demonstrated that intravenous injection (IV) of MenSCs secretomes could improve oxygen levels, decrease radiologic pulmonary involvement and mortality rates. There were no infusion-related adverse events in MenSCs secretomes treated groups [45].

A study was conducted by Li et al. to assess the effect of invariant natural killer T (iNKT) cells on SARS-CoV-2 infection. They produced allogeneic HSC-engineered iNKT (AlloHSC-iNKT) cells through TCR engineering of human cord blood CD34+ hematopoietic stem cells (HSCs) and differentiation of these HSCs into iNKT cells in an Ex Vivo HSC-Derived iNKT Cell Culture. The results showed that these AlloHSC-iNKT cells killed SARS-CoV-2 infected cells and eliminated SARS-CoV-2 infection-stimulated inflammatory monocytes. In addition, the AlloHSC-iNKT cells were resistant to T cell-mediated alloreaction and did not cause GVHD[46].

In another study, Liao et al. evaluated the safety and efficacy of interleukin-18-primed hUC-MSCs. This study demonstrated an efficient effect of IL-18-primed hUC-MSCs therapy than hUC-MSCs therapy alone. They found out the level of VCAM-1, MMP-1, TGF-β1, CCL2, and CXCL12 were highly expressed, and the immunosuppressive effect of CD3+ T-cells in IL-18-primed hUC-MSCs group in vitro. Also, the IL-18-primed hUC-MSCs therapy reduced the body weight loss caused by a viral infection and clinical symptoms, including reduced activity, ruffled fur, hunched backs, and lung injuries in vivo [47].

Also, two separate studies evaluated the effect of MSCs-derived exosomes in vitro. In the first one, A. Hussein et al.

conducted a study to evaluate the effect of Human Wharton's Jelly Mesenchymal Stem Cells Secretome (hWJ-MSC-S) on an in vitro model of SARS-Cov-2 infection. The results showed a significant reduction in viral infection as a promising way to overcome SARS-Cov-2 infection and its complications [48]. In addition, in 2022, a study was conducted to evaluate the anti-SARS-CoV-2 effects of extracellular vesicles released from mesenchymal stem cells (MSCs-EVs) that were applied on in vitro anti-SARS-CoV-2 assays. The result was suppression in viral replication.

The potential and safety of ADMSCs were documented by Sanchez-Guijo et al. examined 13 adult patients with COVID-19 who underwent invasive mechanical ventilation and were previously treated by antiviral and anti-inflammatory interventions. The administered dose of ADMSCs was 0.98×106 cell/kg body weight (BW). The results demonstrated no complications associated with MSC therapy, and clinical improvement was seen in about 70% of the patients discharged from the ICU. Moreover, the MSC therapy elevated the lymphocyte count and reduced the levels of CRP, IL-6, ferritin, LDH, and D-dimer; therefore, they suggested the ADMSCs therapy as a safe approach with promising clinical outcomes in COVID-19 patients [49].

Further studies need to be conducted to optimize MSCs-based therapies in moderate to severe cases of COVID-19 infection, in terms of the number of cells, administration intervals (single or multiple infusion), source of MSCs, local (inhalational or nebulized) or systemic route of administration [9][30].

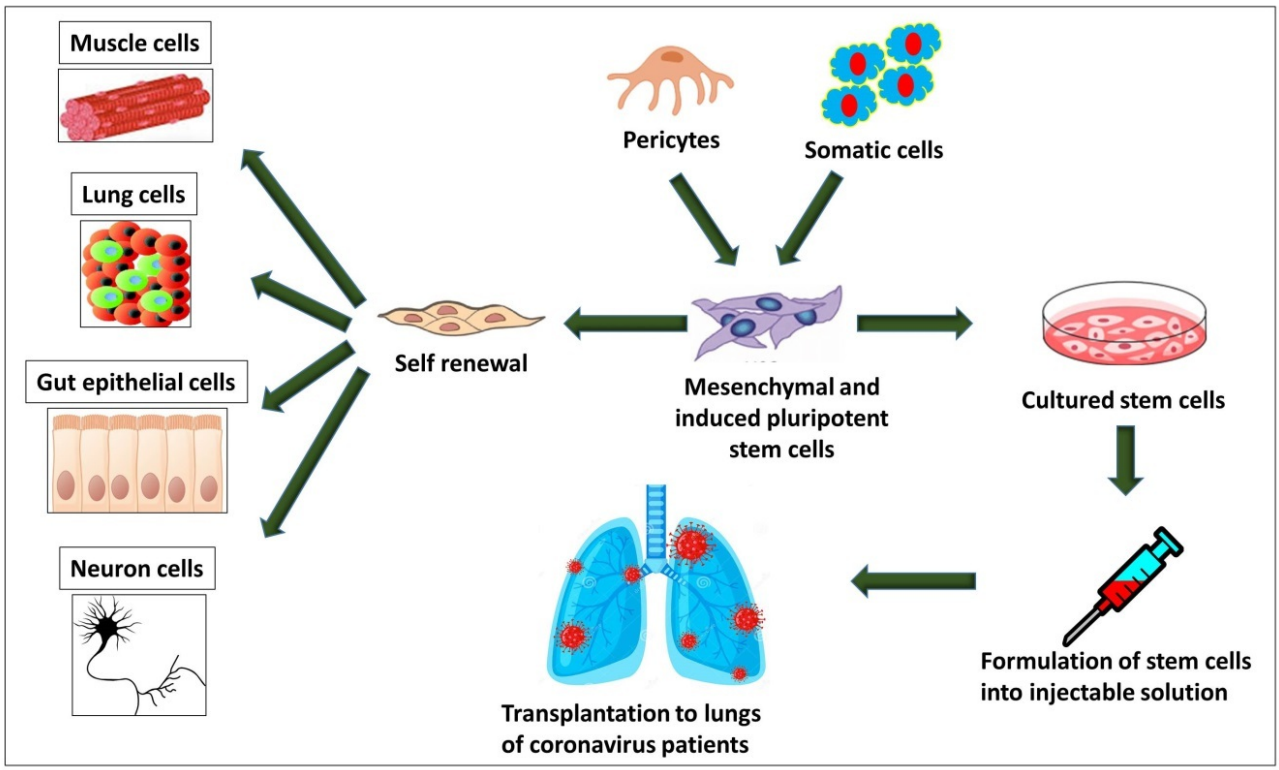

Figure 3. The main characteristics and applications of induced pluripotent stem cells and mesenchymal stem cells are heterogeneous populations derived from somatic cells and pericytes, respectively. These cells are characterized by two properties the ability to self-renew and the ability to differentiate into different types of cells, with possible clinical potentials in the treatment of COVID-19 patients.

4. Human-induced pluripotent stem cells (hiPSCs)

Adult human somatic cell reprogramming to generate iPSCs using transcription factors was performed by Takahashi et al. [50]. It was reported that iPSCs could be generated from a patient's specific somatic cells to be used in various diseases as an in-vitro disease model[51][52]. One of the recent advances is the somatic cell-derived iPSCs with different clinical applications. The production of iPSCs, an effective cell source in cell therapy, occurs with the entry of a certain class of reprogramming agents into somatic cells [22][51]. Stem cells have been able to restore sperm count in some differentiation studies, so a significant increase was reported in the survival pathways and anti-apoptotic protein expression [53].

Compared to the extraction and employment of embryonic stem cells (ESCs), iPSCs have fewer ethical issues, particularly for autologous stem cell therapy. These cells and ESC-like cells have limited differences in gene expression patterns [54][55]. These cells have the potential for clinical applications and can be produced in different ways. However, the employment of retroviral and lentiviral vectors and proto-oncogenes, such as KLF4 and c-Myc, as well as the approaches applied to reprogram the cells, may impair the developmental characteristics and clinical application of these cells [56].

Anyone with a specific phenotype or genotype can donate hiPSCs for in vitro disease modeling. Differentiated cell types of a particular disease can be achieved from patient-derived hiPSC models. For example, hiPSC-derived cardiomyocytes or neurons can help understand the pathogenesis of particular diseases and screen for the choice of drug [57]. One of the most valuable models for infectious diseases has been reported to be hiPSC-derived cells.

Furthermore, the mixture of human iPSC with recent advancements in the field of gene editing and 3D organoids makes iPSC-based platforms more efficient in every area of their usage such as precision medicine [58]. The hiPSC can cover human genetic diversity. Despite its ability to produce different types of human cells, it can be used in the drug-production process [59][60].

A study summarized the cytopathogenic impacts and cytokine/chemokine response in hiPSCs-derived cardiomyocytes in an in vitro model of SARS-CoV-2 myocarditis, suggesting an opportunity for drug screening [5]. As seen in Figure 2, there are also reports of the ability of lung epithelial cell-derived hiPSCs to produce a sensitive model of SARS-CoV-2 infection and drug screening [61].

5. Mesenchymal Stem Cells (MSCs)

The MSCs are fibroblast-like cells with the capacity to attach to plastic surfaces and proliferate in vitro that can be isolated from various sources of fetal or adult tissues [35][62]. Different tissues can be used as a source to isolate the MSCs, depending on the practical, logistical, and in vitro properties of the source. Some of these sources are dental pulp, endothelial progenitor cells, umbilical cord blood, adipose tissue, umbilical cord stroma, and bone marrow [27][35]. Adult adipose-derived MSCs (ADMSCs) can repair tissues due to their ability to proliferate for a long time without

differentiation [63].

The ability for proliferation and regeneration of MSCs is almost indeterminate and could be potentially used for stem cell therapy in the COVID-19 treatment [64][65]. In response to harsh environmental conditions at the target site, the autophagic and apoptotic processes of MSCs occur, which eventually results in the release of growth factors and cytokine-rich exosomes, which can reduce disease pathophysiology. Thus, this has shed light on new therapeutic approaches concerning stem cell-derived as a new modality to address the challenges which are associated with parent cells. Additionally, MSCs are also capable of inhibiting the abnormal activation of T lymphocytes and macrophages, as well as inducing the differentiation of regulatory T cells (Tregs) and anti-inflammatory macrophages [65][66].

Multiple processes are accelerated in the presence of MSCs through some pathways such as chemical absorption, anti-scarring, supporting the growth and differentiation of local stem and progenitor cells, angiogenesis, anti-apoptosis, and immunomodulation [67] through immunomodulation; MSCs could play a role in the repairing and regenerating process in many pathological lung diseases, including idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, acute lung injury, asthma, and bronchopulmonary dysplasia [68].

6. The hiPSCs and hPSCs as Invitro models for COVID-19 treatment

Several limitations became apparent in primary laboratory studies for modeling SARS-CoV-2 as a complex human respiratory disease. Although the drug's effects can be determined directly through patient cells, there are limitations to the availability and expansion capacity of these cells compared to tumor-derived cell lines or immortalized and transformed cells. Besides, genetic, and metabolic abnormalities can be a barrier to proper drug screening. Therefore, human cell models must be physiologically appropriate to find out the pathophysiology of SARS-CoV-2, which facilitates drug analysis [61].

The literature review showed that most researchers extracted lung epithelial lineage from hiPSC using a directed differentiation method as a human model through a three-step protocol [69][70]. A microenvironment was remodeled by Activin-A/BMP4 integration to interact with mesenchymal and epithelium cells. Subsequently, the expression of NKX2.1, the main transcription factor in the generation of lung epithelial lineage, was enhanced by increasing the levels of growth factors (EGF and bFGF). Moreover, the proximal airway epithelial cells were generated increasingly by adding retinoic acid (RA), activating KGF1 and WNT pathways, and blocking MAPK and BMP4 pathways. The anterior-posterior endodermal fate was strongly affected by the Wnt/β-catenin signaling pathway, FGF10, and the lung bud formation and development [71].

Two-dimensional cultured cell lines are the current in vitro systems to investigate different coronaviruses' behavior and drug responses. Because of differences in the infectivity rate of SARS-CoV-2 among different ethnic people, the application of a three-dimensional human lung organoid (3D-HLO) model isolated from iPSCs of various populations has been suggested recently. The 3D-HLO systems can optimally mimic the normal lung tissue of human beings. The challenge of severity/infectivity rate in human populations precludes the suggestion of animal models as the best option

for such studies [72]. Dye et al. designed a 3D-HLO model for adult airways that uses poly (lactide-co-glycolide) (PLG) or polycaprolactone (PCL) scaffolds for HLO transplantation. This protocol provides a porous and degradable scaffold for HLO, so it assists tissue maturation and is an appropriate model for adult airways [73].

In a study by Zhou et al., the iPSCs-derived organoids were introduced as an appropriate infection model to mimic the viral life cycle and drug screening under ex vivo conditions. The human iPSC-3D organoids from self-organized tissues having multiple cell environments are functionally and structurally similar to real human organs, thereby providing more efficient viral infection, mimicking regular host-virus interaction, and allowing long-term experiments. A functional hiPSC-derived organoid has been introduced as a feasible and reliable ex vivo model of infection for virological studies, which allows the study of the critical molecular dynamics of SARS-CoV-2 to develop effective treatment and prevention strategies [74].

The researchers developed a platform utilizing system-wide human cell lineages and organoids. They found that both pseudo-entry and live SARS-CoV-2 could infect liver organoids, alpha and beta cells of the pancreas, heart cells, and dopaminergic neurons. As it is still unknown that SARS-CoV-2 can be vertically transmitted to fetuses, there is a controversy about using hPSC-derived cells to model SARS-CoV-2 infection [75][76].

In a study, Yang et al.[77] assessed the infectivity rate of human cells with SARS-CoV-2 infection via a library generated from hPSC-derived cells and organoids, such as dopaminergic neurons, cortical neurons, microglia, macrophages, cardiomyocytes, endothelial cells, liver organoids, and pancreatic endocrine cells. These results demonstrate that pancreatic, hepatic, and cholangiocyte cells derived from hPSCs are permissive to SARS-CoV-2 infection, as confirmed by adult human islets, liver, and cholangiocyte organoids, as well as a humanized mouse model [77].

The expression of chemokine was upregulated according to the determination of transcript profiles in the hPSC-derived liver organoids and pancreatic endocrine cells infected by SARS-CoV-2, in line with tissue profiling following the autopsy of COVID-19 patients [78]. Low or no permissiveness to both pseudo-entry and live SARS-CoV-2 was interestingly reported for some ACE2-expressing cells by analyzing a human lung single-cell sequencing dataset (GSE132914) for the levels of expression of ACE2 and transmembrane serine protease 2 (TMPRSS2), the two receptors that are the primary sites of entry for the SARS-CoV-2 [79].

Including cortical neurons, macrophages, and endothelium, which means factors other than ACE2 are also involved in virus penetration (such as TMPRSS2). The need to replace ACE2-overexpressing cells with hPSC-derived primary-like cells is highlighted in the SARS-CoV-2 biology by looking at the nonlinear relationship between permissiveness to SARS-CoV-2 infection and ACE2 [80]. According to these researchers, drug screening and evaluation of possible antiviral drugs can be done directly using protocols based on disease-relevant human cells/organoids [76].

7. Clinical application of MSCs in the treatment of COVID-19

Much attention has recently been drawn to MSC-based therapies due to their self-renewable capacity and

pluripotency [81][82]. The immunoregulatory activity of MSCs mitigates body inflammation via immunosuppression[83][84], which can be a promising approach for the treatment of COVID-19 [85]. According to recent findings, there were no critical adverse events, such as ventricular tachycardia, cardiac arrhythmia, and hypoxemia, in nine ARDS patients receiving allogeneic MSCs transplantation [86].

The MSCs-based therapy for SARS-CoV-2 was reported to be effective and safe, although further clinical trials with prolonged follow-up duration are needed to detect the long-term impacts of the treatment on patients with COVID-19 [87]. Chrzanowski et al. reported that the MSCs could repair rapidly damaged tissue owing to their regenerative potential and prevent long-term COVID-19-related lung injuries [6]. In the severe SARS-CoV-2 infection, the respiratory alveolars infiltrated with various immune cells such as neutrophils, macrophages, NK cells, and T cells leading to high concentrations of inflammatory cytokines and cytokine storm. The ultimate consequence of severe infection is alveolar lung fibrosis. The MSCs can stabilize the leakage of endothelial fluid and maintain the activity of the alveolar-capillary barrier. These stem cells can be attracted to the inflammatory sites due to different chemokine secretions, and subsequently transform the overreaction of the inflammatory response. MSCs can ameliorate respiratory alveolar fibrosis due to their regenerative and differentiating characteristics [31]. Several studies evaluating the pathophysiology, molecular signaling, and underlying cellular mechanisms revealed that MSCs can alter the course of moderate to severe COVID-19 infection by following pathways including, decreasing recruited cellular apoptosis, direct and indirect immune defense enhancement via secretion of anti-pathogenic peptides and activating phagocytic immune cells, ameliorating oxidative stress, alveolar epithelial regeneration, decreasing the alveolar-capillary permeability and enhancing alveolar fluid clearance [30]. The ameliorating effect of inflammatory cascades is mostly assigned to the paracrine-releasing factors derived from MSCs, therefore some studies investigated MSCs' conditioned medium application in in vitro alveolar injury models [88][89]. Due to the lower chance of MSC engraftment, some studies evaluated the therapeutic potentials of MSCs' extracellular vehicles (EVs) in ALI models [90][91] as well as clinical trials conducted on COVID-19 patients[48][92].

A study conducted by Ren et al. depicted that the lung epithelial cells are protected against oxidative stress-induced cell death by delivering miR-21-5p via the MSC exosomes [93]. Bari et al. demonstrated that Alpha-1-antitrypsin (AAT) was present on the surface of exosome-derived MSCs [94]. The anti-inflammatory and immunomodulatory effects of AAT enhanced the protection of lung epithelial cells by inhibiting neutrophil-derived proteolytic enzymes, reducing inflammation-imposed lung permeability, and declining interstitial lung edema [94][95].

Chrzanowski et al. examined female cases with intravenous MSC transplantation (1×10^6 per kg) in lung tissue in comparison with female placebo controls; they observed a significant improvement in pulmonary function. In addition, a significant reduction was seen in tissue inflammation in the intervention group [6].

Although, Several studies support the evidence that MSCs can be a suitable candidate for controlling and treating cytokine storm-induced SARS-CoV-2 infection and ALIs due to their critical immunomodulatory, anti-inflammatory, and regenerative properties, respectively [36]. There are challenges in optimizing the engraftment and survival of applied MSCs. Several studies overcoming these challenges by modifying gene expression to improve MSCs homing or even increasing the anti-inflammatory properties in ALI models [30]. Overexpression of Chemokine receptor 4 (CXC4),

chemokine receptor 7 (CXC7), and E-prostanoid 2 (EP2) can enhance MSCs migration into the injured respiratory sites [96][97][98]. Heme oxygenase-1 (HO-1) overexpression in MSCs regulates inflammatory cytokine concentration[99].

The clinical trial launched in 2020 to investigate MSC therapy for COVID-19 management revealed a significant elevation in the count of regulatory dendritic cells (DCs) following MSC transplantation [100]. Regulation of the immune system by regulatory DCs is essential to maintaining immune homeostasis by inducing the expression of immunosuppressive cytokines like IL-10 and TGF-β and thus preventing the lungs from the detrimental effects of macrophage and DC-driven systemic immune responses. In addition, the COVID-19 patients with MSC transplantation showed an elevation in IL-10 level and a reduction in TNF-α level compared to controls [101]. Furthermore, it is demonstrated that MSC therapy for ARDS caused by H9N2 avian influenza viruses and H5N1 infections results in reduced pulmonary inflammation and lung injuries [1][102].

In a case series by Yao et al., the efficacy of human umbilical cord-derived mesenchymal stem cell (hUC-MSCs) therapy was assessed. 5 patients with severe COVID-19 infection went through the salvage therapy of hUC-MSCs intravenous infusion. The results showed a significant advance in laboratory biomarkers and lung computed tomography images in all patients [103].

In addition, two cases were reported by Kim et al. and Balzanelli et al. The first was at Wonju Severance Christian Hospital. The patient was a 73-year-old man with positive real-time PCR that developed ARDS. Allogenic human bone marrow-derived mesenchymal stem cell (hBMSC) was administered intravenously and, the clinical symptoms, signs, and laboratory findings, including PaO2/FiO2 and O2 saturation, were improved[104]. The second case was a 56-year-old man with a positive PCR test for COVID-19 infection who received Peripheral Blood Stem Cells and Plasma (PB plasma/SCs). No adverse effects were reported during PB plasma/SCs administration. Also, CT showed a 98% reduction in lung damage after a total of five plasma transfusions [105].

Shu et al. evaluated the safety and efficacy of UC-MSCs administration in the management of COVID-19. They found the hUC-MSC therapy as an excellent, effective achievement with clinical values. Moreover, the hUC-MSC therapy group exhibited a significant alleviation in chest tightness, dyspnea, and fatigue, in a shorter time compared to the controls [106].

Although, multiple MSC-related studies are being performed on COVID-19 patients with respiratory complications. Few reports demonstrate the ability of these therapies to promote recovery and survival in these patients. It can be reasoned that variable factors including the number of applied MSCs, route of administration, cell infusion intervals, and source of applied MSCs, could play a part in these studies' results [30][107][108]. Antebi et al. depicted that autologous transplantation of BM-MSCs which are harvested from an ARDS patient, can affect the immunoregulatory properties of harvested MSCs. Although inconclusive evidence is available to support optimized sources of MSC-based therapies for relieving COVID-19 respiratory complications. Further studies need to be conducted to optimize MSC-based therapy protocols. MSCs route of administration is another factor to be considered in the interpretation of study results. Miller et al. depicted that intravenous application of MSCs can significantly decrease ECMO flow due to cell adherence to the oxygenator membrane. Indicating the MSCs intravenous injection before the ECMO application. Local administration of MSCs via inhalational route can increase the number of transplanted MSCs in the site of injury in ARDS cases and genetic

modification can help to enhance cell engraftment and survival. Although there is an urgent need to develop MSC-based therapies for COVID-19, MSC production must be under Good Manufacturing Practices (GMP) and must follow human use regulations before adoption [30][108].

8. Conclusion

Consistent with the findings of the present review article, studies are still ongoing to support stem cell and stem cell-derived strategies as valuable tools for the treatment of COVID-19. There is little evidence so far about the safety and efficacy of such treatments in the short term, at least in severe and very severe patients. Mesenchymal stem cells and Human-induced pluripotent stem cells are promising candidates for developing new therapies for COVID-19.

Due to their ability to produce disease-related differentiated cells, these stem cells can be exploited to approve large-scale antiviral drugs as an in vitro model system to scrutinize the biology of virus-host interaction. The complexity and high cost of cell therapies emphasize the careful evaluation of such treatment strategies concerning sensitive parameters, including ICU time, recovery time, and length of hospital stay. Advanced therapies are hardly a suitable candidate for controlling the pandemic, but they can still help rescue patients in severe or very severe conditions.

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The authors declare no competing interests.

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