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Concise Review

Efficacy and Safety of MSC Cell Therapies for Hospitalized Patients with COVID-19: A Systematic Review and Meta-Analysis

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Abstract

MSC (a.k.a. mesenchymal stem cell or medicinal signaling cell) cell therapies show promise in decreasing mortality in acute respiratory distress syndrome (ARDS) and suggest benefits in treatment of COVID-19-related ARDS. We performed a meta-analysis of published trials assessing the efficacy and adverse events (AE) rates of MSC cell therapy in individuals hospitalized for COVID-19. Systematic searches were performed in multiple databases through November 3, 2021. Reports in all languages, including randomized clinical trials (RCTs), non-randomized interventional trials, and uncontrolled trials, were included. Random effects model was used to pool outcomes from RCTs and non-randomized interventional trials. Outcome measures included all-cause mortality, serious adverse events (SAEs), AEs, pulmonary function, laboratory, and imaging findings. A total of 736 patients were identified from 34 studies, which included 5 RCTs (n = 235), 7 non-randomized interventional trials (n = 370), and 22 uncontrolled comparative trials (n = 131). Patients aged on average 59.4 years and 32.2% were women. When compared with the control group, MSC cell therapy was associated with a reduction in all-cause mortality (RR = 0.54, 95% CI: 0.35-0.85, I^2 = 0.0%), reduction in SAEs (IRR = 0.36, 95% CI: 0.14-0.90, I^2 = 0.0%) and no significant difference in AE rate. A sub-group with pulmonary function studies suggested improvement in patients receiving MSC. These findings support the potential for MSC cell therapy to decrease all-cause mortality, reduce SAEs, and improve pulmonary function compared with conventional care. Large-scale double-blinded, well-powered RCTs should be conducted to further explore these results.

Key words: MSC; COVID; cytokine storm; pulmonary; hospital recovery.

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Significance Statement

This systematic review and meta-analysis of clinical studies synthesized evidence to date and concluded that MSC cell therapy is associated with decreased mortality and lowered incidence of serious adverse events in patients hospitalized with COVID-19. Future large randomized controlled studies are needed to further evaluate the effectiveness and safety of MSC cell therapy for COVID-19.

Introduction

As of December 2021, the pandemic caused by COVID-19 (SARS-CoV-2) has infected more than 270 million and contributed to the death of more than 5 million individuals worldwide.[1] While the rapid development of effective vaccines is helping to mitigate this pandemic, there is a rising incidence of infection with the more highly transmissible Delta variant and Omicron variant that is expected to increase COVID-related diseases and is capable of breakthrough disease in vaccinated individuals.[2,3] To date, most (81%) infected patients have a mild-to-moderate disease and recover within 2 or 3 weeks.[4] However, among patients requiring hospitalization mortality ranges from 5% to 17%[5,6] and among those requiring ICU admission, range from 26% to 78%.[6-8]

Additionally, emerging new variants of the virus have raised concerns about vaccine efficacy,[2,9] virus transmissibility, susceptibility, and disease severity.[3,10] Although viral mutation occurs in a natural cycle, often including removal of lethal or deleterious variants from the pool, new variants will likely extend the duration of the pandemic.[10] It is now clearly appreciated that the pandemic is very long lasting and characterized by the ongoing appearance of variants that may have different infectivity rates and proclivity to involve the lung.[11,12]

In severe cases, SARS-CoV-2 leads to fatal acute respiratory distress syndrome (ARDS) with diffuse alveolar damage and cellular fibromyxoid exudate associated with monocyte and macrophage infiltration.[13,14] Respiratory distress typically arises 7 to 10 days post-symptom onset, with manifestations of immune dysregulation including cytokine release syndrome (a.k.a. "cytokine storm"), lymphopenia (CD4+ and CD8+ T cells), and decreased interferon-γ (INF-γ) expression in CD4+ T cells.[14,15] IL-6, IL-8, IL2R, IL-10, and tumor necrosis factor-α (TNF-α) were reported to be increased on average in 18.8 (IL-8)-81.3% (IL-6) patients by Chen et al and Del Valle et al[15,16]The inverse correlation between cytokine storm and lower CD4+ and CD8+ counts suggests that the cytokine response may dampen adaptive immunity.[17]

Treatments for patients with respiratory complications from COVID infection have evolved since the onset of the pandemic. These have focused on supportive approaches including mechanical ventilation, high-flow nasal oxygen, and ECMO, convalescent plasma, as well as anti-inflammatory and immuno-modulatory therapies ranging from corticosteroids to monoclonal antibodies targeting-specific cytokines such as IL-6.[18,19] Several treatments have become standard of care including dexamethasone, remdesivir, tocilizumab, or baricitinib depending on the disease severity.[20, 21-23] While several drug therapies have suggested promising results,[18,19] their potential benefits must be balanced with concerns about side effects and secondary infections.[18] New treatments focused on mitigating the underlying cellular and molecular mediators of diseases are urgently needed to address the pathophysiological processes that lead to death or long-term sequelae.

MSC cell therapies have shown promise in modulating responses in inflammatory diseases.[24-26] Previously known as "mesenchymal stem cells", "mesenchymal stromal cells", and more recently as "medicinal signaling cells."[27] MSCs are small spindle-shaped cells wrapping around microvasculature and are most commonly sourced from bone marrow, adipose tissue, and umbilical cord.[28] They express cell surface markers CD44, CD90, CD105 but do not express CD34, CD45, or HLA-DR.[29] MSCs home to sites of injury and inflammation where they exert immunomodulatory effects, largely via a paracrine mode of action.[30,31] Their immunomodulatory activity arises through several well-characterized effects that include: (a) suppression of proliferation and action of B cells, T cells, natural killer cells, and dendritic cells; (b) polarization of monocytes to anti-inflammatory M2 macrophages; (c) differentiation of T effector cells toward Treg cells; and (d) modulation of cytokine secretion towards increased production of IL-4, IL-10 with reduced production of TNF-α, IL-12, and IL-6.[24,29,32,33] MSCs may also enhance tissue repair and regeneration by secretion of factors that limit apoptosis and foster endogenous progenitor cell cycling.[34,35]

MSC cell therapy has been shown to repair lung epithelium by increasing alveolar denosine triphosphate (ATP), transferring mitochondria to the damaged alveolar epithelium,[36] maintaining balance in the renin-angiotensin system, and improving endogenous repair of pulmonary endothelial cells by enhancing their microenvironment. They also improve the alveolar-capillary barrier function of the lung.[30,37,38] Studies of COVID-19 patients suggest that MSC cell therapy can reduce inflammation by ameliorating anti-inflammatory and trophic factor expression with notable decreases in C-reactive protein (CRP), TNF-α, and cytokine-secreting immune cells.[39,40] In addition, MSCs have powerful antifibrotic effects and may alleviate pulmonary fibrosis.[41] Finally, MSCs demonstrate antimicrobial activity via enhanced production of peptide cathelicidin/LL-37 production,[42] which also has antiviral activity.[43] Preclinical study suggests that MSCs have antimicrobial properties in vivo and thus may limit microbial superinfections in the context of viral infections.[44]

Clinically, MSC cell therapy has been studied in viral and non-viral-induced ARDS and appears to reduce mortality as reported in the recent systematic review[24] as well as in Covid-19 patient population as shown in another current meta-analysis study on the topic.[45] Importantly, early data from the pandemic suggested that infusion of various MSC preparations could potentially reduce COVID-19 mortality and morbidity.[46] However, these initial clinical reports had small patient numbers and limited outcome measures. To address this issue, we conducted a systematic review of the current literature on safety, efficacy, and cytokine responses to MSC cell therapy in patients with COVID-19 infections.

Methods

We followed the steps outlined by the US Agency for Healthcare Research and Quality Methods Guide for Effectiveness

and Comparative Effectiveness Reviews.[47] The study was conducted and analyzed based on pre-planned study protocol which was not publically registered or published because of the fast pace of the research. However, the protocol is available upon request.

Search Strategy

An extensive search of databases from the database inception to November 3, 2021 in all languages was performed. Databases included EBM Reviews—Cochrane Central Register of Controlled Trials, EBM Reviews – Cochrane Database of Systematic Reviews, Ovid MEDLINE, Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Scopus. A medical reference librarian developed and implemented the search strategy, with feedback from the investigators. Controlled vocabulary supplemented with keywords were used to search for MSC cell therapy for patients with COVID-19 or SARS-CoV-2 infection. The exact strategy is available in Supplementary Appendix A.

Eligibility Criteria

We included all published randomized clinical trials, non-randomized interventional trials and uncontrolled trials that evaluated the safety and/or efficacy of stem cells administered to patients hospitalized with COVID-19 or SARS-CoV-2 infection. Studies were excluded if original data were not reported (such as a narrative review, editorials, or erratum). The detailed inclusion and exclusion criteria were listed in Supplementary Appendix Table A1.

Outcome Measures

The primary outcomes of interest included all-cause mortality as a function of treatment with MSC cell therapy, safety as evaluated by the occurrence of serious adverse events (SAEs) and adverse events (AEs). SAEs and AEs were defined according to the original studies or CBER criteria.[48] In this review, mortality was reported as a separate outcome and not included in SAEs.

Other secondary outcomes included pulmonary functional measures [eg, PaO_2/FiO_2 ratio and oxygenation index; laboratory measures including lymphocyte count, D-dimer, procalcitonin (PCT), CRP, IL-6; and imaging findings including computed tomographic (CT) of the lung].

Study Selection Process

Independent reviewers, working in pairs, screened the titles and abstracts of all citations. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible studies. Conflicts between the reviewers were resolved by a third senior investigator (Fig. 1).

Data Collection

A pilot-tested standardized data extraction form was used to extract data. Independent reviewers extracted study details. An additional reviewer reviewed data extraction and resolved conflicts.

Risk of Bias

We used the Cochrane Collaboration's Risk of Bias 2 tool to assess risk of bias for RCTs,[49] the Newcastle-Ottawa tool for non-randomized interventional trials,[50] and the risk of bias tool developed by Murad et.al for case series/case report.[51]

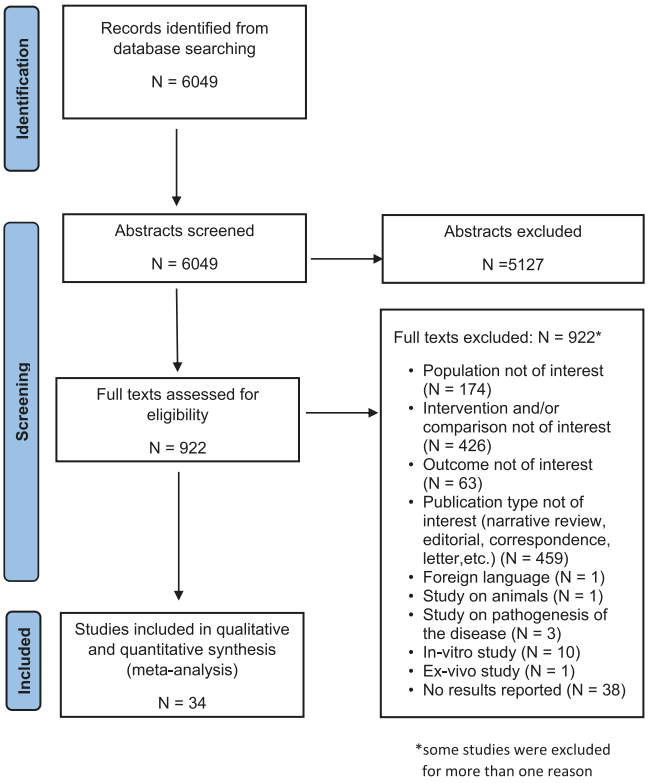

Figure 1. PRISMA 2009 flow diagram.

Statistical Analysis

To evaluate the comparative efficacy of MSC cell therapy versus control groups, we calculated relative risk (RR) for mortality and incidence rate ratio (IRR) for SAEs and AEs from RCTs and non-randomized interventional trials. The DerSimonian-Laird random-effects model with Hartung-Knapp-Sidik-Jonkman variance correction was used to combine effect size from included studies.[52] Treatment group continuity corrections were used to adjust double-zero-event studies (ie, 0 event in both groups).[53] Heterogeneity between studies was evaluated with the I^2 indicator. We conducted sensitivity analyses by excluding studies with inadequate randomization.[46] Two-tailed P-value < .05 was considered as statistically significant. RR < 1 suggests benefit for the MSC arm. All statistical analyses were conducted using Stata version 17 (StataCorp LLC, College Station, TX).

Results

The literature search identified 6049 distinct citations. Thirty-four studies with a total of 736 unique patients met the inclusion and exclusion criteria and were included in the analyses as shown in Fig. 1.

Of the 34 included studies, we included 5 RCTs,[46,54,55] 7 non-randomized interventional trials,[56-60] and 22 nonrandomized trials.[61-77] The studies were conducted in 11 countries, including Asia (n = 22), Europe (n = 8), North America (n = 2), and South America (n = 2).

The average age of participants was 59.4 years (range: 19 to 83 years), with 158 (30.0%) treated female and 367(69.9%) treated male patients. Among the reported patients, 296 (40.2%) were deemed critically ill, 402 (54.6%) were severely ill, and 27 (3.7%) were moderately ill. Hypertension, diabetes

Table 1. Patient and product characteristics.

Publication author, year	Country	Study type	Number of patients (treatment; Control)	Age, mean ± SD (years) or median (IQR)	Female, *N* (%)	Comorbidities, *N* (%)	COVID-19 severity *N* (%)	MSC source	Dosage [MSCs]	Route	Frequency, number of infusions (day of infusion)/cohort (*N*)	Concurrenttherapy	Timing for administration of MSCs
Shu et al., 2020[44]	China	RCT	41 (12; 29)	Treatment 61 ± 17.8 Control 57.8 ± 15.7	Treatment 4 (33.3) Control 13 (44.8)	Treatment HTN: 3(25) DM: 3(25) Control HTN: 6(20.6) DM: 5(17.2)	Treatment Severe: 12(100) Control Severe: 29(100)	Umbilical cord	2M cells/kg	IV	1	none	The median time from onset of symptoms to enrollment was 13 days (11.5 days in the hUC-MSC group vs. 14 days in the control group)
Shi et al, 2021[53]	China	RCT	100 (65; 35)	Treatment 60.7 ± 9.1 Control 59.9 ± 7.7	Treatment 28 (43.1) Control 16 (45.7)	Treatment HTN: 17(26.2) DM: 12(18.5) COPD: 4(6.2) Control HTN: 10(28.5) DM: 5(14.28) COPD: 3(8.5)	Treatment Severe: 65(100) Control Severe: 35(100)	Umbilical cord	40M cells/ infusion	IV	3 (D0, D3, D6)	Antivirals, antibiotics, steroids	NR
Dilogo et al, 2021[88]	Indonesia	RCT	40 (20; 20)	Treatment Mean 51.8 ** Control Mean 54.3 **	Treatment 5(25) Control 5(25)	Treatment HTA 6(30) CAD 2(10) DM 8(40) HF/MI 1(5) Control HTA 10(50) CAD 3(15) DM 12(60) HF/MI 1(5)	Treatment Critically ill 20(100) Control Critically ill 20(100)	Umbilical cord	1M cells/kg	IV	1	Oseltamivir, azithromycin	Average on day 8 (ranged from days 2 to 30) of treatment in the ICU
Adas et al, 2021[89]	Turkey	RCT	30(10; 20)	56 **	11(36.6)		Moderate (0; 10), Critically ill (10;10)	Adipose tissue	3 × 10M cells/ kg	IV	3 (D0, D3, D6)	Piperacillin-tazobactam, favipiravir, dexamethasone, hydroxychloroquine	NR
Lanzoni et al, 2021[52]	Usa	RCT	24 (12; 12)	Treatment 58.5 ± 15.9 Control 58.8 ± 11.6	Treatment 7 (58.3) Control 4 (33.3)	Treatment HTN: 7(58.3) DM: 5(41.6) CAD: 1(8.3) Obesity: 11(91.6) Control HTN: 9(75) DM: 6(50) CAD: 3(25) Obesity: 5(41.6) Cancer: 1(8.3)	Treatment Severe: 12(100) Control Severe: 12(100)	Umbilical cord	100 ± 20M cells/infusion	IV	2 (D0, D3)	prophylactis heparin, therapeutic heparin, remdesivir, convalescent plasma, tocilizumab, hydrohychloroquine, alteplase	Days 0 and 3 of hospitalization

Table 1. Continued

Publication author, year	Country	Study type	Number of patients (treatment; Control)	Age, mean ± SD (years) or median (IQR)	Female, *N* (%)	Comorbidities, *N* (%)	COVID-19 severity *N* (%)	MSC source	Dosage [MSCs]	Route	Frequency, number of infusions (day of infusion)/cohort (*N*)	Concurrenttherapy	Timing for administration of MSCs
Leng et al, 2020[55]	China	NRIT	10 (7; 3)	Treatment 57 ± 7.4 Control 65 ± 16.4	Treatment 3(42.8) Control 3(100)	Treatment HTN: 1(14.2)	Treatment Critically ill:1 (14.2) Severe: 4(57.1) Moderate: 2(28.5) Control Severe: 3(100)	NR	1M cells/kg	IV	1	Standard treatments	NR
Meng et al, 2020[56]	China	NRIT	18 (9; 9)	Treatment 45.1 ± 10.1 Control 49.5 ± 10.6	Treatment 2(22.2) Control 5(55.5)	Treatment HTN: 2(22.2) DM: 1(11.1) FLD: 1(11.1) Control HTN: 1(11.1) BA: 1(11.1)	Treatment Severe: 4(44.4) Moderate:5(54.3) Control Severe: 4(44.4) Moderate: 5(54.3) [a]	Umbilical cord	30M cells/infusion	IV	3 (D0, D3, D6)	Antivirals, Steroids	
SINGH et al, 2020[58]	USA	NRIT	40(6; 34)	Treatment 56.3 ± 19.9 Control 66.8 ± 13.6	Treatment 1(16.6) Control 8(23.5)	Treatment HTN: 3(50) DM: 2(33.3) HL: 3(50) Obesity: 3(50) CKD: 1(16.6) AF: 16.6% Osteoporosis: 1(16.6) COPD/BA: 1(16.6) Control HTN: 18(52.9) DM: 8(23.5) Obesity: 6(17.6) COPD/BA: 7(20.5)	Treatment Critically ill: 6(100) Control Critically ill 34(100)	Heart tissue*	150M cells/infusion	IV	1 (D0)/A (N = 4) 2 (D0, D7)/B (N = 2)	hydroxychloroquine, tocilizumab	Days after ICU admission. patient 1: 12; patient 2: 5; Patient3: 7; Patient 4: 8; Patient 5: 3; Patient 6: 2
Ercelen et al, 2021[90]	Turkey	NRIT	210 (210; -)	59.1 ± 12	57(27.1)		Critically ill 99(47.1); Severe 111(52.8)	Umbilical cord	1-2 × 10M cells/kg	IV	1	None	NR
Xu et al, 2021[57]	China	NRIT	44 (26; 18)	Treatment 58.3 ± 12.4 Control 61.1 ± 11	Treatment 9 (50) Control 5(27.7)	NR; NR	Treatment Critically ill: 10(38.4) Severe: 16(61.5) Control Critically ill: 8(44.4) Severe: 10(55.5)	Menstrual blood	30M cells/infusion	IV	3 (D0, D2, D4)	None	Same day of diagnosis

Table 1. Continued

Publication author, year	Country	Study type	Number of patients (treatment; Control)	Age, mean ± SD (years) or median (IQR)	Female, *N* (%)	Comorbidities, *N* (%)	COVID-19 severity *N* (%)	MSC source	Dosage [MSCs]	Route	Frequency, number of infusions (day of infusion)/cohort (*N*)	Concurrenttherapy	Timing for administration of MSCs
Haberle et al, 2021[54]	Germany	NRIT	23 (5; 18)	Treatment 39 ± 32-50 Control 59 ± 54-79	Treatment 2(40) Control 5(27.7)	Treatment HTN: 1(20) Control HTN: 13(72.2) DM: 2(11.1) CAD: 2(11.1) COPD: 1(5.5) AF: 2(11.1) BA: 1(5.5) Smoking: 3(16.6)	Treatment Critically ill: 5(100) Control Critically ill: 18(100)	NR	1M cells/kg	IV	3 (NR)/A (N = 2) 2 (NR)/B (N = 3)	None	NR
Wei et al, 2021[91]	China	NRIT	25 (12; 13)	Treatment Median: 67(56-70) Control Median: 68(65-78)	Treatment 5(41.6) Control 8(61.5)	Treatment DM 1(8.3)	Treatment Moderate 5(41.7), Severe 6(50), Critically ill 1(8.3) Control Critically ill 2(10)	Umbilical cord	1M cells/kg	IV	1	Arbidol, lopinavir, Ritonavir, methylprednisolone	Day 18 (median) of admission
Chen et al, 2020[59]	China	UT	25 (25; -)	Median 70 ± 59-71	5(20)	NR	Severe: 25(100)	NR	1M cells/kg	IV	1 (D0)/A (n = 7) 2 (D0, D5)/B (N = 7) 3 (D0, D5, D10)/C (N = 11)	NONE	NR
Guo et al, 2020[61]	China	UT	31 (31; -)	Median 70 ± 62-71	6(19.3)	HTN: 13(41.9) COPD: 6(19.3) DM: 5(16.1) CAD: 5(16.1)	Critically ill: 8(25.9) Severe: 23(74.1)[a]	Umbilical cord	1M cells/kg	IV	1 (NR)/A (N = 11) 2 (NR)/B (N = 9) 3 (NR)/C (N = 11)	Oxygen, antivirals drugs, antibiotics, intravenous immunoglobulin, intravenous albumin, methylprednisolone	NR
Peng et al, 2020[66]	China	UT	1 (1; -)	66	1(100)	0(0)	Severe: 1(100)	Umbilical cord	1M cells/kg	IV	3 (D0, D3, D6)	Lopinavir/ritonavir, interferon-α, ribavirin, iv meropenem, methylprednisolone, and immunoglobulin	Days 27 and 28 since disease onset for convalescent plasma. Days 31, 34 and 37 for UC-MSCs since disease onset
Zhang et al, 2020[75]	China	UT	1 (1; -)	54	0(0)	DM: 1(100)	Critically ill: 1(100)	Wharton-Jelly	1M cells/kg	IV	1	Lopinavir/ritonavir, IFN-α inhalation, iv levofloxacin, tanreqing capsule, xuebijing, thymosin α1, methylprednisolone, immunoglobulin, potassium chloride, plasma exchange and regulated intestinal microflora of patient	Day 15 since disease onset

Table 1. Continued

Publication author, year	Country	Study type	Number of patients (treatment; Control)	Age, mean ± SD (years) or median (IQR)	Female, *N* (%)	Comorbidities, *N* (%)	COVID-19 severity *N* (%)	MSC source	Dosage [MSCs]	Route	Frequency, number of infusions (day of infusion)/cohort (*N*)	Concurrenttherapy	Timing for administration of MSCs
Sanchez-Guijo et al, 2020[68]	Spain	UT	13 (13; -)	60.3 ± 7.8	1(7.6)	HTN: 5(38.4) COPD: 2(15.3) Obesity: 2(15.3) DM: 1(7.6) HTD: 1(7.6) HBV: 1(7.6) Hypothyroidism: 1(7.6)	Critically ill: 13 (100)	Adipose tissue	0.98M cells/kg	IV	1 (D0)/A (N = 2) 2 (D0, D2)/C (N = 10) 3 (D0, D2, D4)/B (N = 1)	Dexchlorpheniramine corticosteroids, prophylactic, low molecular weight heparin. hydroxychloroquine and azithromycin, tocilizumab, Anakinra lopinavir/ritonavir	NR
Tang et al, 2020[69]	China	UT	2 (2; -)	54 ± 24	1(50)	HTN: 1(50) CAD: 1(50)	Severe: 2(100)	Menstrual blood	1M cells/kg	IV	3 (D0, D1, D3)	oseltamivir, arbidol hydrochloride; ribavirin, arbidol hydrochloride, cefoperazone-sulbactam, cefoperazone-sulbactam	Pt 1: Day 5, 6, 8 of hospitalization; Pt 2: Day 1, 2,4 of hospitalization
Zhu et al, 2020[73]	China	UT	1 (1; -)	48	0(0)	0(0)	Critically ill: 1(100)	Umbilical cord	1M cells/kg	IV	1	Antiviral; antibiotics; immunoglobulin; corticosteroids	Day 3 of hospitalization
Yilmaz et al, 2020[71]	Turkey	UT	1 (1; -)	51	0(0)	0(0)	Critically ill: 1(100)	Wharton-Jelly	3M cells/kg (1st -3rd infusions), 2M cells/kg (4th infusion)	IV (1-3 infusions) IV + Intrathecal (4 infusion)	4 (D0, D2, D5, D7)	Tocilizumab, steroids	Day 13 of hospitalization
Tao et al, 2020[70]	China	UT	1 (1; -)	72	0(0)	HTN: 1(100) DM: 1(100)	Critically ill: 1(100)	Umbilical cord	1.5M cells/kg	IV	5 (D0, D2, D4, D6, D8)	Antiviral therapy; IV antibiotics; antifungal therapy; glucocorticoids; iv immune globulin treatment	Day 23 of hospitalization
Zengin et al, 2020[72]	Turkey	UT	1 (1; -)	72	0(0)	HTN: 1(100) DM: 1(100) HL: 1(100)	Critically ill: 1(100)	Umbilical cord	0.7M cells/kg; 0.3M cells/kg	IV and Intratracheal	2 (D0, D5)	Oseltamivir, levofloxacine, piperacillin/tazobactam and vancomycin, Chloroquine and lopinavir/ritonavir, tocilizumab	Day 12 of hospitalization
Feng et al, 2020[60]	China	UT	16 (16; -)	61.7 ± 10	4(25)	HTN: 8(50) DM: 6(37.5) CKD: 3(18.7) Anemia: 1(6.25) BA: 1(6.25) HBV: 1(6.25)	Critically ill 7(43.7) Severe 9(56.3)	Umbilical cord	100M cells/infusion	IV	4 (D0, D2, D4, D6)	None	
Liang et al, 2020[64]	China	UT	1 (1; -)	65	1(100)	HTN: 1(100) DM: 1(100) Anemia: 1(100)	Critically ill: 1(100)	Umbilical cord	50M cells/infusion	IV	3 (D0, D3, D6)	antibiotics; antiviral; corticosteroid; Thymosin a1; Immunoglobulin	Day 13 of hospitalization
Rich et al, 2020[74]	Spain	UT	1 (1; -)	NR	NR	NR	Severe; 1(100)	Bone marrow	1M cells/kg	IV	1		Day 7 of hospitalization
Sahin et al, 2021[67]	Turkey	UT	1 (1; -)	33	1(100)	NR	Critically ill: 1(100)	NR	NR	IV	2 (D0, D3)		Case 1: day 3 of hospitalization; Case 2: day 7 of hospitalization

Table 1. Continued

Publication author, year	Country	Study type	Number of patients (treatment; Control)	Age, mean ± SD (years) or median (IQR)	Female, *N* (%)	Comorbidities, *N* (%)	COVID-19 severity *N* (%)	MSC source	Dosage [MSCs]	Route	Frequency, number of infusions (day of infusion)/cohort (*N*)	Concurrenttherapy	Timing for administration of MSCs
Lu et al, 2021[65]	China	UT	1 (1; -)	32	0(0)	0(0)	Severe: 1(100)	Menstrual blood	3000U (1st and 3rd infusion, 2000U (2nd infusion)	IV	3 (D0, D1, D3)	Immunoglobulin and antiviral, methylprednisolone and vaccination antiviral, antibiotic.	Days 11, 12, and 14 of hospitalization
Iglesias et al, 2021[63]	Mexico	UT	5 (5; -)	52.6 ± 13.5	1(20)	HTN: 1(20) DM: 2(40) HL: 1(20) Obesity: 3(60) Hypothyroidism: 1(20) PAD: 1(20) PF: 1(20)	Critically ill: 5(100)	Umbilical cord	1M cells/kg	IV	1	None	Pt 1: Day 27; Pt 2: Day 12; Pt 3: Day 22; Pt 4: Day 10; Pt 5: Day16 since disease onset
Hashemian et al, 2021[62]	Iran	UT	11 (11; -)	53.8 ± 10.3	3(27.2)	HTN: 3(27.2) DM: 4(36.3) Cardiomyopathy: 1(9.1) HD/CLL: 1(9.1)	Critically ill: 11(100)	Umbilical cord (6 pts) or Placenta (5 pts)	200M cells/ infusion	IV	3 (D0, D2, D4)	None	NR
Zhang et al, 2021[75]	China	UT	1 (1; -)	66	1(100)		Critically ill 1(100)	Umbilical cord	1M cells/kg	IV	5 (D0, D3, D31, D35, D38)	Tigecycline, polymyxin B, and voriconazole	Day 28 and 31 of hospitalization
Primorac et al, 2021[92]	Croatia	UT	1 (1; -)	50	0(0)		Severe 1(100)	Bone marrow	1 × 10M cells/ kg	IV	3 (D0, D3, D7)	Methylprednisolone, moxifloxacin, colistin, fosfomycin, linezolid	NR
Senegaglia et al, 2021[93]	Brazil	UT	1 (1; -)	51	NR	HTA 1 (100)	Severe 1(100)	Umbilical cord	0.5 × 10M cells/kg	IV	3 (D0, D2, D4)	Dexamethasone, enoxaparin, tocilizumab	Day 10 following positive Covid-19 PCR test
Saleh et al, 2021[94]	Iran	UT	5 (5; -)	50.8 ± 3.4	2(40)	HTA 1 (20), DM 1(20)	Severe 5(100)	Adipose tissue	150M cells/ infusion	IV	3 (D0, D3, D6)	Heparin, dexamethasone, hydrocortisone	NR
Sadeghi et al, 2021[95]	Iran	UT	10 (10; -)	46.8 ± 15.4	2(20)	HTN 2(20) CAD 1(10) DM 3(30) Hyperlipidemia 1(10)	Severe 10(100)	Umbilical cord	1 × 10M cells/ kg	IV	2 (D0, D3) 3 (D0, D3, D6)	Chlorphenamine hydrocortisone	Day 2-7 of hospitalization

[a]Criteria not well defined.
[*]Cardiosphere-derived cells (CDCs).
[**]SD not reported.
Abbreviations: RCT, randomized control trial; NRIT, non-randomized interventional trial; UT, uncontrolled trial; HTN, hypertension; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HBV, hepatitis B virus; HL, hyperlipidemia; HD, hodgkin's disease; CLL, chronic lymphocytic lymphoma; AF, atrial fibrillation; FLD, fatty liver disease; BA, bronchial asthma; CHF, congestive heart failure; HTD, hyperthyroidism; PAD, pulmonary artery disease; PF, pulmonary fibrosis; NA, not applicable; NR, not reported; F/U, follow-up; SD, standard deviation; IQR, interquartile range; D, Day

mellitus, and obesity were the most 3 common comorbidities (Table 1). The average follow-up duration is 42 days after the first infusion as reported in 30 studies ranging 7 to 196 days after the onset of treatment.

The overall risk of bias was deemed low for RCTs and high for comparable and single-arm observational studies (Supplementary Appendix Tables A2-A4). The sensitivity analysis that excluded a RCT with inadequate randomization[46] showed no significant changes in the results (Supplementary Appendix Table A6).

Intervention Characteristics

Allogeneic culture-expanded MSCs were used in all 34 studies (n = 525 patients), of which MSCs were derived from umbilical cord in 18 studies (n = 409 treated patients), Wharton-Jelly in 2 studies (n = 2), menstrual blood in 3 studies (n = 29), bone marrow in 2 studies (n = 2), adipose tissue in 3 studies (n = 28), heart tissue in 1 study (n = 6), combined placenta (n = 5), and umbilical cord (n = 6) in 1 study, and non-specified sources in 4 studies (n = 38). MSCs were administered via the systemic intravenous (IV) route in all 34 studies (n = 525 treated patients), whereas in 2 studies IV was combined with intratracheal infusion (n = 2). The dosage was either weight-adjusted ranging from 0.3 to 3 million cells per kilogram body weight (23 studies, n = 372), or a fixed dose of 30 million to 200 million MSCs (9 studies, n = 151). One study used 2000U and 3000U MSCs, with unit undefined.[67] One study did not report the dosage[69] and one study reported injectate volume but not number of cells. Frequency of the doses used are between 1 and 5 (Table 1). Patients in treatment groups received MSC cell therapy in addition to institutionally defined standard of care while patients in reference groups received institutionally defined standard of care only. Some studies administered concurrent therapy in addition to supportive care selected from antibiotics, remdesivir, convalescent plasma, anticoagulants, dexamethasone, and tocilizumab (Table 1).

Mortality

When compared with the control group, MSC cell therapy administration was associated with reduced mortality (RR = 0.54, 95% CI: 0.35-0.85, I^2 = 0.0%; 5 RCTs and 5 non-randomized comparative trials, 370 patients; Fig. 2). In all 34 studies including case series and case reports, 18 patients (10.5%) who received MSC cell therapy died.

Serious Adverse Events

MSC cell administration was associated with fewer SAEs compared with control group (IRR = 0.36, 95% CI: 0.140.90, I^2 = 0.0%; 3 RCTs and 2 non-randomized interventional trials, 219 patients; Fig. 3). Of all 34 studies that reported SAEs, a total of 50 SAEs were reported in 525 patients who received MSC cell therapy.

Adverse Events

No significant difference in AEs was found between MSC cell administration group and control group (IRR = 0.86, 95% CI: 0.53-1.38, I^2 = 32.6%; 3 RCTs and 2 non-randomized interventional trials, 219 patients; Fig. 4). Of all 26 studies that reported AEs, a total of 176 incidences of AEs were reported in 238 patients who received MSC cell therapy.

Pulmonary and Systemic Changes

Longitudinal assessments of PaO_2 to FiO_2 ratios before and after MSC cell therapy was reported in 22 patients with MSC cell therapy, of whom 18(81.8%) showed increased PaO_2/FiO_2, 4 (18.1%) patients showed decreased PaO_2/FiO_2 (Table 2).

Laboratory Findings in Patients

IL-6 levels were reported in 66 patients with MSC cell therapy, of whom 43 (65.1%) reported a decrease. WBC count was reported in 26 patients with MSC cell therapy, with an increase in 11 (42.3%). D-dimer was reported in 26 MSC cell therapy patients with a decrease in 15 (57.6%; Table 2).

Computed Tomographic Findings

Computed Tomographics of the lungs were reported in 91 patients with MSC cell therapy, of whom improvement was reported in 85 (93.4%) patients, and no improvement/change in 6 (6.6%) patients (Table 2).

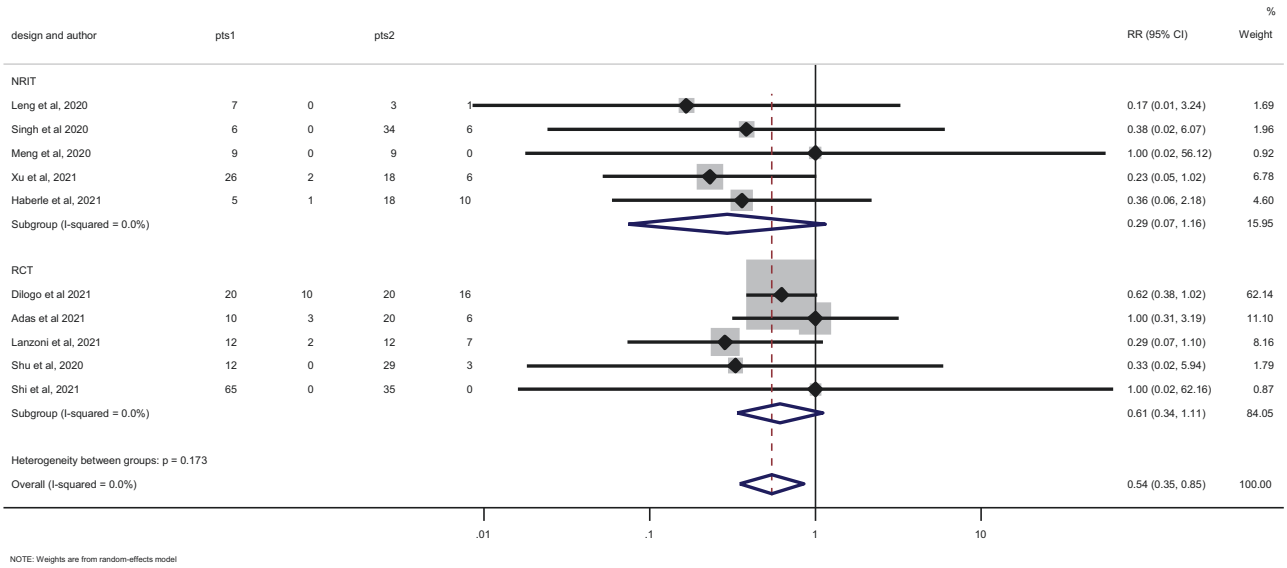

Figure 2. Pooled estimate of all-cause mortality.

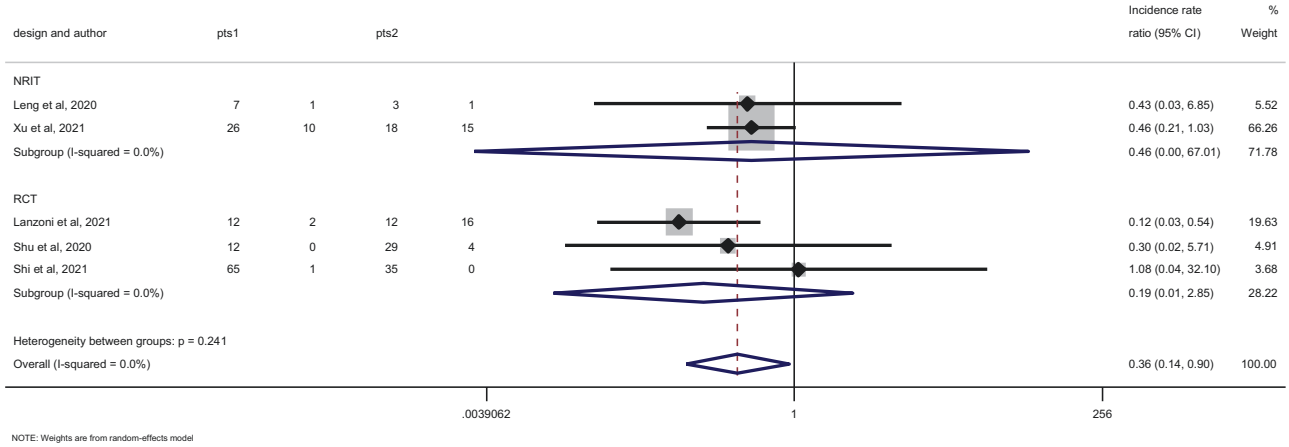

Figure 3. Pooled estimate of all-cause serious adverse events.

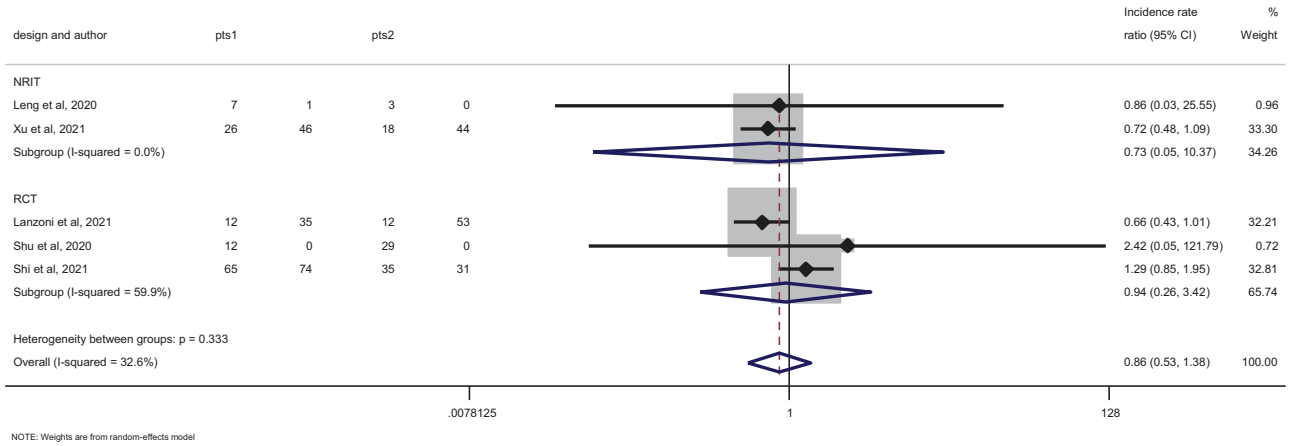

Figure 4. Pooled estimate of all-cause adverse event.

Discussion

This systematic review and meta-analysis evaluated 736 patients hospitalized for COVID-19. Of the 605 patients evaluated in 5 RCTs and 7 non-randomized interventional trials, MSC cell administration was associated with significant reduction of 46% in all-cause mortality risk. MSC cell therapy was also associated with significant reduction of SAE risk by 64%. There was no significant difference in the occurrence of mild AEs. Of all patients who have received MSC cell therapy, pulmonary function was reported in 22 patients, showing improvement in 18 patients and worsening in 4 patients. IL-6 level was reported in 64 patients, showing increase in 21patients and decrease in 43 patients. Lung CTs showed improvement in 85 of the 91 patients reported. Hospitalized COVID-19 patients are at significant risk of developing ARDS, multi-organ dysfunction syndrome, and acute respiratory failure that is associated with a poor prognosis. Those complications are thought to be the consequence of enhanced inflammation with inflammatory cytokine production and immune dysfunction triggered by SARS-CoV-2 infection.[78-80] MSC cell therapy has been an ongoing focus of investigation because it possesses a unique and safe immunomodulatory effect that has been hypothesized to downregulate and suppresses the inflammatory processes in COVID-19 patients, and potentially couple to pulmonary reparative and anti-viral responses.[24]

Safety is a critical issue for any new treatment, particularly in patients at high risk of death from the disease being managed. This analysis suggests a favorable safety profile with reduction of SAEs and no change in AEs in patients receiving MSC cell therapy. This safety profile is consistent with findings of other cell-based therapy trials targeting various pathologies.[81-84] It is unlikely that these findings were affected by age differences between the treated and untreated groups, since the baseline ages were comparable (59.2 years of age in therapy groups and 60.0 years in control groups); this is important because older age is associated with increased rates of mortality from COVID-19.[85,86]

Other outcomes examined included pulmonary function, clinical outcomes, and immune responses. Eighteen studies reported improvement of opacity in chest computed tomography within days of treatment. The improvement in pulmonary function and imaging findings also support further investigation of using MSC cell therapy for ARDS, especially in COVID-19-infected patients.

The findings from this meta-analysis also suggest beneficial effects of cell-based therapy on vital immunologic and inflammatory processes contributing to organ injury in

Table 2. Pulmonary, laboratory, and imaging outcomes.

Author, year	Pulmonary and systemic outcomes	Inflammatory biomarkers and leukocyte count	CT imaging	F/U (no. of days after first dose)
Shu et al, 2020[37]	Time of the oxygenation index to return to the normal range was faster in the MSC group, total 12 pts	Decreased IL-6, CRP in comparison to control; lymphocyte count return to normal faster after treatment in MSC group total 12 pts	Time for lung inflammation absorption was significantly shorter on CT imaging in the MSC group than in the control group.	28
Shi et al, 2021[45]	NR	No significant difference: IL-6 in 64 pts in therapy group in comparison to 35 pts in control group	Improvement in whole lung lesion volume from baseline to day 28 in MSC group (65 pts) compared with the control group (35 pts)	28
Dilogo et al, 2021[88]	NR	IL-10 increased in all pts in MSC group in comparison to 10 pts in control group; IL-6 decreased in MSC group in comparison to control group	NR	15
Adas et al, 2021[89]	NR	Serum ferritin increased from normal after treatment (mean). No change on WBC in 10 pts (mean). Decreased IL-6, CRP and PCT in 10 pts (mean). Increased lymphocyte count and D-dimer in 10 pts (mean).	NR	31 to 108
Lanzoni et al, 2021[44]	NR	IL-6 decreased in MSC group in comparison to control group (median)	NR	31
Leng et al, 2020[47]	NR	Lymphocyte and WBC count increased in 1 pt, CRP decreased in 1 pt after treatment.	Improved in 1 pt of MSC group	14
Meng et al, 2020[48]	PaO_2/FiO_2 increased in 3 pts and decreased in 1 pt among MSC group	IL-6 decreased in 4 pts. CRP increased in 2 pts and decreased in 7 pts. D-dimer increased in 8 pts, decreased in 1 pt	Improved in 1 representative pt	28
Singh et al, 2020[50]	NR	WBC, IL-6 decreased in 4 pts and increased in 2 pts. Lymphocyte count increased in 3 pts and decreased in 3 pts. CRP increased in 1 pt and decreased in 5 pts	NR	5 to 18
Ercelen et al, 2021[90]	PaO_2/FiO_2 increased in therapy group	NR	NR	14 to 21
Xu et al, 2021[49]	PaO_2/FiO_2 increased in 26 pts (mean)	No significant differences in CRP and IL-6 after treatment in 26 pts (mean)	Improved in 17 pts, no change in 3 pts among 20 pts of MSC group	30
Haberle et al, 2021[46]	PaO_2/FiO_2 increased in therapy group (5 pts)	Increased lymphocyte, decreased WBC count, CRP, IL-6, and no change of D-dimer in MSC group (5 pts)	NR	NR
Wei et al 2021[91]	PaO_2/FiO_2 increased in 8 pts	Increased WBC and lymphocyte count in 12 pts (median). Decreased IL-6 and CRP in 12 pts (median). No change on PCT in 12 pts (median).	Improved in 11 pts	60
Chen et al, 2020[51]	NR	No change of IL-6, WBC, CRP, PCT in 25 pts (mean)	Improved in 16 pts[#]	NR
Guo et al, 2020[53]	PaO_2/FiO_2 increased in 31 pts (median)	No change of WBC count in 31 pts (mean). Elevated lymphocyte count and decreased CRP, PCT, IL-6, D-dimer in 31 pts (median)	NR	NR
Peng et al, 2020[58]	Oxygenation index increased in 1 pt	Decreased lymphocyte count, CRP, and IL-6 in 1 pt	Improved in 1 pt	10
Zhang et al, 2020[67]	NR	Decreased CRP, IL-6, and increased in lymphocyte count in 1 pt	Improved in 1 pt	7
Sanchez-Guijo et al, 2020[60]	NR	Lymphocyte count increased in 5 pts among 6 pts. Decreased CRP in 8 pts among 9 pts and D-dimer in 5 pts among 8 pts	NR	4 to 28
Tang et al, 2020[61]	PaO_2/FiO_2 increased in 2 pts	WBC, IL-6 increased both in 1 pt and decreased in another 1 pt. Increased lymphocyte count in 2 pts, decreased CRP in 2 pts	NR	12 & 14

Table 2. Continued

Author, year	Pulmonary and systemic outcomes	Inflammatory biomarkers and leukocyte count	CT imaging	F/U (no. of days after first dose)
Zhu et al, 2020[65]	NR	Decreased CRP, PCT, and D-dimer level in 1 pt. WBC and lymphocyte count increased in 1 pt	Improved in 1 pt	14
Yilmaz R et al, 2020[63]	NR, ejection fraction improved from 25% to 60%	Decreased CRP, PCT, D-dimer, and increase in lymphocyte, WBC count in 1 pt	Improved in 1 pt	26
Tao et al, 2020[62]	PaO_2/FiO_2 decreased in 1 pt	Decreased D-dimer and CRP in 1 pt. Increased lymphocyte, WBC count and PCT in 1 pt	No improvement in 1 pt	78
Zengin et al, 2020[64]	NR	Decreased CRP in 1 pt	Improved in 1 pt	60
Feng et al, 2020[52]	Oxygenation index increased in 8 pts (mean)	IL-6, CRP are in normal range after treatment. Increased lymphocyte and decrease WBC total count 16 pts (mean)	Improved in 16 pts	28
Liang et al, 2020[56]	NR	Decreased CRP, PCT, D-dimer, WBC, and increased lymphocyte count in 1 pt	Improved in 1 pt	17
Rich et al, 2020[66]	NR	Decreased CRP and D-dimer in 1 pt	Improved in 1 pt	32
Sahin et al, 2021[59]	NR	NR	NR	NR
Lu et al, 2021[57]	NR	Decreased WBC and IL-6 in 1 pt	Improved in 1 pt	196
Iglesias et al, 2021[55]	PaO_2/FiO_2 increased in 3 pts decreased in 2 pts	D-dimer increased in 3 pts and decreased in 2 patients. Lymphocyte count, PCT increased in 2 patients, and decreased in 3 patients. CRP decreased in 5 pts	Improved in 3 pts	21
Hashemian et al, 2021[54]	NR	IL-6 decreased in 5 pts and CRP decreased in 6 pts	Improved in 2 pts, no improvement in 1 pt	60
Zhang et al, 2021[96]	NR	NR	Improved in 1 pt	133
Primorac et al, 2021[92]	PaO_2/FiO_2 increased in 1 pt	Decreased WBC, CRP and D-dimer in 1 pt after treatment. No change on PCT in 1 pt	Improved in 1 pt	40
Senegaglia et al, 2021[93]	PaO_2/FiO_2 increased in 1 pt	Decreased CRP and D-dimer in 1 pt.	Improved in 1 pt	120
Saleh et al, 2021[94]	NR	WBC increased in 4 pts and decreased in 1 pt. Lymphocyte count increased in 3 pts and decreased in 1 pt. Decreased CRP in all pts in therapy group (5 pts). No change on PCT in 2 pts, increased in 1 pt and decreased in 2 pts	Improved in 4 pt and no improvement in 1 pt	28
Sadeghi et al, 2021[95]	NR	Decreased IL-6 and CRP in 6 pts	Improved in 3 pt	5 to 14

*Criteria not well defined.
Abbreviations: CRP, C-reaction protein; IL-6, interleukin-6; PCT, procalcitonin; WBC, white blood cell; NR, not reported; NA, not applicable; pts, patients.

SARS-CoV-2-infected patients. Seventeen of the studies reported reduction of inflammatory biomarkers after MSC cell therapy. MSC treatment appeared to mitigate the effects of cytokine release syndrome, a pathophysiological process in ARDS, and multi-organ dysfunction syndrome in severe cases of COVID-19. These findings suggest a potential mechanism of action and are consistent with previous results of preclinical and clinical studies for other diseases.[33]

Several important conclusions emerged from this review of the outcomes of MSC cell therapy for COVID-19. First, these data confirm previous findings of the low risks associated with MSC cell therapy. Our findings, combined with comparable studies treating various conditions provide strong support for MSC cell therapy having a favorable safety profile, even in this seriously ill population.[82-84,87] Second, MSC cell therapy was associated with markedly reduced mortality and SAEs in hospitalized COVID-19 patients. Among the patients included in this study, the risk of death in the group treated with MSC cell therapy was lowered by 46%. Third, although reported in limited studies, the biomarker findings support the hypothesis that MSC cell therapy reduces pathophysiologic and immunologic responses that contribute to death with SARS-CoV-2 infection.

To date, registry searches indicate that there are at least 62 clinical trials investigating the potential benefits of cell-based interventions in COVID-19 patients unresponsive to other available treatments. Nevertheless, additional larger trials are needed to further explore this promising therapeutic modality, given the limited success of other approaches to effectively manage severe cases of COVID-19. Other questions needing further study to be resolved include the best source of cells or cell products, especially for different stages of disease; the optimal dose and frequency of administration; whether the cells should be expanded in culture and, if so, for how long; and whether preconditioning the cells would improve their efficacy. The results seen in this meta-analysis also suggest that MSC cell therapy may reduce the time to recovery and long-term complications from SARS-CoV-2 infection. Additional studies of cell-therapy in earlier phases of disease progression also are needed, especially to determine their potential ability to reduce the need for ICU admission, mechanical ventilation, and development of chronic inflammatory diseases.

Limitations

Although this analysis found a reduction in mortality associated with MSC cell therapy, it is important to note that the conclusion was derived by comparing MSC cell therapy to the institutionally defined standard of care in the early phase of the COVID-19 pandemic. More recently, refinements of therapeutic approaches and vaccinations have considerably reduced mortality. The benefit of MSC cell therapy may be reduced or absent in patients not responding to these more contemporary treatments.

Conclusions

This systematic meta-analysis demonstrates an association of MSC cell therapy with improvements in clinical outcomes, laboratory findings, and lung imaging in patients hospitalized for COVID-19, and a low incidence of adverse events related to treatment. The putative mechanisms of MSC cell therapy suggested by these and other clinical and pre-clinical studies, include beneficial modulation of inflammatory immune responses. While outcomes have improved with the changes in standard of care and vaccinations, patients continue to die from severe COVID-19, and new variants are emerging as the pandemic progresses. These findings support the urgent need for large, randomized double-blinded controlled trials to assess the safety and efficacy of MSC cell therapy for the treatment and prevention of severe COVID-19. Appropriately designed studies would also allow identification of mechanisms that may potentially contribute to accelerate translation of cell-based therapies to other acute and chronic inflammatory diseases.

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Conflict of Interest

W. Q., J. M. H., J. K., C. R. reported roles as principal investigators of MSC trials. **J.M.H.** reported having a patent for cardiac cell-based therapy, holds equity in Vestion, Inc., and maintains a professional relationship with Vestion, Inc. as a consultant and member of the Board of Directors and Scientific Advisory Board. Vestion Inc. did not play a role in the design, conduct, or funding of the study; **J.M.H.** is also the Chief Scientific Officer, a compensated consultant and advisory board member, for Longeveron and holds equity in Longeveron; **J.M.H.** is the coinventor of intellectual property licensed to Longeveron. Longeveron did not play a role in the design, conduct, or funding of the study. The University of Miami is an equity owner in Longeveron Inc., which has licensed intellectual property from the University of Miami. **J.M.H.** declared inventor or patent holder and research funding from Longeveron, Heart Genomics; advisory role and research funding with Vestion; research funding from NHLBI. **J.K.** declared intellectual property rights with IDF, hCT-MSC for treatment of ASD, HIE, which were licensed to CryoCell Int'l by Duke University; NMDP Scientific Advisor; Celularity SAB; research funding from the Marcus Foundation, NIH, HRSA; leadership position with Istari—CMO (spouse). **G.B.** consults for SciNeuro and Vida Ventures, had consulted for AbbVie, E-Scape, and Eisai, and receives funding from NIH and Cure Alzheimer's Fund. He serves as a Co-Editor-in-Chief for Molecular Neurodegeneration. The other authors indicated no potential conflicts of interest. **K.M.** is a consultant in RESTEM.

Authors Contribution

W.Q., Z.W.: conceptualization, formal analysis, methodology, writing original draft, writing review and editing, final approval of the manuscript. E.E.-C., D.Y., A.B.S., C.R., C.J.P., J.K.: conceptualization, writing original draft, writing review and editing, final approval of the manuscript. G.B., J.G.A., E.K., A.I.C., J.M.H., J.M.P., J.M.M., R.L.R., S.S., E.M.R., K.M., F.P.S.: conceptualization, writing review and editing, final approval of the manuscript. T.N.: conceptualization, formal analysis, writing review and editing, final approval of the manuscript. R.V.D.: writing review and editing, final approval of the manuscript.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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