CONCISE REVIEW

Cell-based therapy to reduce mortality from COVID-19: Systematic review and meta-analysis of human studies on acute respiratory distress syndrome

Wenchun Qu1,2, Zhen Wang3,4, Joshua M. Hare5, Guojun Bu2,6, Jorge M. Mallea7, Jorge M. Pascual7, Arnold I. Caplan8, Joanne Kurtzberg9, Abba C. Zubair2,10, Eva Kubrova11, Erica Engelberg-Cook1, Tarek Nayfeh3,4, Vishal P. Shah12, James C. Hill12, Michael E. Wolf12, Larry J. Prokop13, M. Hassan Murad3,4,12, Fred P. Sanfilippo14

1Department of Pain Medicine, Mayo Clinic, Jacksonville, Florida
2Center for Regenerative Medicine, Mayo Clinic, Jacksonville, Florida
3Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota
4Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota
5Interdisciplinary Stem Cell Institute and Cardiology Division, Department of Medicine, University of Miami, Miller School of Medicine, Miami, Florida
6Department of Neuroscience, Mayo Clinic, Jacksonville, Florida
7Division of Pulmonary, Allergy and Sleep Medicine, Department of Medicine, Mayo Clinic, Jacksonville, Florida
8Skeletal Research Center, Biology Department, Case Western Reserve University, Cleveland, Ohio
9Marcus Center for Cellular Cures, Duke University Medical Center, Durham, North Carolina
10Transfusion Medicine and Stem Cell Therapy, Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida
11Department of Physical Medicine and Rehabilitation, Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

Abstract

Severe cases of COVID-19 infection, often leading to death, have been associated with variants of acute respiratory distress syndrome (ARDS). Cell therapy with mesenchymal stromal cells (MSCs) is a potential treatment for COVID-19 ARDS based on preclinical and clinical studies supporting the concept that MSCs modulate the inflammatory and remodeling processes and restore alveolo-capillary barriers. The authors performed a systematic literature review and random-effects meta-analysis to determine the potential value of MSC therapy for treating COVID-19-infected patients with ARDS. Publications in all languages from 1990 to March 31, 2020 were reviewed, yielding 2691 studies, of which nine were included. MSCs were intravenously or intratracheally administered in 117 participants, who were followed for 14 days to 5 years. All MSCs were allogeneic from bone marrow, umbilical cord, menstrual blood, adipose tissue, or unreported sources. Combined mortality showed a favorable trend but did not reach statistical significance. No related serious adverse events were reported and mild adverse events resolved spontaneously. A trend was found of improved radiographic findings, pulmonary function (lung compliance, tidal volumes, PaO2/FiO2 ratio, alveolo-capillary injury), and inflammatory biomarker levels. No comparisons were made between MSCs of different sources.

KEYWORDS
acute respiratory distress syndrome, COVID-19, mesenchymal stromal cells, mortality, systematic review

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. © 2020 The Authors. STEM CELLS TRANSLATIONAL MEDICINE published by Wiley Periodicals, Inc. on behalf of AlphaMed Press
INTRODUCTION

As a common enveloped RNA virus that crosses species, the coronavirus has become a source of highly lethal infections in the 21st century, including Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and the current pandemic with COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2). COVID-19 has been associated with an intensive care unit (ICU) admission rate of 5% of proven infections and an overall mortality rate in the range of 0.5% to 7%. Among patients who require hospitalization, mortality may be approximately 5% to 15%. Current treatment for patients with acute lung injuries is supportive, but with a high case fatality rate of 22% to as high as 88% for ICU patients. Importantly, age represents a major risk factor for mortality. New treatment modalities are needed to save lives by addressing the underlying pathophysiological processes that prevent oxygen exchange and destruction of the alveoli.

Similar to prior findings in SARS and MERS, COVID-19/SARS-CoV-2 in severe cases leads to fatal acute respiratory distress syndrome (ARDS), associated with monocyte and macrophage infiltration, diffuse alveolar damage, and cellular fibromyxoid exudates with mortality reported as high as 52.4%. The respiratory distress peaks at 7 to 10 days with manifestations of immune dysregulation, including cytokine release syndrome with elevation of cytokine levels (IL-6, IL-8, IL-1, IL2R, IL-10, and TNF-α), lymphopenia (in CD4+ and CD8+ T cells), and decreases in IFN-γ expression in CD4+ T cells. The inverse correlation between cytokine storm with lower CD4+ and CD8+ counts suggests that the cytokine response may dampen adaptive immunity against COVID-19 infection, which is associated with atrophy of the secondary lymphoid tissues. Anti-inflammatory treatment has been proposed but challenged with the dilemma of balancing the risk of secondary infection.

Mesenchymal stromal cells (MSCs, also known as mesenchymal stem cells and medicinal signaling cells) are characterized by the presence of cell surface markers—CD44, CD90, CD105—and the absence of hematopoietic markers—CD34, CD45—as well as HLA-DR. MSCs, which can be identified in diverse tissues, are most commonly sourced from bone marrow, adipose tissue, or umbilical cord. For translational research, MSCs are categorized into different generations according to their preparation strategy as minimally manipulated (G1), culture-expanded (G2), lineage-induced (G3), or genetically modified (G4). MSCs have been studied as a promising candidate to treat certain inflammatory conditions and immunologic diseases based upon their well-characterized immunomodulatory effects, especially in the treatment of graft-vs-host disease, where MSC therapy was found to substantially improve complete response and overall survival. The immunomodulatory activities are thought to include (a) inhibition of the proliferation and function of T cells, B cells, dendritic cells, and natural killer cells; (b) monocyte polarization to anti-inflammatory M2 macrophages; and (c) production of IL-10 and decreased production of TNF-α and IL-12. In addition, MSCs have powerful antifibrotic effects and may alleviate lung fibrosis.

An urgent question is whether large-scale clinical trials and compassionate use of MSC therapy should be instituted to treat COVID-19-induced ARDS. To address this question, we systematically reviewed the available literature on safety, efficacy, and cytokine responses to MSC therapies in patients with ARDS.

METHODS

The study protocol was finalized at the beginning of the project, which defined objectives, search strategy, inclusion/exclusion criteria, data extraction, outcomes of interest, and analytical approaches.
2.1 | Search strategy

A comprehensive search of databases from 1990 to March 31, 2020, in any language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and ClinicalTrials.gov. The search strategy was designed and conducted by a medical reference librarian with input from the investigators. Controlled vocabulary supplemented with keywords was used to search for cell-based therapy for COVID-19 pneumonia. The actual strategy, listing all search terms, is available in the Appendices.

2.2 | Eligibility criteria

We included randomized controlled trials (RCTs), observational studies, case reports, and case series that evaluated safety and/or efficacy of stem cells administered to adult patients with a diagnosis of COVID-19 pneumonia or ARDS from any cause. MSCs that were culture-expanded or minimally manipulated were included. We included studies regardless of language of publication. Studies were excluded if they did not report original data (eg, clinical reviews, editorials, letters, or erratum).

2.3 | Outcome measures

The primary outcome was safety based on the frequency of serious adverse events (SAEs), adverse events (AEs), and if they were related to the treatment with MSCs.

Other outcomes of interest were clinical and laboratory findings, including mortality, level of oxygenation, lymphopenia, PaO₂/FiO₂ ratio, FEV1, FVC, FEV1/FVC, FEF50%, ventilator-free days, ICU-free days, organ failure-free days, inflammatory markers including IL-1, IL-6, IL-8, RAGE, TNF-α, and CRP, angiotensin II, IL-10. Radiographic and computed tomographic (CT) findings were also included.

FIGURE 1  PRISMA 2009 flow diagram
| Author          | Country                  | Study type | Total, n | Mean age(y) | Comorbidities                          | Baseline pulmonary function | Baseline general | F/U | ARDS cause        | ARDS severity |
|-----------------|--------------------------|------------|----------|-------------|----------------------------------------|-----------------------------|------------------|-----|------------------|---------------|
| Leng et al      | China                    | Phase I    | 10 (7; 3)| 57; 65      | HT (1); NR                             | Sat. 92% (0.02) SOB 2.29 (scale 1-3, SD 0.95); Sat 92% (0.02) SOB 2 (scale 1-3, SD 1) | Temp. 38.48 C (0.46); Temp. 37.53 C (1.46) | 14D   | COVID-19         | NR            |
| Wilson et al    | United States            | Phase I    | 9 (9; -) | NR; NA      | NR; NA                                | Tidal vol. 6.2 (0.51) mL/kg PBW, PP 25.125 (9.79) cm H₂O, PEEP 10.22 (1.58) cm H₂O, PaO₂/FiO₂ 141.88 (33.90) mmHg, LIS 287 (0.40); | APACHE III 108.1 (24.4) | 6M    | Pneumonia, aspiration | Moderate     |
| Zheng et al     | China                    | Phase I RCT| 12 (6; 6)| 66.7; 69.8  | HT (3), CAD (1), neurologic disease (5), COPD (1), DM2 (2); HT (1), CAD (1), neurologic disease (3), COPD (0), DM (1) | PaO₂/FiO₂ 1224 (42.0), RR 30.7 (3.3); PaO₂/FiO₂ 1035 (32.2), RR 34 (6.2) | APACHE II 27.2 (6.4), pH 7.42 (0.08); APACHE III 23.0 (5.1), pH 7.36 (0.24) | 28D   | Pneumonia, aspiration | NR            |
| Bellingan et al | United Kingdom, United States | Phase I/II | 36 (26; 10)| 51; 59     | NR; NR                                | PaO₂/FiO₂ 173 mmHg; PaO₂/FiO₂ 128 mmHg | SOFA scores 10.9 (2.2), vasopressor support 45%; SOFA 12.2 (4.2), vasopressor support 30% | 28D   | NR               | Moderate-severe |
| Matthay et al   | United States            | Phase II RCT| 60 (40; 20)| 55; 55     | NR; NR                                | MV (l/min) 11.1 (3.2), RR 27.8 (6.60), TV (cm H₂O) 6.3 (0.9), MAP (cm H₂O) 17.8 (4.9), PAP (cm H₂O) 26.4 (5.7), PEEP cm H₂O 12.4 (3.7), driving pressure (cm H₂O) 140 (4.1), PaO₂/FiO₂ kPa 18.1 (4.3), oxygenation index (kPa) 98.7 (78.1-121.3), LIS 3.1 (0.4); MV (l/min) 9.6 (2.4), RR 24.5 (6.3), TV (cm H₂O) 6.1 (0.7), MAP (cm H₂O) 16.4 (3.6), PAP (cm H₂O) 23.7 (5.1), PEEP (cm H₂O) 10.8 (2.6), driving pressure (cm H₂O) 12.5 (4.3), PaO₂/FiO₂ kPa 19.1 (5.2), oxygenation index (kPa) 95.6 (71.6-113.8), LIS 3.0 (0.5) | SOFA 8.1 (3.3), APACHE III 104 (31); SOFA 6.9 (2.7), APACHE III 89 (33) | 12M   | Sepsis, pneumonia, aspiration | Moderate-severe |
| Yip et al       | Taiwan                   | Phase I dose escalation | 9 (9; -)| 54; -       | HT (33.3%), DM-2 (33.3%) dyslipidemia (22.2%), CHF/D (55.6%), chronic liver dis. (22.2%), heart failure (11.1%), AK; N/A | PaO₂/FiO₂ 108; NA | RR 24; Sepsis or multiorgan dysfunction 67%, dysfunctional organ # 3.1; fulminating myocarditis 22%; NA | NR               | Pneumonia + other | Moderate-severe |
| Chen et al      | China                    | Phase I/II non randomized | 61 (17; 44)| 62.8; 61.6 | HT (58.8%), CAD (9%), COPD (9%), DM2 (29.4%), liver disease (5%), renal failure (9%); HT (52.3%), CAD (18.2%), COPD (2.3%), DM2 (15.9%), liver disease (23.9%), renal failure (22.7%) | Mech. ventilation 14 (82.4%), ECMO 8 (47.1%); Mech. ventilation 31 (70.5%), ECMO 14 (31.81%) | ALSS 13 (76.5%); CRRT 12 (70.6%); ALSS 18 (40.9%), CRRT 16 (36.4%) | 5Y (4 pts), 12 m.o. | H7N9 | NR               |
2.4 | Study selection process

From all citations received through the extensive literature search, duplicate studies were removed. Titles and abstracts were screened for inclusion by pairs of independent reviewers using DistillerSR (Evidence Partners, Ottawa, Canada) (E. K., E. E.-C., V. P. S., J. C. H., M. E. W.). Relevant abstracts were recorded and full text articles were retrieved and screened by the same pairs of independent reviewers. Disagreements were resolved by a third independent reviewer (W. Q.) (Figure 1).

2.5 | Data collection

A standardized data extraction form was developed and piloted. We extracted publication characteristics, study population, intervention and comparison details, and outcomes measures.

2.6 | Risk of bias/certainty in evidence

For RCTs, we used the Cochrane risk of bias tool to evaluate bias from sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. For observational studies, case series, and case reports, we used the Newcastle-Ottawa Scale to evaluate representativeness of study population, ascertainment of exposure, comparability between groups (if applicable), outcome data source, and blinding of outcome assessment (Appendix 1, Tables 1 and 2). We used the GRADE approach (Grading of recommendations, development assessment and Evaluation) to rate certainty in the effect of MSC on mortality.29

2.7 | Statistical analysis

We conducted meta-analysis to quantitatively summarize study findings based on the similarities of PICOTS (patient, intervention, control, outcome, timing, setting) presented by the studies. Mortality was the only outcome deemed to be appropriate for meta-analysis. The DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction30 was used to pool odds ratio (OR) from the included studies. We used I2 indicator to evaluate heterogeneity between studies. Subgroup analyses were conducted based on study design (RCTs vs observational studies). We were unable to evaluate publication bias due to the small number of available studies. All statistical analyses were conducted using Stata version 16.1 (StataCorp, LLC, College Station, Texas).

3 | RESULTS

The literature search identified 2691 unique citations. Abstract and full-text screening identified nine studies with 200 patients to be
| Author          | MSCs source | Donor n (gender) | Surface markers                                                                 | Passage | Culture media                                                                 | MSC dose per kg | Viability | Frequency | Route of delivery | Control       |
|-----------------|-------------|------------------|--------------------------------------------------------------------------------|---------|--------------------------------------------------------------------------------|-----------------|-----------|-----------|-------------------|---------------|
| Chang et al     | Umbilical cord blood | 1 (NR)           | Positive CD29, CD44, CD73, CD105, CD166, and negative CD34, CD45, CD14, and HLA-DR | 6       | NR                                                                               | 1 × 10⁵          | NR        | 1         | Intratracheal     | No control group |
| Simonson et al  | Bone marrow  | 1 (M)            | Positive CD73, CD90, CD105, HLA-ABC, and negative CD14, CD31, CD34,CD45, and HLA-DR | NR      | DMEM-low glucose supplemented with lysed human platelets                           | 2 × 10⁶          | 95%       | 1         | Central venous catheter | No control group |
| Yip et al       | Umbilical cord, Wharton’s jelly | NR              | NR                                                                               | NR      | NR                                                                               | 1.0 × 10⁶, 5.0 × 10⁶, 1.0 × 10⁷ | NR        | 1         | IV                 | No control group |
| Leng et al      | NR          | NR               | NR                                                                               | NR      | NR                                                                               | 1 × 10⁶          | NR        | 1         | IV                | NR            |
| Wilson et al    | Bone marrow  | 1 (M)            | NR                                                                               | NR      | NR                                                                               | 1 × 10⁶, 5 × 10⁶, 10 × 10⁶ | 50%-63% (mean 56%) | 1         | IV                 | No control group |
| Zheng et al     | Adipose tissue | 1 (F)            | CD73, CD90, CD105, CD34, CD45, HLA-DR analyzed                                  | Max4    | DMEM-low glucose + penicillin, streptomycin, 2% FBS, EGF, and FGF                 | 1 × 10⁶          | NR        | 1         | IV                | 100 mL normal saline |
| Chen et al      | Menstrual blood | 1                | NR                                                                               | NR      | NR                                                                               | Total dose: 100 mL | NR        | 3 (9 pts) | IV                | NR            |
| Bellingan et al | Bone marrow  | NR               | NR                                                                               | NR      | NR                                                                               | Total dose: 300 × 10⁶ (3 pts); Total dose: 900 × 10⁶ (23 pts) | NR        | 1         | IV                | NR            |
| Matthay et al   | Bone Marrow  | 3 (1 F, 2 M)     | CD105, CD73, CD90, CD45, CD34, CD14, CD19, and HLA-DR tested                    | NR      | NR                                                                               | 10 × 10⁶         | ≥70%      | 1         | IV                | Plasmalyte A, 100 mL |

Abbreviations: DMEM, Dulbecco’s modified Eagle’s medium; EGF, epidermal growth factor; F, female; FBS, fetal bovine serum; FGF, fibroblast growth factor; IV, intravenous; M, male; MSCs, mesenchymal stem cells; NA, not applicable; NR, not reported; pts, patients.

All MSCs were allogeneic and culture-expanded.
3.1 Study characteristics

Of the nine studies, there were four phase I clinical trials, three phase I/II or phase II clinical trials, one case report, and one case series. Five were comparative studies with control groups, including three RCTs. All nine studies reported SAEs, AEs, mortality, and pulmonary function outcomes (n = 200). Six studies evaluated inflammatory markers (n = 98). A total of 117 patients received MSC therapy, while 83 participated as controls (Table 1). The risk of bias of included randomized trials was high due to unclear random sequence generation and allocation concealment procedures.

3.2 Patient characteristics

The studies were from six countries and regions, including China (n = 3),20,22,26 the United States (n = 2),21,24 United States/United Kingdom (n = 1),23 Sweden (n = 1),28 Taiwan (n = 1),75 and South Korea (n = 1).27 The average age of study participants was 51 to 67 years for the MSC groups and 55 to 70 years for the control groups in the comparative studies. Baseline PaO2/FiO2 was in a range of 100 to 200 in six studies21–25,27 and not reported in two studies in which all patients were on ventilator or extracorporeal membrane oxygenation (ECMO) support.26,28 Baseline Acute Physiology and Chronic Health Evaluation (APACHE) scores were between 23 and 27 in one study,22 averaged 108 in one study,21 and 104 in the MSC group vs 89 in the control group in one study24 (Table 1).

3.3 Intervention characteristics

Culture-expanded allogeneic MSCs were used in all nine included studies. Allogeneic bone marrow-derived MSCs were used in four studies,21,23,24,26 adipose-derived MSCs in one study,22 menstrual blood MSCs in one study,26 umbilical cord Wharton’s jelly-derived MSCs in one study,25 and umbilical cord blood MSCs in one study.27 One study did not report the tissue origin of the MSCs and described their cell-product as commercially obtained20 (Table 2).

The MSCs used in the included studies were each from a different manufacturing facility. Characterization was reported in some studies, with a significant variability of detail. MSCs from one donor were used in five studies,22,24,26,28 from three donors in one study,24 and not specified in three studies.20,23,25 Characterization of MSCs was reported in four studies, with most of the following markers: positive for CD29, CD44, CD73, CD90, CD105, CD166, HLA-ABC, and negative for CD31, CD34, CD45, CD14, and HLA-DR.22,24,25,28 Viability was reported to be 50% to 95% (Table 2).21,24,28 In addition, MSCs were found to be ACE2- or TMPRSS2-negative, indicating that these MSCs were unlikely to become infected by COVID-19.20
MSCs were administered intratracheally \((n = 1)\), intravenously \((n = 115)\), or through a central venous catheter \((n = 1)\). MSC infusion frequency ranged from a single administration in eight studies \((n = 1)\) to 3 to 4 administrations in one study \((n = 1)\). Dosing of the stem cells ranged from 1 to 10 million cells per kilogram of body weight or a uniform dose of 300 or 900 million cells. In one study, dosing was not specified \((n = 1)\) (Table 2). Patients in control groups were treated with placebo, including saline or Plasmalyte A, or standard of care.

### 3.4 Primary outcome: safety

#### 3.4.1 Serious adverse events

There were no reported treatment-related SAEs. One patient experienced an unexpected SAE described as multiple organ embolic infarcts, which was thought to be present before the MSC treatment as noted on a previously performed magnetic resonance imaging scan. Across all studies, none of the 66 deaths were categorized as related to the MSC therapy (Table 4).

### 3.4.2 Adverse events

Mild AEs were reported. One patient experienced a grade I allergic reaction. In another study, patients experienced diarrhea in both treatment groups. Yip et al reported transient desaturation, dyspnea, and hypotension shortly after cell infusion in two patients, and one patient had a generalized skin rash that persisted for 2 days. All reported AEs resolved spontaneously (Table 4).

### 3.5 Secondary outcome: efficacy

#### 3.5.1 Mortality

Mortality was reported in all studies. Comparisons between treatment and control groups were made in five studies \((n = 179)\). In four of five studies, there was a trend toward a decreased mortality rate in the MSC treatment group. In the one study that showed an increased mortality rate, the authors noted that at baseline the MSC treatment group had greater severity of illness as evidenced by higher baseline APACHE and sequential organ failure assessment (SOFA).
The overall mortality rates were 25% (24 of 96) for MSC-treated patients and 43% (36 of 83) in controls. Although there was a favorable trend, the overall difference did not reach statistical significance (Peto OR 0.63, 95% confidence interval 0.21-1.93). The certainty in evidence about an effect on mortality was low, due to imprecision and methodological limitations of the included trials, as presented in Figure 2 and Table 5.

3.5.2 | Pulmonary function changes

All studies reported pulmonary function tests as outcome measures. Lung injury score, tidal volumes, lung compliance, PaO$_2$/FiO$_2$, oxygenation, dependence on mechanical ventilators or ECMO, or ICU stay were found to improve within 5 days in most of the studies, while other studies found no long-term differences in a 5-year follow-up. Imaging studies reported in five studies$^{20,25-28}$ all showed post-treatment improvement on CT or chest x-ray (Table 5).

3.5.3 | Systemic changes and symptoms

Systemic changes were reported as any changes to overall patient status, including mental status, SOFA score, quality of life (SF-36), laboratory markers of organ function, symptoms, and relative improvements from baseline (Table 5)$^{20-22,24-28}$.

3.5.4 | Inflammatory cytokines

Inflammatory markers and cytokines were evaluated in six studies. These showed clear decreases in pro-inflammatory cytokines, including IL-1, IL-6, TNF-$\alpha$, and CRP, and increased lymphocytes and IL-10 within 5 days of MSC therapy (Table 5)$^{20-22,24,25,28}$ which supported an immunomodulatory effect of the MSC therapy.

4 | DISCUSSION

4.1 | Main findings

This systematic review examined the published results of MSC therapy for patients with ARDS, with focused analysis on safety, efficacy, and related immunologic and pulmonary responses. ARDS has been identified as a major mortality risk factor in COVID-19 infected patients, with current projections of 50 000 to 100 000 deaths in the United States alone.$^{31}$ Several repurposed and novel therapies for COVID-19 are being examined that include targeting the virus, enhancing host immunity, and reducing organ damage. Numerous
| Author          | Mortality in control (death/n) | Pulmonary function outcomes                                                                 | Systemic outcomes                                                                                      | Inflammatory markers                                                                 | Imaging |
|-----------------|-------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------|
| Leng et al<sup>20</sup> | 0/7                           | At 2-4 d after MSC transplantation, all symptoms disappeared in all patients, oxygen saturations rose to ≥95% at rest, with or without oxygen uptake (5 L/min) | At 2-4 d after MSC transplantation, all symptoms disappeared in all patients | MSC group: Decrease in TNF-α, increase in IL-10 (all group), most sick pt: CRP decreased; cytokine-secreting immune cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells; IP-10, VEGF, lymphocytes, D14 +CD11c+CD11bmid regulatory DC cell population dramatically increased |         |
| Wilson et al<sup>21</sup> | 2/9                           | Mean LIS improved between baseline and D3 in all three dosing groups; no pt received ECMO, 2/9 were extubated before D3 (not statistically significant) | Mean SOFA score: declined in all three dosing groups over the first 3 d | Median levels of IL-6, IL-8, RAGE declined between baseline and D3. Between group comparison P = .3679, .3189, .3189, and .8669, respectively | NR      |
| Zheng et al<sup>22</sup>  | 1/6                           | Ventilator-free days and ICU-free days at D28 after treatment were similar in both groups PaO2/FiO2 did not differ significantly between MSCs and placebo groups at all time points | Length of hospital stay, at D28 after treatment were similar | MSC group: serum SP-D levels at day 5 were significantly lower than those at day 0. Changes in IL-8 levels not significant. IL-6 levels at day 5 showed a trend toward lower levels as compared with day 0, but not statistically significant | NR      |
| Bellingan et al<sup>23</sup> | 5/26                          | ICU-free days 10.3 ± 8.9, ventilator-free days 12.9 ± 10.7 in MSCs group and 8.1 (8.9) and 9.2 (9.6) in the control group, respectively | NR                                                                                                   | NR                                                                                     | NR      |
| Matthay et al<sup>24</sup> | 15/40 (to day 60)             | Mortality higher in the MSC group (thought to be due to higher APACHE baseline score in the MSCs group), ventilator-free and organ-failure-free days were all lower in the MSC group than in the placebo group (not significant). At 2 d post-transplantation, oxygen index in the MSC group reduced (not significant) more than in the placebo group (oxygenation similar at baseline) | Number of ventilator-free and organ-failure-free days were all lower in the MSC group than in the placebo group, but the differences were not significant; number of intensive-care-free days was higher in the placebo group than in the MSC group | Concentrations of angiopeptin 2 had reduced by 6 h after the start of infusion in the MSC group. No changes from baseline were seen for IL-6, IL-8, RAGE, or protein C concentrations at 6 or 24 h in either group | NR      |
| Author          | Mortality MSCs (death/n) | Mortality in control (death/n) | Pulmonary function outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Systemic outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Inflammatory markers                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Imaging                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------|-------------------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yip et al²⁵     | 3/9                     | NA                            | Trend of improvement in PaO₂/FiO₂, ventilator-free days was 12.9 (10.7) and in ICU-free days was 10.3 (8.9)                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Two patients who died expressed initial dramatic clinical improvement after MSC infusion for 3 d; another pt was improving and weaning off the ventilator but expired due to severe septic shock                                                                                                                                                                                                                                                                                                                                 | Serial flow-cytometric analyses of circulating inflammatory biomarkers were progressively reduced. The immune cell markers were notably increased after cell infusion.                                                                                                                                                                                                                                                                                                                                 | Lobar consolidation improvements noted, 2 pts complete resolution, 3 pts progressive improvements, 3 mixed results                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                 |                         |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Chen et al²⁶    | 3/17                    | 24/44                         | Four MSC patients followed up for 5 y. No long-term significant difference among pts in the resp. functions (FEV1, FVC, FEV1/FVC, and FEF 50%)                                                                                                                                                                                                                                                                                                                                                                                       | After following up for 2 y, the scores for all elements of the SF-36 did not significantly differ during the follow-up                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | After MSC transplantation for 24 wk and 1 y, all patients showed improvement on CCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Chang et al²⁷   | 1/1                     | NA                            | D1 improvement from 191 to 334 (334 on D3) in PaO₂/FiO₂, improved inspiratory pressure from 26 to 24 mmHg, dynamic compliance improved from a preprocedure value of 22.7 to 26.5, 27.3, and 27.9 mL/cmH₂O after 24, 48, and 72 h, respectively                                                                                                                                                                                                                                                                 | Mental status, lung compliance, P/F ratio, chest radiography all showed improvement over the course of at least 3 d                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Chest radiography slight decrease in bilateral infiltrates                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Simonson et al²⁸| 0/2                     | NA                            | Patient 1: pulmonary compliance increased from 6 to 20 mL/cm H₂O at 2 d, to 44 mL/cm H₂O at day 8, tidal volume from 100-420 mL at D2, 720 mL at D5. Patient 2: pulmonary compliance increased from 20 mL/cm H₂O to 35 mL/cm H₂O at D1, to 73 mL/cm H₂O at D12. Tidal volumes increased.                                                                                                                                                                                                                                                       | In both patients: improved with resolution of respiratory, hemodynamic, and multiorgan failure                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | In both patients: BAL surfactant protein B increased (better alveolar-epithelial integrity, pro-inflammatory microRNAs significantly declined within 24 h of infusion, Pt1: decrease in epithelial apoptosis [ccK18, K18]: IL-6 and albumin levels in BAL fluid decreased; IL-8 and IFN-g in plasma initially decreased after injection)                                                                                                                                                                                                                                                                                                                                 | Serial CXRs demonstrated progressive decreases in pulmonary infiltrates at 24 h after infusion in both patients                                                                                                                                                                                                                                                                                                                                                                                                                                           |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BAL, bronchoalveolar lavage; CCT, cardiac computerized tomography; CT, computed tomography; CXR, chest X-ray; D, day; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LIS, lung injury score; MSC, mesenchymal stromal cell; NA, not applicable; NR, not reported; PaO₂/FiO₂, arterial oxygen partial pressure/fractional inspired oxygen; pt, patient; SF-36, 36-Item Short Form Survey; SOFA, sequential organ failure assessment score.
clinical studies have demonstrated that MSC therapy is safe and has
the potential to mitigate inflammatory and physiologic damage for a
variety of conditions involving the central nervous, cardiac, renal,
gastrointestinal, and respiratory systems. Our analysis of the literature suggests similar results for MSC therapy for
treating ARDS in COVID-19 patients.

Safety is the most important concern for all new therapies, espe-
cially in patients at high risk for death from the condition being
treated, and was carefully evaluated for MSC-treated patients in the
studies reviewed. Of the 200 patients with ARDS that were treated
with intravenously or intratracheally administered MSCs or placebo,
66 patients died, of which 30 were in the active treatment group.
None of these 30 deaths were found to be related to MSC therapy,
nor were any other SAEs attributed to the MSC therapy. Transient
AEs were reported, but all of them resolved spontaneously in the
short term. This safety profile is consistent with the experience of
other human clinical trials involving MSC therapy.

The potential efficacy of MSC therapy for ARDS in COVID-
19-infected patients was examined in this project considering death
as the primary outcome. Of five controlled studies of MSC therapy in
patients with ARDS, four reported a numeric reduction in mortality. In
the one study showing higher mortality in MSC group, the MSC group
had more severe baseline illness, which may have masked the efficacy
of MSC treatment. If that study is excluded from the analysis, the
mortality was 49% (31/63) in control patients compared with the 16%
(9/56) in MSC-treated patients. While not statistically significant, the
difference suggests MSC therapy may be effective in reducing mortal-
ity in these patients.

Other outcomes examined included pulmonary function, systemic
outcomes, and immune responses. Pulmonary function was evaluated
in seven studies. Despite the heterogeneous nature of measures used
in different studies, six reports showed improvement in pulmonary
function within 3 to 5 days, and one study reported no change. Of
the reported improved cases, there were notable improvements in lung
compliance and tidal volumes. Imaging findings were reported in five
studies, showing improvement of opacity in chest radiograph and chest
CT within days after treatment. ICU- and ventilator-free days were
reported in three studies and had mixed results of improvement or no
change in MSC treated patients compared to controls. These results
showing improved pulmonary function and imaging findings further
support consideration of MSC treatment for COVID-19-induced ARDS.

Findings from this study also suggest the impact of MSC ther-
apy on important immunologic and inflammatory processes that
lead to organ injury in COVID-19-infected patients. Cytokine
release syndrome is a major underlying pathophysiological process
in ARDS and was found to decrease with MSC therapy in seven of
the studies analyzed.

In addition, MSCs have been hypothesized to neutralize free virus
particles through the production of antibiotic proteins like LL37,
which bind to virus and lung cell binding sites.

As recently reported, COVID-19 not only affects the lung, but
also the heart and kidney with reported cardiomyopathy and kidney
injury. Two of the analyzed studies reported improved
resolution of multiple organ failure or increased organ failure-free
days with MSC treatment, which further supports their consider-
ation for clinical use. Future clinical trials should include multior-
gan failure parameters.

Senior age is associated with higher rate of mortality and has
been reported to be associated with higher risk of death in
patients with COVID-19. In comparative studies included in
this review, the age ranges were similar in both the MSC and the
control groups at baseline and appeared to have minimal impact
on outcomes.

4.2 Clinical and research implications

This comprehensive systematic review of published reports of MSC
therapy for ARDS has yielded several important findings. First, a sig-
nificant number of individuals with ARDS (117) have been treated
with MSC without evidence of SAEs. This finding, along with the simi-
lar safety profile for many other patients treated with MSC for a vari-
ety of conditions in the United States and globally, provides evidence
of low risk. Second, MSC treatment was found to have a suggested
benefit in reducing death and improving pulmonary function in
patients with ARDS. Third, MSC treatment had a suggested benefit in
mitigating the physiologic and immunologic responses leading to
ARDS, supporting the potential mechanism of action, which has also
been demonstrated with MSC therapy for other inflammatory
disorders.

Since the closing date of this project (March 30, 2020), we have
learned that patients in Israel have received MSC treatment under
compassionate use with apparent beneficial results. A study per-
formed in the United States by industry has shown improved survival
rate in preliminary results. In addition, from personal communica-
tions, MSCs had been used in six patients at another site in the Unit-
ed States by April 26, 2020.

Therefore, we believe that the current evidence suggests a poten-
tial favorable risk-benefit ratio and mechanistic justification to con-
tinue compassionate use and initiate large-scale trials of MSC therapy
for COVID-19 patients in the United States, using MSCs that have
already demonstrated safety in FDA-approved studies. Multicenter
clinical trials should be conducted with MSCs characterized according
to standard protocol.

4.3 Limitations

The limitations of this systematic review include the lack of large-scale
RCTs, the heterogeneity of outcome measures on pulmonary function,
and the lack of studies collecting extra-pulmonary pathology. In addi-
tion, variability of MSC products prevents the assessment of which
MSC type or preparation may be effective. Moreover, there may exist
selection bias in published results and case reports that favors positive
findings for MSC therapy for ARDS vs results that were equivocal or
negative and not published.
CONCLUSION

This analysis of published reports demonstrated the potential benefits, minimal risks, and presumptive mechanisms of MSC therapy for ARDS, which support the rationale for treatment of COVID-19 patients with pulmonary disease. Adequately powered clinical trials are urgently needed to test clinical outcomes in patients with COVID-19 syndrome and SARS-CoV-2 infection, and should use well-characterized MSC products with documented safety profiles from FDA-approved studies.

CONFLICT OF INTEREST

W. Q., J. M. H., J. K., and J. M. M. reported roles as principal investigators of MSC trials. F. P. S. is a paid consultant as Medical Director of The Marcus Foundation, which funds numerous clinical trials involving MSCs. J. M. M. is an unpaid Scientific Advisor for BreStem Therapeutics. 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; 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. 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. declare Intellectual property rights with IDF, hCT-MSC for treatment of ASD, HIE, CP; NMDP Scientific Advisor; Celularity SAB; research funding from the Marcus Foundation, NIH, HRSA; leadership position with Istari—CMO (spouse). F. P. S. declared advisory role with the Marcus Foundation, Neuvana, Radix Health. The other authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

W.Q. E.K., E.E.C.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; Z.W.: conception and design, collection and/or assembly of data, data analysis and interpretation, final approval of manuscript; J.M.H., F.P.S.: conception and design, critical review of the manuscript, manuscript writing, final approval of manuscript; G.B., J.M.P., J.M.M., A.L.C., J.K, A.C.Z., M.H.M.: conception and design, critical review of the manuscript, final approval of manuscript; T.N., V.P.S., J.C.H., M.E.W., L.J.P.: collection and/or assembly of data, final approval of manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Wenchun Qu https://orcid.org/0000-0003-2402-8318
Joshua M. Hare https://orcid.org/0000-0002-7751-5032
Arnold I. Caplan https://orcid.org/0000-0002-8677-6621
Abba C. Zubair https://orcid.org/0000-0003-4827-4740
Michael E. Wolf https://orcid.org/0000-0001-6385-9128

REFERENCES

1. Huynh J, Li S, Yount B, et al. Evidence supporting a zoonotic origin of human coronavirus strain NL63. J Virol. 2012;86:12816-12825.
2. Woo PC, Lau SK, Lam CS, et al. Discovery of seven novel mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. J Virol. 2012;86:3995-4008.
3. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. JAMA. 2020;323:1499.
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; [Epub ahead of print].
5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-481.
6. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020; [Epub ahead of print].
7. Xu T, Chen C, Zhu Z, et al. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. Int J Infect Dis. 2020;94:68-71.
8. Zhang X, Cai H, Lian J, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis. 2020;94:81-87.
9. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620-2629.
10. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130:2202-2205.
11. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.
12. Hunt CL, Her Y, Law L, et al. Five generations of cell preparation: a translational framework for categorizing regenerative stem cell therapies. J Am Acad Regen Med. 2017;11:246–250.
13. Le Blanc K, Rasmussen I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet. 2004;363:1439-1441.
14. Zhao Q, Zhang L, Wei Y, et al. Systematic comparison of hUC-MSCs at various passages reveals the variations of signatures and therapeutic effect on acute graft-versus-host disease. Stem Cell Res Ther. 2019;10:354.
15. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med. 2013;45:e54.
16. Pittenger MF, Discher DE, Peault BM, et al. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regen Med. 2019;4:22.
17. Chow L, Johnson V, Impastato R, Coy J, Strumpf A, Dow S. Antibacterial activity of human mesenchymal stem cells mediated directly by constitutively secreted factors and indirectly by activation of innate immune effector cells. Stem Cells Translational Medicine. 2020;9:235-249.
18. Ni K et al. Human mesenchymal stem cells alleviate bleomycin-induced pulmonary fibrosis in humanized mice. J Immunol. 2017;198(suppl 1):82.21
19. Tzouvelekis A, Toonkel R, Karampitsakos T, Medapalli K, Ninou I, Aidinis V, Bouros D, Glassberg MK. Mesenchymal Stem Cells for the Treatment of Idiopathic Pulmonary Fibrosis. Frontiers in Medicine. 2018;5. http://dx.doi.org/10.3389/fmed.2018.00142.
20. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2− mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020;11:216-228.

21. Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med. 2015;3:24-32.

22. Zheng G, Huang L, Ton H, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. Respir Res. 2014;15:39.

23. Bellingeran G, Jacono F, Bannard-Smith J, et al. Primary analysis of a phase 1/2 study to assess MultStem® cell therapy, a regenerative advanced therapy medicinal product (ATMP), in acute respiratory distress syndrome (MUST-ARDS). American Thoracic Society 2019 International Conference. B14 Late Breaking Clinical Trials; 2019; 199:AT7353.

24. Matthay MA, Calfee CS, Zhuo H, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med. 2020;48:e391-e399.

25. Yip HK, Fang WF, Li YC, et al. Human umbilical cord-derived mesenchymal stem cells for acute respiratory distress syndrome. Crit Care Med. 2020;48:e391-e399.

26. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic influenza a (H7N9) infection, a hint for COVID-19 treatment. Engineering. 2020; [Epub ahead of print].

27. Chang Y, Park SH, Huh JW, Lim CM, Koh Y, Hong SB. Intratracheal administration of umbilical cord blood-derived mesenchymal stem cells in a patient with acute respiratory distress syndrome. J Korean Med Sci. 2014;29:438-440.

28. Simonson OE, Mougialakos D, Heldring N, et al. In vivo effects of mesenchymal stromal cells in two patients with severe acute respiratory distress syndrome. Stem Cells Transl Med. 2015;4:1199-1213.

29. Murad MH. Clinical practice guidelines: a primer on development and dissemination. Mayo Clin Proc. 2017;92:423-433.

30. Rover C, Knapp G, Friede T, Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Med Res Methodol. 2015;15:99.

31. Institute of Health Metrics and Evaluation. University of Washington. COVID-19 Projections. https://covid19.healthdata.org/united-states-of-america. Accessed May 4, 2020.

32. Staff NP, Madigan NN, Morris J, et al. Safety of intrathecal autologous adipose-derived mesenchymal stromal cells in patients with ALS. Neurology. 2016;87:2230-2234.

33. Bydon M, Dietz AB, Goncalves S, et al. CELLTOP clinical trial: first report from a phase 1 trial of autologous adipose tissue-derived mesenchymal stem cells in the treatment of paralysis due to traumatic spinal cord injury. Mayo Clin Proc. 2020;95:406-414.

34. Heldman AW, DiFede DL, Fishman JE, et al. Transcardiac mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. JAMA. 2014;311: 62-73.

35. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transcendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA. 2012;308:2369-2379.

36. Saad A, Dietz AB, Hermann SMS, et al. Autologous mesenchymal stem cells increase cortical perfusion in renovascular disease. J Am Soc Nephrol. 2017;28:2777-2785.

37. Dietz AB, Dozois EJ, Fletcher JG. Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with Crohn’s disease. Gastroenterology. 2017;153:59-62.

38. Lee WY, Park KJ, Cho YB, et al. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn’s fistula. Stem Cells. 2013;31:2575-2581.

39. Dozois EJ, Lightner AL, Mathis KL, et al. Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transphincteric cryptoglandular fistulas. Dis Colon Rectum. 2019;62:615-622.

40. Keller CA, Gonwa TA, Hodge DO, Hei DJ, Centanni JM, Zubac AR. Feasibility, safety, and tolerance of mesenchymal stem cell therapy for obstructive chronic lung allograft dysfunction. Stem Cells Translational Medicine. 2018;7:161-167.

41. Glassberg MK, Minkiewicz J, Toonkel RL, et al. Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis via intravenous delivery (AETHER): a phase I safety clinical trial. Chest. 2017;151:971-981.

42. Krasnodembskaya A, Song Y, Fang X, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. Stem Cells. 2010;28:2229-2238.

43. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020; 323:1612.

44. Li Z, Wu M, Guo J, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. https://ssrn.com/abstract=3559601 or https://doi.org/10. 2139/ssrn.3559601. Accessed May 4, 2020.

45. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848.

46. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. China CDC weekly, vital surveillance. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;2:113-122.

47. Pluristem Therapeutics, Inc. Pluristem Expands Its Compassionate Use Program: Treated First COVID-19 Patient in U.S. Under FDA Single Patient Expanded Access Program. https://www.pluristem.com/news-and-events/pluristem-expands-compassionate-use-program-treated-first-covid-19-patient-us-fda-single-patient-expanded-access-program/. Accessed May 4, 2020.

48. Pluristem Therapeutics, Inc. Pluristem Reports Preliminary Data from Its COVID-19 Compassionate Use Program, Treating Seven Patients with Acute Respiratory Failure. https://www.pluristem.com/wp-content/uploads/2020/04/PS1-PR-Follow-up-on-Covid-19-treatments-FINAL-FOR-RELEASE.pdf. Accessed May 4, 2020.

49. House DW. Mesoblast Cell Therapy Shows Significant Benefit in COVID-19 Patients. Seeking Alpha News. https://seekingalpha.com/news/3564093-mesoblast-cell-therapy-shows-significant-benefit-in-covidminus-19-patients. Accessed May 4, 2020.
APPENDIX A: RISK OF BIAS ASSESSMENT

**TABLE A1**  Risk of bias of randomized controlled trials

| Author          | Year | Sequence generation | Allocation concealment | Participants and personnel blinding | Outcome assessment blinding | Incomplete outcome data | Selective reporting | Other sources of bias | Overall risk of bias |
|-----------------|------|---------------------|------------------------|-------------------------------------|-----------------------------|------------------------|---------------------|---------------------|---------------------|
| Bellingan et al | 2019 | Unclear             | Unclear                | Low risk                            | Unclear                     | Unclear                | Unclear             | Unclear             | Moderate risk       |
| Matthay et al   | 2019 | Low risk            | Low risk               | Low risk                            | Low risk                    | Low risk               | Low risk            | Low risk            | Low risk            |
| Zheng et al     | 2014 | Unclear             | Unclear                | Low risk                            | Unclear                     | Unclear                | Low risk            | Low risk            | Moderate risk       |

**TABLE A2**  Risk of bias of observational studies, case series, and case studies

| Author          | Year | Representativeness of study cohort | Ascertainment of exposure | Comparability between groups | Outcome data source | Independent blind assessment of outcome | Overall risk of bias |
|-----------------|------|-----------------------------------|--------------------------|------------------------------|--------------------|----------------------------------------|---------------------|
| Chang et al     | 2014 | Low risk                          | Low risk                 | Not applicable               | Low risk           | High risk                              | Moderate risk       |
| Simonson et al  | 2015 | Low risk                          | Low risk                 | Not applicable               | Low risk           | High risk                              | Moderate risk       |
| Yip et al.      | 2020 | Low risk                          | Low risk                 | Not applicable               | Moderate risk      | High risk                              | High risk           |
| Leng et al      | 2020 | Low risk                          | Low risk                 | Moderate risk                | Moderate risk      | High risk                              | High risk           |
| Wilson et al    | 2015 | Low risk                          | Low risk                 | Not applicable               | Moderate risk      | Moderate risk                          | Moderate risk       |
| Chen et al      | 2020 | Low risk                          | Low risk                 | Moderate risk                | Low risk           | Low risk                               | Moderate risk       |

APPENDIX B: ACTUAL SEARCH STRATEGY

Ovid

Database(s): EBM Reviews—Cochrane Central Register of Controlled Trials February 2020, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to March 25, 2020, Embase 1974 to March 30, 2020, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 30, 2020.

Search strategy is given below.

Scopus

1 TITLE-ABS-KEY("Corona virinae" OR "corona virus" OR Coronavirus or coronavirus or COVID or nCoV or HCoV) W/4 ("19" OR "2019" OR novel or new or pneumonia)) OR ("Corona virinae" OR "corona virus" OR Coronavirus or coronavirus or COVID or nCoV or HCoV and Wuhan) OR "Acute Respiratory Distress Syndrome" OR ARDS OR "Corona virinae19" OR "Corona virinae2019" OR "corona virus19" OR "corona virus2019" OR Coronavirus19 OR Coronavirus2019 OR COVID19 OR COVID2019 OR "cytokine storm" OR "interstitial pneumonia" OR MERS OR "Middle East Respiratory Syndrome" OR nCOV19 OR nCoV2019 OR "SARS Corona virus" OR "SARS Coronavirus" OR "SARS-COV" OR "Severe Acute Respiratory Syndrome Corona virus" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "viral pneumonia" OR "virus pneumonia")

2 TITLE-ABS-KEY("adipose derived stromal cell" OR "adipose derived stromal stem cell" OR "adipose stromal cell" OR "adipose stromal stem cell" OR "bone marrow derived stromal cell" OR "bone marrow derived stromal stem cell" OR "bone marrow stromal cell" OR "bone marrow stromal stem cell" OR "colony forming unit" OR "mesenchymal cell" OR "mesenchymal progenitor cell" OR "mesenchymal stem cell" OR "mesenchymal stromal cell" OR "mother cell" OR MSC OR MSCs OR "progenitor cell" OR "stem cell" OR "umbilical cord derived stromal cell" OR "umbilical cord derived stromal stem cell" OR "umbilical cord stromal cell" OR "Wharton's jelly cell" OR "Wharton's jelly cell")

3 PUBYEAR AFT 1989
4 1 and 2 and 3
5 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
6 4 and not 5

**ClinicalTrials.gov**

**Condition or disease**

("2019 novel coronavirus" OR "2019-nCoV" OR "acute respiratory distress" OR "acute respiratory syndrome" OR ARDS OR Coronavirus OR "COVID 19" OR "cytokine storm" OR "interstitial pneumonia" OR MERS OR "Middle East Respiratory Syndrome" OR "SARS-CoV"

("viral pneumonia" OR "virus pneumonia")

**Other terms**

("colony forming unit" OR "mesenchymal cell" OR "mother cell" OR MSC OR MSCs OR "progenitor cell" OR "stem cell" OR "stromal cell" OR "wharton jelly cell" OR "whartons jelly cell")

**First posting**

January 1, 1990 to March 31, 2020