Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the DOH AHEAD Program through the PCHRD

EVIDENCE SUMMARY

Should mesenchymal stem cell therapy be used in adults with COVID-19?

Evidence Reviewers: Cary Amiel G. Villanueva, Christopher G. Manalo, MD & Howell Henrian G. Bayona, MSc

RECOMMENDATION

There is insufficient evidence to recommend using umbilical cord-derived mesenchymal stem cell therapy among adults with severe COVID-19 (PaO2/FiO2 ratio ≤ 300 mmHg). *(Very low quality of evidence)*

Consensus Issues

Although the current available evidence shows benefit in terms of mortality and time to clinical improvement, no recommendation was made due to the small sample size of the included studies. Further, more patients in the mesenchymal stem cell (MSC) therapy arm received co-interventions (i.e., remdesivir and corticosteroids) compared to the control arm which may have overestimated the true effect of MSC.

Key Findings

We found 3 randomized controlled trials (RCTs) evaluating the effectiveness and safety of mesenchymal stem cell (MSC) therapy in COVID-19 treatment. One RCT was at high risk of bias while the remaining 2 RCTs were of moderate quality. Validity issues included unclear allocation concealment, lack of blinding and incomplete outcome reporting. Based on very low quality evidence, umbilical cord-derived MSC (UC-MSC) therapy reduces mortality and hastens clinical improvement in adults with severe COVID-19. Limited by small sample sizes, adverse events were not significantly different between MSC and control groups.

Introduction

Cell-based therapies including MSC, natural killer cells and dendritic cells have been proposed as investigational treatment for COVID-19 [1]. MSCs, which may be isolated from bone marrow, adipose and umbilical cord tissue, are multipotent cells that can attenuate inflammatory responses and induce regeneration [2]. Early-stage clinical trials in acute respiratory distress syndrome and chronic obstructive pulmonary disease have demonstrated the apparent safety of MSC therapy and their potential to reduce inflammatory markers like C-reactive protein [2]. However, stem cell therapy is more expensive compared to other anti-COVID-19 medications and may cost around $4,000 to $8,000 without cell culture expansion in developed countries [1].

At least four hospitals in the Philippines have experience with stem cell therapy [4]. Locally, a single-center case series of patients with severe COVID-19 and cytokine response syndrome found that UC-MSC infusion was well-tolerated. Most patients concurrently received steroids (10/11) and remdesivir (9/11). Hydroxychloroquine and intravenous immunoglobulin (IVIg) were given to one patient each. Seven (63.6%) enrolled patients were eventually discharged [3].

This review sought to summarize the available evidence on the clinical effectiveness and safety of MSC therapy in treating adults with COVID-19.

Review Methods

An electronic search was conducted on several databases (MEDLINE through PubMed and Cochrane Library), preprint servers (medRxiv, bioRxiv, ChinaXiv) and clinical trial registries (ClinicalTrials.gov, WHO ICTRP, ChiCTR) until April 24, 2021 using the following terms and their variations: mesenchymal stem cell transplantation, mesenchymal stem cells, COVID-19 and SARS-CoV-2. MeSH terms were also used whenever available. No language restrictions were applied. We also searched the COVID-19 Living NMA initiative's Living Synthesis of Published Trials for studies involving stem cells on May 14, 2021.

Randomized controlled trials (RCTs) investigating the use of mesenchymal stem cells (MSC) derived from any source in treating adult patients with COVID-19 were included. Outcomes included mortality, endotracheal intubation or invasive mechanical ventilation, length of hospital stay, time to clinical improvement and safety. Systematic reviews were used to identify additional studies that may potentially be eligible.

Dichotomous endpoints were presented as relative risks (RR). Continuous outcomes were reported as presented by the respective study authors. Meta-analyses using random-effects models using Review Manager 5.4.1 (The Cochrane Collaboration 2020) were performed for outcomes similarly reported by multiple studies. Subgroup analyses according to disease severity and stem cell origin were planned but not pursued due to limited available data.

Results

Characteristics of Included Studies

We found 3 RCTs (n = 148) comparing MSC therapy with placebo or standard care in severe COVID-19 patients with P_aO_2/FiO_2 ratio ≤ 300 mmHg (**Appendix 1**) [5-7]. Two studies were conducted in China [5,7] while another was performed in the United States [6]. All trials used UC-MSC delivered via intravenous infusion. The dose was either fixed ($100 \pm 20 \times 10^6$ cells each for 2 doses [6] or 4.0×10^7 cells each for three doses [7]) or determined by weight (2×10^6 cells/kg single dose [5]).

Quality of evidence

The quality of evidence for effectiveness and safety outcomes was very low (**Appendix 2**). Across all outcomes, we downgraded one to two levels due to issues with study quality (allocation concealment, blinding and attrition). We also downgraded for imprecision in most outcomes due to the small sample sizes and wide interval estimates.

One RCT was judged to be at high risk of bias because of unclear allocation concealment and lack of blinding [5]. There were also more participants in the treatment group with respiratory rates above 24 breaths/min (91.67% vs. 68.97%, p = 0.231) suggesting that they may have been worse off. The remaining 2 RCTs were of moderate quality: one trial limited to a modified intention-to-treat analysis (1 patient was randomized to receive MSC therapy but was excluded due to withdrawal of consent) [7] while re-inclusion could be performed to generate the intention-to-treat population for mortality in the another [6]. In the latter study, allocation sequence concealment was unclear and differences in co-interventions probably favored the MSC arm (more treatment group patients received remdesivir [75% vs. 58.3%] and corticosteroids [83.3% vs. 75%]).

Mortality
Three RCTs (n = 148, with re-inclusion of one excluded death in Lanzoni 2021) reported mortality at 28 or 31 days from the first infusion. UC-MSC therapy significantly reduced the risk of death in severe COVID-19 patients: RR 0.25 (95% CI 0.07 to 0.86, I^2 = 0%; **Appendix 3, Figure 1**).

Invasive mechanical ventilation
Only one randomized trial (n = 100) reported the incidence of endotracheal intubation [7]. MSC appears to be non-inferior to placebo in avoiding mechanical ventilation (0% vs. 11.4%; RR 0.06 [95% CI 0 to 1.09]; **Appendix 3, Figure 2**). The wide confidence intervals are largely a function of the small sample size.

Length of hospital stay
Duration of hospital stay was provided in one RCT (n = 100) [7]. Although the treatment group patients appeared to have shorter hospital stays (median [IQR]: 20.00 days [16.00, 24.00] vs. 24.00 days [20.00, 26.50]), the difference was not statistically significant (p = 0.054).

Time to clinical improvement
UC-MSC therapy appeared to hasten clinical improvement according to 2 studies (n = 48) [5,6]. Clinical improvement, which was defined as hospital discharge or a decline in two categories of a seven-point ordinal scale of clinical status, was achieved about five days earlier with treatment (median [IQR]: 9.00 days [6.00, 13.00] vs. 14.00 days [9.50, 21.00], p = 0.006) in one study [5] In another RCT of similar size, time to recovery (i.e., discharge or no longer requiring COVID-19-related medical care) was more favorable in the MSC arm: HR 0.2891 (95% CI: 0.088 to 0.948) [6].

Adverse events
Adverse reactions associated with treatment were reported in 3 RCTs (n = 165) [5-7]. A study which reported adverse events for patients receiving MSC but made no explicit mention for the comparison group was assumed to have zero events in the control arm [5].

In 2 RCTs (n = 141), the risk of developing any adverse event did not significantly differ between MSC and control groups (RR 0.95 [95% CI 0.67 to 1.34; **Appendix 3, Figure 3**). The most common side effects recorded were laboratory derangements, e.g., increased lactate dehydrogenase and alanine aminotransferase [7].

Only one trial (n = 24) reported infusion-associated adverse events within 6 hours of administration (RR 1.00 [95% CI 0.07, 14.2]) [6]. Bradycardia requiring an increase in vasoactive agent dose occurred in one patient who received UC-MSC while another patient in the placebo group experienced cardiac arrest.

As for serious adverse events (n = 124, 2 studies), the likelihood did not differ significantly between treatment and control groups (RR 0.36 [95% CI 0.08 to 1.57]; **Appendix 3, Figure 4**). In one RCT, pneumothorax developed in a patient who received UC-MSC [5].

Recommendations from Other Groups

The **U.S. National Institutes of Health** (21 Apr 2021) [8] COVID-19 Treatment Guidelines Panel recommends against using MSCs for COVID-19 treatment except within clinical trials. They cited that the U.S. Food and Drug Administration (FDA) has not yet approved any MSC product for COVID-19 treatment, and that there is limited data on MSCs in COVID-19.

Research Gaps

There are 5 completed RCTs that used MSCs in COVID-19 patients from the United States, China and Russia and Indonesia. However, their results have yet to be published.

There are at least another 59 ongoing randomized trial investigating MSCs or exosomes in COVID-19 treatment (**Appendix 4**). The MSCs, sourced from umbilical cord, bone marrow or adipose tissue, are given singly or in combination with another drug (e.g., ruxolitinib). These trials are conducted in the United States, Germany, France, Spain, Mexico, Brazil, Australia, Colombia, China, Russia, Indonesia, Iran and Pakistan.

References

[1] Golchin A. Cell-Based Therapy for Severe COVID-19 Patients: Clinical Trials and Cost-Utility. Stem Cell Rev Reports. 2021;17(1):56–62.

[2] Durand N, Mallea J, Zubair AC. Insights into the use of mesenchymal stem cells in COVID-19 mediated acute respiratory failure. npj Regen Med [Internet]. 2020;5(1). Available from: http://dx.doi.org/10.1038/s41536-020-00105-z

[3] De Vera MJ, Buensalido MJ, Francisco JJ, Bello A, Olavere A, Calavera A, et al. Use of Umbilical Cord Mesencymal Stem Cells in the Treatment of Severe COVID-19 Pneumonia. J Embryol Stem Cell Res. 2021;5(1).

[4] Picazo OF. Medical Tourism in the Philippines: Market Profile, Benchmarking Exercise and S.W.O.T. Analysis [Internet]. 2013. Available from: https://pidswebs.pids.gov.ph/CDN/PUBLICATIONS/pidsdps1345.pdf

[5] Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther. 2020;11(1):1–11.

[6] Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Transl Med. 2021;10(5):660–73.

[7] Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduct Target Ther. 2021;6(1).

[8] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 14 May 2021.

Appendix 1: Characteristics of Included Studies

Study ID Design	Sample Size	Population / Setting	Intervention/s	Control	Outcomes
Shu 2020 RCT	41	Patients with severe COVID-19 (PaO2/FiO2 ≤ 300 mHg)	hUC-MSC: 2 doses x 10^6 cells/kg MSCs (The Jiangsu Cell Tech Medical Research Institute and The Jiangsu Cell Tech Biotechnology Co.) suspended in 100 mL normal saline IV infusion	Placebo *Standard care included supplemental oxygen, abidor/oseltamivir, antibiotics, glucocorticoids	Mortality at D28 Length of hospital stay Time to clinical improvement Adverse events
Lanzoni 2021 RCT	24	Patients ≥ 18 years with COVID-19 ARDS (PaO2/FiO2 ratio < 300 mmHg)	UC-MSC: Intravenous infusions (IV) of 100 ± 20 x 10^6 UC-MSC* each, in vehicle solution containing Human Serum Albumin (HSA) and heparin, two doses within 72 +/- 6 hours apart *Culture-expanded from a previously established and characterized Master Cell Bank (MCB) derived from the subepithelial lining of a UC, collected from a healthy term delivery (kindly provided by Jadi Cell and Amit Patel, MD)	Two infusions of vehicle solution containing HSA and heparin	Mortality at D31 (D28 after last infusion) Time to recovery Serious adverse events Infusion-associated adverse events
Shi 2021 RCT	100 (modified intention-to-treat)	Patients with severe COVID-19 (PaO2/FiO2 ≤ 300 mHg)	UC-MSC: 4.0 x 10^7 cells (VCANBIO Cell & Gene Engineering Corp, Tianjin, China) each infusion on days 0, 3 and 6 after randomization	Placebo	Mortality at D28 Invasive mechanical ventilation Adverse events (Grades 1-2, Grades 3-4)

Appendix 2: GRADE Evidence Profile

Mesenchymal stem cell therapy compared to control for adults with COVID-19

Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With mesenchymal stem cell therapy	Relative effect (95% CI)	Risk with control	Risk difference with mesenchymal stem cell therapy
Mortality (follow up: range 28 days to 31 days)											
148 (3 RCTs)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	10/59 (16.9%)	2/89 (2.2%)	**RR 0.29** (0.09 to 0.88)	169 per 1,000	**120 fewer per 1,000** (from 154 fewer to 20 fewer)
Invasive mechanical ventilation											
100 (1 RCT)	serious [c]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	4/35 (11.4%)	0/65 (0.0%)	**RR 0.06** (0.00 to 1.09)	114 per 1,000	**107 fewer per 1,000** (from -- to 10 more)
Length of hospital stay											
100 (1 RCT)	serious [c]	not serious	not serious	very serious [e]	none	⨁◯◯◯ VERY LOW	• In one RCT (n = 100), the duration of hospital stay was not significantly different between MSC and control groups (median [IQR]: **20.00 days [16.00, 24.00] vs. 24.00 days [20.00, 26.50], p = 0.054**).				
Time to clinical improvement											
48 (2 RCTs)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	• Clinical improvement was achieved earlier with MSC therapy than control in one RCT (n = 24, median [IQR]: **9.00 days [6.00, 13.00] vs. 14.00 days [9.50, 21.00], p = 0.006**). • In another RCT (n = 24), time to recovery was more favorable in the MSC arm: **HR 0.2891 (95% CI: 0.088 to 0.948)**.				
Any adverse event											
124 (2 RCTs)	very serious [a]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	8/47 (17.0%)	3/77 (3.9%)	**RR 0.36** (0.08 to 1.57)	170 per 1,000	**109 fewer per 1,000** (from 157 fewer to 97 more)
Serious adverse events											

141 (2 RCTs)	serious [f]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	21/64 (32.8%)	37/77 (48.1%)	**RR 0.95** (0.67 to 1.34)	328 per 1,000	**16 fewer per 1,000** (from 108 fewer to 112 more)

Infusion-associated adverse events

24 (1 RCT)	serious [g]	not serious	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	1/12 (8.3%)	1/12 (8.3%)	**RR 1.00** (0.07 to 14.20)	83 per 1,000	**0 fewer per 1,000** (from 77 fewer to 1,000 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded twice due to unclear allocation concealment, unequal baseline characteristics between groups, lack of blinding and exclusion of a patient that was randomized
b. Downgraded once due to small sample size
c. Downgraded once due to attrition (exclusion of a patient that was randomized)
d. Downgraded twice due to wide confidence interval and small sample sizes
e. Downgraded twice due to significant overlaps in confidence intervals (difference likely due to chance) and small sample size
f. Downgraded once due to issues on allocation concealment and attrition (exclusion of a patient that was randomized)
g. Downgraded once due to unclear allocation concealment

Appendix 3: Forest Plots

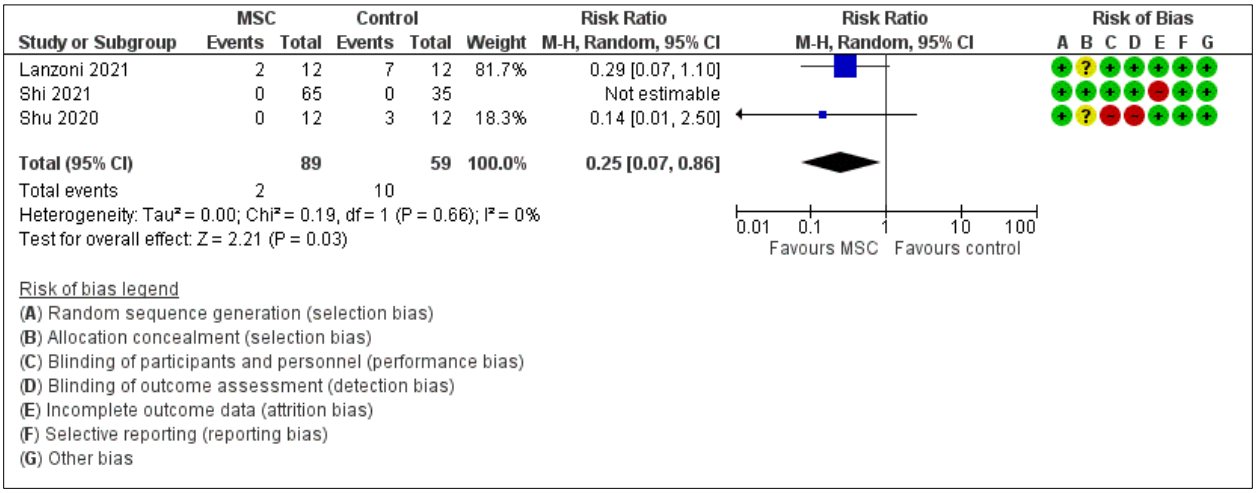

Figure 1. Forest plot for mortality

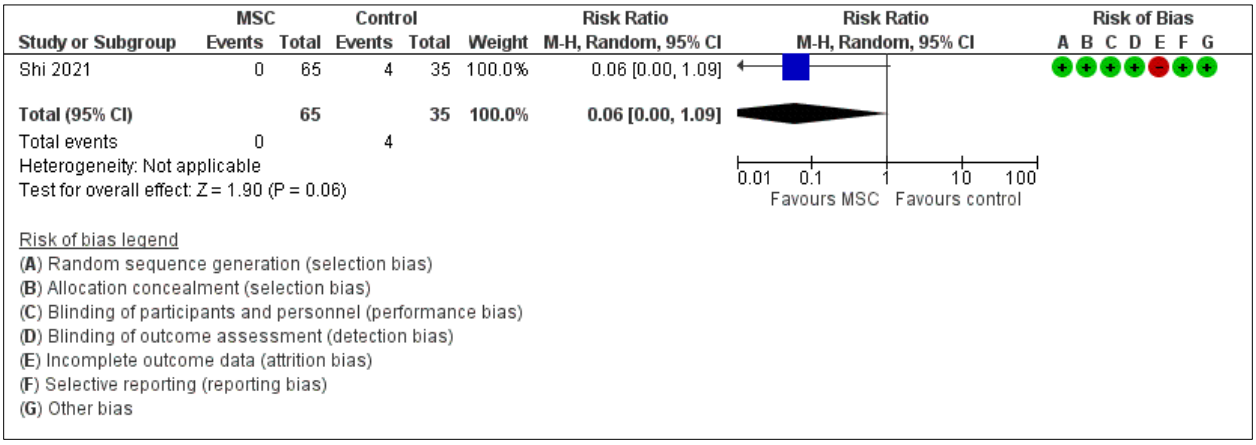

Figure 2. Forest plot for invasive mechanical ventilation

Figure 3. Forest plot for patients with any adverse event

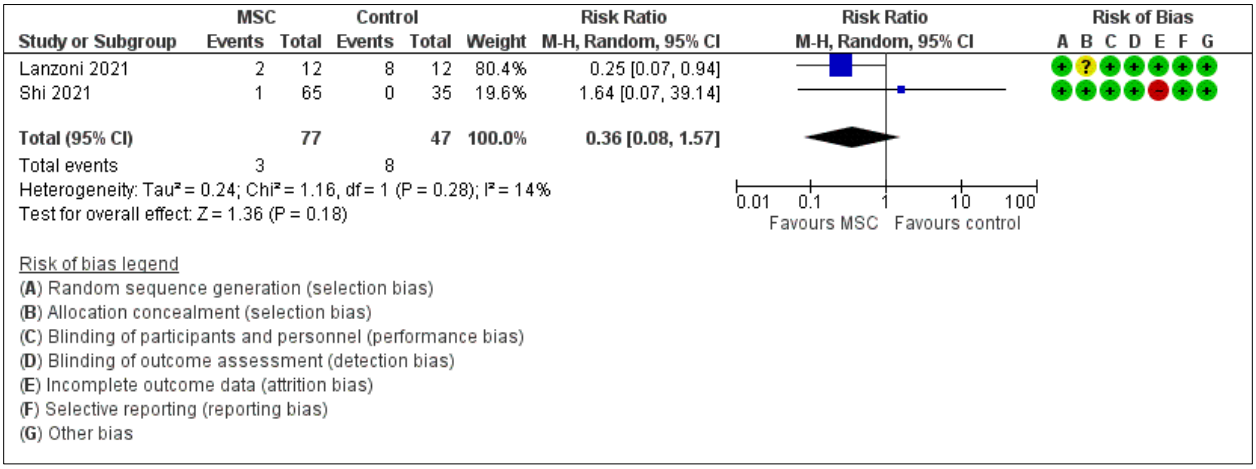

Figure 4. Forest plot for patients with serious adverse events

Appendix 4: Characteristics of Ongoing Studies

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
IRCT20190717044241N3 Iran (Islamic Republic of)	COVID-19	Intervention 1: Intervention group: Patients with coronavirus 19 who undergo mesenchymal stem cell transplantation at a rate of 2 million per kilogram body weight (based on IBW) through peripheral blood (IV)on days 0, 3, and 6. Intervention 2:	Control group: Participants with COVID19 receiving routine and placebo treatment (based on IBW) intravenously on days 0, 3, and 6.	Clinical response. Timepoint: 28 days-From the time of cell injection until the 28th day. Method of measurement: clinical observation by Infectious Diseases Specialist.;O2 saturation. Timepoint: Since the injection of the cell; 0,3,6 days. Method of measurement: ventilator. Inflammation cytokines. Il-6 & Il-10. Timepoint: On days 0,3,6,14 - from the time of cell injection. Method of measurement: Assay by the Elisa.;CD4 and CD8 markers. Timepoint: On days 0,3,6,14 - from the time of cell injection. Method of measurement: Flow Cytometry.;Evaluation of lung function. Timepoint: On days 0,14 - from the time of cell injection. Method of measurement: CT scan of the lungs.
IRCT20200426047206N2 Iran (Islamic Republic of)	COVID-19 disease. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: This group receiving mesenchymal stem cells. In this group, patients are received 1 million Umbilical core-derived MSCc/BW by intravenous injection (provided by volunteer donors at Fatemieh Hospital) (Through the catheter and the Central vein and from the superior vena cava vein). Also, in addition to cell therapy, Other routine treatments (The last national protocol for COVID-19 treatment) will be given to patients according to the physician's supervision.The umbilical cord will be provided by volunteer donors at Fatemieh Hospital and after that will be cultured and expanded in the cleanroom of Hamadan University of Medical Sciences	Intervention 2: Control group: Receiving routine therapies (The last national protocol for COVID-19 treatment) (without stem cell).	Patient respiratory status. Method of measurement: Using CT scan image, physical examination, oxygen saturation percentage.;Inflammatory factors. Timepoint: Before and two week after intervention. Method of measurement: Elisa.
ISRCTN33578935 Germany	Hypercytokinemia in patients with COVID-19 and severe respiratory	Intervention Intravenous infusion of purified exosomes, XoGloÂ®, which	Control: 15ml of saline, i.v. on Day 1 and Day 3	1. Safety and adverse events measured using i.v. administration of 0.2mg/kg of placental, mesenchymal stem cell-derived exosome preparations (KTA 100,= XoGloÂ®) at day 1 and day 3

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
	distress syndrome (SARS) due to CoV-2 infection Infections and Infestations	are isolated, neonatal, mesenchymal stem cell-derived extracellular vesicles at a dose of 0.2 mg/kg each in a total of 15ml on day 1 and day 3.		2. Improved respiration measured using PaO2/FiO2 at day 1, 2, and onwards daily 3. Mechanical ventilator and vasopressors treatment-free days (number of days that a patient is alive and free from mechanical ventilation and vasopressors) over 28 days. 4. Percentage of patients alive and free of mechanical ventilation at Day 29 5. Ventilator free days (VFD) over 28 days. VFD are defined as one point for each day during the measurement period that are both alive and free of mechanical ventilation. 6. Percentage of patients alive and free of vasopressors at Day 29 7. Vasopressor treatment-free days over 28 days defined as one point for each day during the measurement period that subjects are both alive and free of vasopressors. 8. Time to end of invasive mechanical ventilation 9. Time to end of invasive and/or non-invasive mechanical ventilation 10. Time to end of vasopressors treatment 11. sVP-ARDS-COVID-19 Clinical Response at Day 14 assessed as follows: 11.1 Cure: complete resolution of pneumonia signs and symptoms present at baseline, no new symptoms or complications attributable to the pneumonia 11.2. Non-response: any of the following: 11.2.1. Failure related to pneumonia: Persistence/progression of baseline signs/symptoms of pneumonia; or baseline radiographic abnormalities after at least 2 days of treatment; or development of new pulmonary/extra pulmonary findings consistent with active infection, or development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy; or persistence/progression of baseline signs/symptoms of severe sepsis; or development of new signs/symptoms of severe sepsis; or death due to sepsis 11.2.2. Failure unrelated to pneumonia: Any other cause of clinical response failure than in the investigator's judgement is unrelated to the index pneumonia (myocardial infarction, pulmonary thromboembolism, sepsis of urinary origin, etc.). 11.2.3. Indeterminate: extenuating circumstances precluding classification to one of the above 12. Clinical response at Day 8-10 and Day 29 or early discontinuation: 12.1. Time to sVP-ARDS-COVID-19 cure 12.2. Duration of antiviral treatment 12.3. Rate of pneumonia recurrence/reinfection after clinical cure 12.4. Pneumonia recurrence is defined as a new acute clinical episode of pneumonia, after clinical cure of the episode that qualified the patient for the study, based on the presence of two relevant signs (fever, tachypoea, leukocytosis, or hypoxemia) and

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				radiographic findings of new pulmonary infiltrates or clinically significant worsening of previous ones. If a pathogen isolated in the recurrent episode is phenotypically different from the one isolated in the previous episode this will be considered as reinfection. 13. Time to recurrence/reinfection of pneumonia after clinical cure at sVP-ARDS-COVID-19 clinical response assessments. 14. Survival 28-day all-cause mortality 15. 28-day sVP-ARDS-COVID-19-associated mortality 16. Survival at Day 7, 14, 29, and 90 visits 17. Time to death 18. Time to discharge from ICU 19. Time to discharge from hospital 20. Length of stay in ICU and hospital after randomization 21. Number of ICU-free days over 28 days 22. Changes in Sepsis-related Organ Failure 23. Assessment score daily during stay at ICU 24. Changes on chest X-ray assessed at Screening, and then as medically required with at least one CXR per sVP-ARDS-COVID-19 clinical response assessment until clinical cure from Day 1 to Day 28 and for pneumonia recurrence/reinfection assessment. 25. Evolution of partial pressure of oxygen/fraction inspired oxygen (PaO2/FiO2) daily until Day 7 26. Need of mechanical ventilation or need for non-invasive ventilation 12 hours after the second XoGlo infusion 27. Use of rescue antibiotics i.e. addition or change of antibiotic treatments due to the occurrence of antibiotic resistance posterior to microbiology results at baseline or insufficient efficacy during the course of the study 28. Cell responses on Day 0 Pre-dose and Days 7, 14 and 29 or early discontinuation: 28.1. Cell proliferative capacity in the presence and absence of stimulation 28.2. Cell activation status (phenotype pro/anti-inflammatory monocytes, pro/antiinflammatory T cells, HLADR, CD69) 28.3. Secretion assay of peripheral blood mononuclear cells in response to stimulation 28.4. Evaluation of RNA expression profiles of blood leukocytes on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose and Days 7 and 14 or early discontinuation (only if early termination [ET] is before V9 [Day 14]). 28.5. Evaluation of plasma concentrations of biomarkers on Screening, Day 0 Post-dose, Day 2, Day 3 Post-dose, and Days 7 and 14 or early discontinuation (only if ET is before V9 [Day 14]) 28.6. Protein biomarkers may include, but are not restricted to: TNF-a, IL-1, IL-6, IL-8, IL-10, IL-17, soluble triggering receptor expressed on myeloid cells 1, C-reactive

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				protein, plasminogen activator inhibitor-1, protein C, sE selectin, angiopoietin-1, and angiopoietin-2, troponin-I
IRCT20160809029275N1 Iran (Islamic Republic of)	Covid-19 disease. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: Group receiving mesenchymal stem cells. In this group, patients in 3 times (1, 3 and 6 days) are received 1 million Umbilical core-derived MSCc/BW by intravenous injection (Through the catheter and the Central vein and from the superior vena cava vein). Also, in addition to cell therapy,Other common treatments will be given to patients according to the physician's supervision.Mesenchymal Stem cells had an ISCT standard and were given from a healthy donor. Blood samples were given from patients on days 0, 2, and 7, as well as 14 days after the second injection and patients will follow for 20 days (in terms of clinical and immunological parameters).It should be noted that of all patients at the beginning of the study conscious consent form will be received	Intervention 2: Control group: Receiving common therapies (without stem cell). In this group, patients are received other common treatments including antiviral drugs and etc In accordance with the physician's opinion and do not receive stem cells.	Respiratory symptoms and pulmonary function in patients. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using CT scan image , physical examination , Oxygen saturation Percentage.;Evaluation of IFN-?,IL4,TGF-ÃŸ,IL1-ÃŸ , IL-6 and TNF-a cytokine levels in patients blood. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using Elisa kits.;Cell markers and populations. Timepoint: In onset of study and days 2, 7 and 14 after the second injection. Method of measurement: Using Flow cytometery technique.
NCT04444271 Pakistan	COVID-19	Drug: Mesenchymal stem cells	Other: Placebo	Overall survival Clinical improvement;Time of COVID19 PCR negativity;Radiological improvement (day 15 and day 30 assessment);days required to discharge from hospital
ACTRN12620000612910 Australia	COVID-19;	Treatment: Other-Mesenchymoangioblast-derived mesenchymal stem cells (CYP-001 Intervention group: Mesenchymoangio	Control group: standard of care in ICU. The active agent in CYP-001 is allogeneic mesenchymoangioblast-derived mesenchymal stem	To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in intensive care units (ICU), based on improvements in P/F ratio compared to controls. This outcome is defined as a trend in trajectory of P/F ratio between groups by day 7. P/F ratio is collected from ventilatory support data combined with arterial blood

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
		blast-derived mesenchymal stem cells (CYP-001) at a dose of 2 million cells/kg (up to a maximum of 200 million cells) by IV infusion on two occasions (Day 1 and Day 3) PLUS standard of care in ICU	cells (MCA-derived MSCs), which are produced using the proprietary Cymerusâ„¢ platform technology. Cymerus refers to the process of generating cell-based products from intermediate cells, MCAs, which in turn are derived from induced pluripotent stem cells or iPSCs. The iPSCs used in the Cymerus process were derived from blood donated by a fully-consented healthy adult donor, and were reprogrammed using a transgene-free, viral-free and feeder-free technique	gas measures[By day 7 in the study (within days 1-7). P/F ratio will be collected as per routine standard collection of data to inform respiratory function (at least 4 hourly when relevant) plus every 15 minutes during cell adminstration and 1, 2, 3, 4 and 5 hours after];To assess the safety and tolerability of CYP-001 in adults with COVID-19 being treated in ICU measured by the incidence and severity of treatment-emergent adverse events (including events related with reactions to cryoprotectant; fever read from digital thermometer, allergy, olfactory/taste disturbances), safety laboratory evaluations (immunology screen with full blood examination) and vital signs (including significant fluctuations from clinically acceptable BP, and HR and SaO2 levels measured via pulse oximetry)[Up to day 28 in the study. On days 0-7 this will be collected routinely in standard care (at least 4-hourly) plus every 15 minutes during cell administration and 1, 2, 3, 4 and 5 hours after, then daily after day 8] To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, measured by changes in blood inflammatory marker, C-reactive protein[Up to day 7 after patient enrolment in study, collected as part of standard care pathology analysis occurring daily];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on changes in physiological indices of respiratory dysfunction (including exploratory measures of P/F ratio, respiratory rate, oxygenation index (OI), respiratory compliance, positive end-expiratory pressure (PEEP), fever monitoring, ICU length of stay, ventilator free days (VFDs)) from data collected routinely in standard care (i.e. records of extubation, reintubation) up to day 28. [Up to day 28 after patient enrolment in study, collected as per routine standard collection of data to inform respiratory function (at least 4 hourly when relevant) and at the same intervals as P/F ratio];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups on the Clinical Improvement Scale[Assessed on day 28 after patient enrolment in study, based on health and hospitalisation status];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups in Quality of Life and Disability assessments measured by the 36-Item Short Form Survey (SF-36)[Assessed on day 28 after patient enrolment in study];To evaluate the early efficacy of CYP-001 in adults with COVID-19 being treated in ICU, based on proportional differences between groups in Quality of Life and Disability assessments measured by the Standardised Mini-Mental

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				State Examination (SMMSE)[Assessed on day 28 after patient enrolment in study]
IRCT20200421047150N1 Iran (Islamic Republic of)	COVID-19	Intervention 1: Intervention group: In this group, umbilical cord Whartonâ€™s jelly mesenchymal stem cells are infused at an initial dose of 0.5-2 milion/ kg. This process is performed on the first, third and sixth days. This intervention is done along with other standard treatments for this type of patients, varying in severity of COVID-19 Infectious, and in accordance with national and international guidelines.	Intervention 2: Control group: This group, like the intervention group, will receive all standard medication according to national and international guidelines, depending on the severity of COVID-19. But on the first, third and sixth day, placebo (normal saline) is infused.	Death. Timepoint: Up to 28 days after starting the study. Method of measurement: Patient observation and evaluation of vital signs. Evaluation of Pneumonia Severity Index. Timepoint: Up to 28 days. Method of measurement: PSI.;Evaluation of oxygen supply index. Timepoint: Discharge from ICU. Method of measurement: Pulse Oximeter.;Improve pneumonia evaluated by CT scan. Timepoint: After the second and third infusions. Method of measurement: CT scan.;+ CD4 + / CD8 ratio. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Counting of CD3 +, CD4 + and CD8 + T cells. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Lymphocyte count. Timepoint: Until the marker is normalized. Method of measurement: CBC.;Procalcitonin. Timepoint: Until the marker is normalized. Method of measurement: Blood sample.;C-Reactive protein. Timepoint: 28 days or until the marker is normalized. Method of measurement: Blood sample.
IRCT20200413047063N1 Iran (Islamic Republic of);Iran (Islamic Republic of)	Acute Respiratory Distress Syndrome of COVID-19. COVID-19;U07.1	Intervention 1: Intervention group:Intervention group: The intervention group 1, Patients will receive three doses of MSCs. Two doses of 100Ã—10e6 (Â±10%) cells will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2 and day 4.	Intervention 2: Control group: Patients will receive conventional therapy.	Adverse events assesment. Timepoint: At the same time of each intervention, 24 hours after each intervention, on days 6, 7, 14 and 28 after the first intervention. Method of measurement: Number of participants with treatment-related adverse events as assessed by CTCAE v4.0.;Blood oxygen saturation. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement. Biomarkers concentrations in plasma. Timepoint: At baseline, 7, 14, 28 days after the first intervention. Method of measurement: Biochemical examination.;Respiratory efficacy. Timepoint: From baseline to day 7. Method of measurement: Evaluated by the increase in PaO2/FiO2 ratio.;Intensive care unit-free days. Timepoint: Up to day 8. Method of measurement: Number of day.;Change in clinical symptoms. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement.
NCT04348435 United States	COVID-19	Drug: HB-adMSCs	Drug: Placebo	Incidence of hospitalization for COVID-19;Incidence of symptoms associated with COVID-19 Absence of upper/lower respiratory infection;Leukocyte differential;C Reactive protein;TNF alpha;IL-6;IL-10;Glucose;Calcium;Albumin;Total protein;Sodium;Total carbon

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				dioxide;Potassium;Chloride;BUN;Creatinine; Alkaline phosphatase;Alanine aminotransferase;Total bilirubin;white blood cells;red blood cells;hemoglobin;hematocrit;mean corpuscular volume;mean corpuscular hemoglobin;mean corpuscular hemoglobin concentration;red cell distribution width;neutrophils;Lymphs;Monocytes;Eosinophils;Basophils;Absolute neutrophils;Absolute lymphs;Absolute monocytes;Absolute eosinophils;Absolute basophils;Immature granulocytes;Platelets;Prothrombin time;INR;SF-36;PHQ-9
IRCT20200217046526N2 Iran (Islamic Republic of);Iran (Islamic Republic of)	Acute Respiratory Distress Syndrome of COVID-19.	Intervention 1: Intervention group: The intervention group 1, Patients will receive three doses of MSCs. Two doses of 100Ã—10e6 (Â±10%) cells will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2	Intervention 2: The intervention group 3, Patients will receive two doses of MSCs intravenously and EVs. Two doses of 100Ã—10e6 (Â±10%) MSCs will intravenously infuse as a normally dropped single dose over 10-12 minutes at the infusion speed of 4-5 mL/minute in day 0 and day 2. In days 4 and 6, the patients will receive two times the infusion of MSCs-EVs. Intervention 3: Control group: Patients will receive conventional therapy.	Adverse events assesment. Timepoint: At the same time of each intervention, 24 hours after each intervention, on days 6, 7, 14 and 28 after the first intervention. Method of measurement: Number of participants with treatment-related adverse events as assessed by CTCAE v4.0.;Blood oxygen saturation. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement. Biomarkers concentrations in plasma. Timepoint: At baseline, 7, 14, 28 days after the first intervention. Method of measurement: Biochemical examination.;Respiratory efficacy. Timepoint: From baseline to day 7. Method of measurement: Evaluated by the increase in PaO2/FiO2 ratio.;Intensive care unit-free days. Timepoint: Up to day 8. Method of measurement: Number of day.;Change in clinical symptoms. Timepoint: At Baseline, simultaneously with each intervention and on days 5, 6, 7, 14 after the first intervention. Method of measurement: Evaluation of Pneumonia Improvement.
NCT04341610 Denmark	COVID-19	Drug: allogeneic adipose-derived mesenchymal stromal cell	Placebo: saline	Changes in clinical critical treatment index Days of respirator treatment;Improvement of clinical symptoms including duration of fever and respiratory need;Mortality;Marker of Immunological function -CD4+ and CD8+ T cell count;C-reactive protein and leucocyte;Cytokine profile;Glomerular Filtration Rate;Duration of hospitalization
IRCT20140528017891N8 Iran (Islamic Republic of)	COVID-19. Severe Acute Respiratory Syndrome coronavirus;RA01.0	Intervention 1: Intervention group: In this group, mesenchymal stem cells will be injected at an initial dose of 0.5-1 milion/ kg. This process will be performed on the first, third and sixth days. This	Intervention 2: Control group:This group, like the intervention group, will receive all routine medication according to national and international guidelines, depending on the	Death. Timepoint: Up to 28 days after starting the study. Method of measurement: Patient observation and evaluation of vital signs. Evaluation of Pneumonia Severity Index. Timepoint: Up to 28 days. Method of measurement: PSI.;Evaluation of oxygen supply index. Timepoint: Discharge from ICU. Method of measurement: Pulse Oximeter.;C- Reactive protein. Timepoint: 28 days or until the marker is normalized. Method of measurement: Blood

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
		intervention will be done along with other treatments for this type of patients, varying in severity of COVID Infectious, and in accordance with national and international guidelines. Mesenchymal Stem Cell is GMP-approved by SinaCell	severity of COVID-19. But on the first, third and sixth day, placebo (normal saline) will be injected.	sample.;Procalcitonin. Timepoint: Until the marker is normalized. Method of measurement: Blood sample.;Lymphocyte count. Timepoint: Until the marker is normalized. Method of measurement: CBC.;Counting of CD3 +, CD4 + and CD8 + T cells. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;+ CD4 + / CD8 ratio. Timepoint: Before the first injection and after the third injection. Method of measurement: Flow cytometry.;Improve pneumonia evaluated by CT scan. Timepoint: After the second and third infusions. Method of measurement: CT scan.
NCT04346368 China	Coronavirus Disease 2019 (COVID-19)	Biological: BM-MSCs	Biological: Placebo	Changes of oxygenation index (PaO2/FiO2);Side effects in the BM-MSCs treatment group Clinical outcome;Hospital stay;CT Scan;Changes in viral load;Changes of CD4+, CD8+ cells count and concentration of cytokines;Rate of mortality within 28-days;Changes of C-reactive protein
NCT04429763	COVID-19	Biological: Umbilical cord derived mesenchymal stem cells	Biological: Placebo	Clinical deterioration or death
NCT04315987 Brazil	COVID-19 Pneumonia	Biological: NestaCell	Biological: Placebo	Change in Clinical Condition|Rate of mortality within 10-days|Change of Clinical symptoms - respiratory rate|Hypoxia|PaO2 / FiO2 ratio|CD4+ and CD8+ T cell count|Changes of blood oxygen|Side effects in the treatment group|Complete blood count, cardiac, hepatic and renal profiles;
NCT04336254 China	COVID-19	Biological: allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC)	Other: Intravenous saline injection (Placebo)	TTCI|Lung lesion|Immune function|Time of SARS-CoV-2 clearance|Blood test|SPO2|RR|Body temperature|Side effects in the treatment group|C-reactive protein (mg/L)
NCT04611256 Mexico	Covid19	Biological: MSC	Drug: Control	Change form baseline in Arterial oxygen saturation|Days to clinical improvement|Change Form Baseline in C reactive protein at 25 days|Change Form Baseline Immune cells: CD3+, CD4+, CD8+, CD16+, CD19+, and CD56+ lymphocytes|Change Form Baseline in pro-inflammatory cytokines: IL-1Î², IL- 2, TNF-Î±, ITN-Î³, IL-4, IL-6, IL-10|Change Form Baseline in Immunoglobulins; IgA, IgG, IgM, and IgE.
NCT04288102 China *Completed	Corona Virus Disease 2019(COVID-19)	Biological: UC-MSCs	Saline with albumin	Change in lesion proportion (%) of full lung volume from baseline to day 28.|Change in lesion proportion (%) of full lung volume from baseline to day 10 and 90|Change in consolidation lesion proportion (%) of full lung volume from baseline to day 10, 28 and 90.|Change in ground-glass lesion proportion (%) of full lung volume from baseline to day 10, 28 and 90.|Pulmonary fibrosis - related

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				morphological features in CT scan at day 90 a. cord-like shadow b. honeycomb-like shadows c. interlobular septal thickening d. intralobular interstitial thickening e. pleural thickening|Lung densitometry: Change in total voxel 'weight' in lesion area voxel 'weight'=voxel density (in HU) Ã— voxel volume (in voxel)|Lung densitometry: volumes histogram of lung density distribution (<-750, -750~-300, -300~50, >50) at day 10, 28 and 90.|Time to clinical improvement in 28 days.|Oxygenation index(PaO2/FiO2)|Duration of oxygen therapy(days)|Blood oxygen saturation|6-minute walk test|Maximum vital capacity (VCmax)|Diffusing Capacity (DLCO)|mMRC (Modified Medical Research Council) dyspnea scale|Changes of absolute lymphocyte counts and subsets from baseline to day 6, 10, 28 and 90.|Changes of cytokine/chemokine levels from baseline to day 6, 10, 28 and 90.|Adverse events|Serious adverse events|All-cause mortality
NCT04366271 Spain	COVID	Biological: Mesenchymal cells	Drug: Standard of care	Mortality due to lung involvement due to SARS-CoV-2 virus infection at 28 days of treatment|Mortality due to lung involvement due to SARS-CoV-2 virus infection at 14 days of treatment|Mortality from any cause at 28 days|Days without mechanical respirator and without vasopressor treatment for 28 days|Patients alive without mechanical ventilation and without vasopressors on day 28|Patients alive and without mechanical ventilation on day 14|Patients alive and without mechanical ventilation on day 28|Patients alive and without vasopressors on day 28|Days without vasopressors for 28 days|Patients cured at 15 days|Incidence of Treatment-Emergent Adverse Events
NCT04371601 Fujian, China	COVID-19 Pneumonia	Mesenchymal stem cells	Drug: Oseltamivir	Changes of oxygenation index (PaO2/FiO2) ,blood gas test|Detection of TNF-Î± levels, IL-10 levels|Detection of immune cells that secret cytokines, including CXCR3+, CD4+, CD8+, NK+ cells, and regulatory T cells (CD4 + CD25 + FOXP3 + Treg cells).|Changes of c-reactive protein and calcitonin
NCT04366323 Spain	Sars-CoV2	Drug: allogeneic and expanded adipose tissue-derived MSCs	No intervention	Safety of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Adverse Event Rate|Efficacy of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Survival Rate
NCT04625738	COVID19 ARDS	Biological: Ex vivo expanded Wharton's Jelly Mesenchymal Stem Cells	Biological: Placebo	PaO2 / FiO2 ratio|respiratory function evolution|respiratory assistance|organ failures 1|organ failures 2|organ failures 3|duration of intensive care|Cause of death|respiratory morbidity (TDM, functional respiratory measures)|viral load|Anti-HLA

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				antibody rate|immediate hypersensitivity reactions|thromboembolic adverse events 1|thromboembolic adverse events 2|infectious adverse events
NCT04273646 China	2019 Novel Coronavirus Pneumonia|COVID-19	Biological: UC-MSCs	Drug: Placebo	Pneumonia severity index|Oxygenation index (PaO2/FiO2)|Side effects in the UC-MSCs treatment group|28-days survival|Sequential organ failure assessment|C-reactive protein|Procalcitonin|Lymphocyte count|CD3+, CD4+ and CD8+ T celll count|CD4+/CD8+ratio
NCT04348435 United States	COVID-19	Drug: HB-adMSCs	Drug: Placebos	Incidence of hospitalization for COVID-19|Incidence of symptoms associated with COVID-19|Absence of upper/lower respiratory infection|Leukocyte differential|C Reactive protein|TNF alpha|IL-6|IL-10|Glucose|Calcium|Albumin|Total protein|Sodium|Total carbon dioxide|Potassium|Chloride|BUN|Creatinine|Alkaline phosphatase|Alanine aminotransferase|Total bilirubin|white blood cells|red blood cells|hemoglobin|hematocrit|mean corpuscular volume|mean corpuscular hemoglobin|mean corpuscular hemoglobin concentration|red cell distribution width|neutrophils|Lymphs|Monocytes|Eosinophils|Basophils|Absolute neutrophils|Absolute lymphs|Absolute monocytes|Absolute eosinophils|Absolute basophils|Immature granulocytes|Platelets|Prothrombin time|INR|SF-36|PHQ-9
NCT04339660 China	COVID-19	Biological: UC-MSCs	Other: Placebo	The immune function (TNF-alpha, IL-6)|Blood oxygen saturation|Rate of mortality within 28-days|Size of lesion area by chest imaging|CD4+ and CD8+ T cells count|Peripheral blood count recovery time|Duration of respiratory symptoms (fever, dry cough, difficulty breathing, etc.)|COVID-19 nucleic acid negative time
NCT04629105 United States	ARDS, Human|Covid19	Biological: Longeveron Mesenchymal Stem Cells (LMSCs)	Other: Placebo	Incidence of Treatment-Emergent Serious Adverse Events|Number of Participants with Abnormal Clinical Significant Laboratory Values in Hematology.|Number of Participants with Changes in Echocardiography Overall Assessment|Number of Participants with Changes to overall assessment of Electrocardiogram|Time to recovery of Sp02|Number of Participants with Abnormal Clinical Significant Lab Values in the Blood Chemistry testing.|Number of Participants with Abnormal Clinical Significant Lab Values in the Coagulation.|Number of Participants with Abnormal Clinical Significant Lab Values in the Urinalysis|Immunity|Change in Imaging via X-ray|Change in Imaging via Computerized Tomography

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
NCT04753476 Indonesia	Covid-19|Cytokine Storm	Biological: Injection of Secretome-MSCs	Drug: Standard treatment of Covid-19	Change in patients clinical manifestation|Need for a ventilator|Duration of using a ventilator|Length of stay|Routine blood profile|CRP|D-dimer|Blood Gas Analisis (BGA)|Photo thorax|Survival
NCT04428801	COVID-19	Biological: autologous adipose-derived stem cells	Placebo	Tolerability and acute safety of AdMSC infusion by assessment of the total number of AEs/SAEs related and non-related with the medication|The overall proportion of subjects who develop any AEs/SAEs related and non-related with the AdMSC infusions as compared to the control group|COVID-19 incidence rates in both the study and control groups|The proportion of subjects who are infected by SARS-Cov-2 measured by PCR or other nuclear level-based SARS-Cov-2 virus testing in respiratory tract specimens (oropharyngeal samples) collected by oropharyngeal swab using the CDC standard method.|The proportion of subjects who are infected by SARS-Cov-2 virus develop symptoms including mild, classic, severe and critical sever cases between study group and control group.|Change of proportion of subjects who are infected by SARS-Cov-2 and develop IgM/IgG antibodies against SARS-Cov-2 between study group and control group.|Change of lymphocyte count in white blood cell counts from the baseline|Change of PaO2 arterial blood gases from the baseline|Compare the proportion of subjects who develop severe COVID-19 pneumonia cases for both study and control groups|COVID-19 mortality rates for both study and control groups|Change of C-reactive protein (CRP) (mg/L) from the baseline|Change of D-dimer (mg/L) from the baseline|Change of Procalcitonin (ug)/L from the baseline|Change of pro-type B natriuretic peptide (pro-BNP) (pg/mL) from the baseline|Change of Bilirubin (mg/dL) from the baseline|Change of Creatinine (mg/dL) from the baseline|Change in blood test values for cytokine panels (IL-1Î², IL-6, IL-8, IL-10, TNFÎ±) from the baseline|The proportion of subjects from SARS-CoV-2 RT-PCR positive to negativity in respiratory tract specimens (oropharyngeal samples) collected by oropharyngeal swab using the CDC standard method. as compared to control group|Quantifying viral RNA in stool for baseline and final follow-up.
NCT04728698 United States	Covid19|ARDS	Drug: COVI-MSC	Drug: Placebo	Mortality at Day 28|Mortality at Days 60 and 90|Number of ventilator-free days|Improvement in oxygenation|SOFA score at Day 28
NCT04457609 Indonesia	COVID|Pulmonary Infection|Sars-CoV2	Biological: Umbilical Cord Mesenchymal Stem Cells	Drug: Oseltamivir Drug: Azithromycin	Clinical improvement: Presence of dyspnea|Clinical improvement: presence of sputum|Clinical improvement: fever|Clinical improvement: ventilation status|Clinical improvement: blood pressure|Clinical improvement: heart rate|Clinical

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				improvement: respiratory rate|Clinical improvement: oxygen saturation|General laboratory outcome from leukocyte level|General laboratory outcome from lymphocytes level|General laboratory outcome from blood pH|General laboratory outcome from blood level of CO2|General laboratory outcome from blood base excess level|General laboratory outcome from blood oxygen partial pressure|General laboratory outcome from blood level of HCO3|General laboratory outcome from blood level of O2 saturation|General laboratory outcome from level of CRP|General laboratory outcome from level of SGOT/SGPT (AST/ALT)|General laboratory outcome from the level of ureum/creatinine level|General laboratory outcome from the level of eGFR|General laboratory outcome from the level of sodium|General laboratory outcome from the level of potassium|General laboratory outcome from the level of chloride|Changes in procalcitonin level|General laboratory outcome from albumin level|General laboratory outcome from total bilirubin level|Changes in D-Dimer level|Changes in fibrinogen level|Cardiac changes from troponin level|Cardiac changes from NT proBNP level|Changes in Leukemia Inhibiting Factor|Changes in level of IL-6|Changes in level of IL-10|Changes in level of vascular endothelial growth factor (VEGF)|Changes in level of ferritin|Changes in level of CXCR3|Changes in level of CD4|Changes in level of CD8|Changes in level of CD56|Radiologic Improvement from Chest X-Ray/CT Scan
NCT04490486 United States	COVID-19|Acute Respiratory Distress Syndrome|Corona Virus Infection	Biological: UCMSCs	Other: Placebo	Percent of participants with treatment related Serious Adverse Events (SAE)|Change in inflammatory marker levels|Change in systemic inflammatory marker levels|COVID-19 Viral Load|Change in SOFA score|Change in electrolytes levels|Change in LDH levels|Number of subjects discharged from the ICU|Percentage of participants with less requirement for vasoactive agents|Rate of Mortality|Percentage of participants with changes in immune marker expression|Percentage of participants with changes in radiologic findings|Percentage of participants with less pneumonia symptoms
NCT04366063 Royan Institute, Tehran, Iran, Islamic Republic of	Covid-19	Two MSC infusion Two MSC infusion plus two extracellular vehicles	Conventional therapy	Adverse events assessment|Blood oxygen saturation|Intensive care unit-free days|Clinical symptoms|Respiratory efficacy|Biomarkers concentrations in plasma
NCT04573270 United States *Completed	Covid19|Prophylaxis	Biological: PrimePro (MSC)	Other: Placebo	Survival Rates|Contraction Rates

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
NCT04355728 United States *Completed	Corona Virus Infection|ARDS|ARDS, Human|Acute Respiratory Distress Syndrome|COVID-19	Biological: Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care.	Other: Vehicle + Heparin along with best supportive care	Incidence of pre-specified infusion associated adverse events|Incidence of Severe Adverse Events|Survival rate after 90 days post first infusion|Ventilator-Free Days|Change in Oxygenation Index (OI)|Plat-PEEP|Sequential Organ Failure Assessment (SOFA) Scores|Small Identification Test (SIT) scores|Troponin I levels|C-Reactive Protein levels|Arachidonic Acid (AA)/Eicosapentaenoic Acid (EPA) Ratio|D-dimer levels|25-Hydroxy Vitamin D levels|Alloantibodies levels|Blood white cell count|Platelets count
NCT04362189 United States	COVID-19	Drug: HB-adMSC	Drug: Placebo	Interleukin-6|C Reactive protein|Oxygenation|TNF alpha|IL-10|Return to room air (RTRA)|EKG qt interval|Leukocyte differential|Glucose|Calcium|Albumin|Total protein|Sodium|Total carbon dioxide|Potassium|Chloride|BUN|Creatinine|Alkaline phosphatase|Alanine aminotransferase|Total bilirubin|White blood cells|Red blood cells|Hemoglobin|Hematocrit|Mean corpuscular volume|Mean corpuscular hemoglobin|Mean corpuscular hemoglobin concentration|Red cell distribution width|Neutrophils|Lymphs|Monocytes|Eosinophils|Basophils|Absolute neutrophils|Absolute lymphs|Absolute monocytes|Absolute eosinophils|Absolute basophils|Immature granulocytes|Platelets|Prothrombin time|INR|NK cell surface antigen (CD3-CD54+)|CD4+/CD8+ ratio|Myoglobin|Troponin|Creatinine kinase MB|Serum ferritin|Adverse events|7-point ordinal scale|D-dimer|Chest X-ray|CT scan|PCR test for SARS-CoV-2
NCT04565665 United States	COVID-19 Infection|COVID-19-Associated Acute Respiratory Distress Syndrome|Hematopoietic and Lymphoid Cell Neoplasm|Malignant Solid Neoplasm|Symptomatic COVID-19 Infection Laboratory-Confirmed	Biological: Mesenchymal Stem Cell	Standard of care	Incidence of composite serious adverse events (Phase I)|Patients alive without grade 3, 4 infusional toxicity (Phase II)|Patients alive with grade 3 or 4 infusional toxicity (Phase II)|Patients not alive (Phase II)|Proportion of successfully extubated patients who present intubated on ventilator support (Phase I)|Rate of successful progression to intubation in patients who require supplemental oxygen but who are otherwise able to breathe without assistance (Phase I)|Overall survival rate (Phase I)|Survival rate in patients who present intubated on ventilator support (Phase I)|Survival rate in patients who require supplemental oxygen but who are otherwise able to breathe without assistance (Phase I)|Clinical parameters (Phase I)|Oxygenation parameters (Phase I)|Respiratory parameters (Phase I)|Laboratory markers (Phase I)|Hospitalization stay (Phase I)|Intensive care unit stay (Phase I)|Incidence of infusion-related adverse events (Phase I)

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
NCT04535856 Indonesia *Completed	Covid19|Corona Virus Infection|SAR	Drug: allogeneic mesenchymal stem cell	Other: Placebo	Incidence of TEAE* in Treatment group|Survival rate|Duration of hospitalization|Clinical improvement Ordinal scale|Clinical improvement National EWS|Clinical improvement Oxygenation index|Clinical improvement Lung involvement change|Clinical improvement Inflammation markers change
NCT04390152 Colombia	Acute Respiratory Distress Syndrome	Drug: Wharton's jelly derived Mesenchymal stem cells.	Drug: Hydroxychloroquine, lopinavir/ritonavir or azithromycin and placebo (standard therapy)	Intergroup mortality difference with treatment|Number of patients with treatment related adverse events|Difference in days of mechanical ventilation between groups|Median reduction of days of hospitalization|Median reduction of days of oxygen needs|Difference between "Sequential Organ Failure Assessment" score between groups|Difference between median Murray score between groups|Difference in APACHE II score between groups|Difference in lymphocyte count between groups|Changes in C reactive protein concentration between groups|Changes in D dimer concentration|Changes in ferritin concentration|Changes in lactate dehydrogenase concentration|Impact on interleukin 6 concentrations between groups.|Impact on interleukin 8 concentrations between groups.|Impact on interleukin 10 concentrations between groups.|Impact on tumor necrosis factor alpha concentrations between groups.
NCT04494386 United States	Covid19|Corona Virus Infection|SARS-CoV Infection|ARDS|Coronavirus	Biological: Umbilical Cord Lining Stem Cells (ULSC)	Other: Placebo (carrier control)	Incidence of Dose Limiting Toxicity (DLT)|Incidence of Dose Limiting Toxicity (DLT), suspected adverse reaction (SAR), or serious adverse event (SAE)|Treatment-emergent adverse events (AE) and serious adverse events (SAE)|Levels of COVID-19 related ARDS as defined by the Berlin Definition of ARDS|Changes from baseline pulse oximetric saturation SpO2/FiO2 ratio or arterial oxygen pressure pAO2/FiO2 ratio|Number of ventilator-free days (VFD)|Changes in Complete Blood Count (CBC) with differential from baseline|Changes in levels of blood glucose (mg/dL) from baseline|Changes in levels of sodium (mEq/L) from baseline|Changes in levels of potassium (mEq/L) from baseline|Changes in levels of blood urea nitrogen (BUN; mg/dL) from baseline|Changes in levels of alanine transaminase (ALT; U/L) from baseline|Change in Urinalysis (UA) from baseline
NCT04377334 Germany	ARDS|COVID-19	Biological: MSC	No intervention	lung injury score|D-dimers|phenotype|pro-resolving lipid mediators|cytokines|chemokines|Survival|extubation|lymphocyte subpopulations|SARS-CoV-2-specific antibody titers|complement molecules (C5-C9)

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
NCT04345601 United States	Sars-CoV2|Acute Respiratory Distress Syndrome|COVID-19	Biological: Mesenchymal Stromal Cells	Other: Supportive Care	Treatment-related serious adverse events (tSAEs)|Change in clinical status at day 14
NCT04397796 United States	COVID	Biological: BM-Allo.MSC	Biological: Placebo	Incidence of AEs|Mortality|Death|Number of ventilator-free days|Improvement of one category|7-point ordinal scale|NEWS|NEWS of â‰¤ 2|Sequential Organ Failure Assessment (SOFA)|Oxygen|Hospitalization|Incidence of SAEs
NCT04390139 Spain	COVID-19|SARS-CoV-2|Adult Respiratory Distress Syndrome	Drug: XCEL-UMC-BETA (Wharton-Jelly mesenchymal stromal cells)	Other: Placebo	All-cause mortality at day 28|Safety of WJ-MSC|Need for treatment with rescue medication|Need and duration of mechanical ventilation|Ventilator free days|Evolution of PaO2 / FiO2 ratio|Evolution of the SOFA index|Evolution of the APACHE II score|Duration of hospitalization|Evolution of markers of immune response (leucocyte count, neutrophils)|Feasibility of WJ-MSC administration|Evolution of disease biomarker: polymerase chain reaction (RT-PCR)|Evolution of disease biomarker: lactate dehydrogenase (LDH)|Evolution of disease biomarker: D-dimer|Evolution of disease biomarker: Ferritin
NCT04780685 United States	Covid19 with ARDS	Biological: hMSC via IV administration	Placebo Comparator: Lactated Ringer's Solution	Survival|Number of patients with treatment-related adverse events as assessed by CTCAE v4.0
NCT04798716 United States	Covid19|Novel Coronavirus Pneumonia|Acute Respiratory Distress Syndrome	Drug: MSC-exosomes delivered intravenously every other day on an escalating dose: (2:4:8)	Drug: MSC-exosomes delivered intravenously every other day on an escalating dose (8:4:8) Drug: MSC-exosomes delivered intravenously every other day (8:8:8)	Measure and report the number of participants with treatment-related-adverse events as assessed by CTCAE v4.0; for patients receiving ARDOXSOâ„¢, perinatal MSC-derived exosome therapy.|Tabulate and report the number of IMV days for patients receiving ARDOXSOâ„¢ perinatal MSC-derived exosome therapy.|Analyze and report organ failure, associated with ICU mortality in participants confirmed with SARS-CoV2 infection, receiving ARDOXSOâ„¢ as an interventional exosome therapy.|Record and analyze respiratory measures (Berlin Score/PEEP) following treatment regime.
NCT04392778 Turkey	Covid19|Pneumonia|Multiple Organ Failure|Corona Virus Infection	Biological: MSC Treatment	Biological: Saline Control	Clinical improvement|Lung damage improvement|Sars-Cov-2 viral infection laboratory test|Blood test
NCT04537351 Australia	Covid19 with Acute Respiratory Distress Syndrome	Biological: CYP-001	Standard of care	Trend in trajectory of PaO2/FiO2 ratio (P/F ratio) between groups|Incidence and severity of treatment-emergent adverse events|Change in C-reactive protein (CRP) levels|Proportional differences between groups on the Clinical Improvement

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
				Scale|Changes in P/F ratio|Changes in respiratory rate|Changes in oxygenation index|Changes in respiratory compliance (the change in lung volume per unit change in transmural pressure gradient)|Changes in positive end-expiratory pressure|Ventilator-free days|Proportional differences between groups on the SF-36|Proportional differences between groups on the mini mental state examination
NCT04398303	COVID-19 Pneumonia	Biological: ACT-20-MSC|Biological: ACT-20-CM	Biological: Placebo	Mortality at day 30|Ventilated Subjects - Ventilator Free Days|Ventilated Subjects - Improvement in Ventilator Settings|High-Flow O2 Support Subjects - Step-Down O2 Therapy|High Flow O2 Support Subjects - Respiration Rate|Both Ventilated and High-Flow O2 Support Subjects - ICU-Free Days|Both Ventilated and High-Flow O2 Support Subjects - Pulmonary Function Improvement|Both Ventilated and High-Flow O2 Support Subjects - Increased Berlin Score
NCT04361942 Hospital Universitario Rio Hortega, Valladolid, Spain	COVID-19 Pneumonia	Biological: Mesenchymal Stromal Cells	Other: Placebo	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation|Rate of mortality|Proportion of patients who have achieved clinical response|Proportion of patients who have achieved radiological responses
NCT03042143 Belfast Health and Social Care Trust, Royal Hospitals, Belfast, Northern Ireland, United Kingdom	COVID-19 with Acute Respiratory Distress Syndrome	Biological: Human umbilical cord derived CD362 enriched MSCs	Biological: Placebo (Plasma-Lyte 148)	Oxygenation index (OI)|Incidence of Serious Adverse Events (SAEs)|Oxygenation index|Sequential Organ Failure Assessment (SOFA) score|Respiratory compliance (Crs)|Partial pressure of arterial oxygen to the fraction of inspired oxygen ratio (P/F ratio)|Driving Pressure|Extubation and reintubation|Ventilation free days at day 28|Length of ICU and hospital stay|28-day and 90-day mortality
NCT04437823 Pakistan	Coronavirus Infection, moderate to severe	Biological: Intravenous Infusions of Stem Cells	Standard of care	Safety and efficacy assessment of infusion associated adverse events|Chest Radiograph or Chest CT Scan|COVID-19 Quantitative Real Time PCR|Sequential Organ Failure Assessment (SOFA) Score|Rate of mortality|Clinical Respiratory Changes
NCT04602442 Russian Federation	Covid19|SARS-CoV-2 PNEUMONIA| COVID-19	Drug: EXO 1 inhalation Drug: EXO 2 inhalation	Drug: Placebo inhalation	Number of participants with non-serious and serious adverse events during trial|Number of participants with non-serious and serious adverse during inhalation procedure|Time to clinical recovery (TTCR)|SpO2 concentration changes|Chest Imaging Changes|Blood biochemistry (CRP)|Procalcitonin concentration|Ferritin concentration|Creatinine concentration|Urea concentration
NCT04371393 United States	Acute Respiratory Distress	Biological: Remestemcel-L	Drug: Placebo + standard of care	Number of all-cause mortality|Number of days alive off mechanical ventilatory support|Number of adverse events|Number

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
	Syndrome|COVID	MSC + standard of care		of participants alive at day 7|Number of participants alive at day 14|Number of participants alive at day 60|Number of participants alive at day 90|Number of participants alive at 12 Months|Number of participants with resolution and/or improvement of ARDS|Severity of ARDS|Length of stay|Readmissions|Length of Stay in Intensive Care Unit|Clinical Improvement Scale|Change in plasma hs-CRP concentration|Change in serum hs-CRP concentration|Change in IL-6 inflammatory marker level|Change in IL-8 inflammatory marker level|Change in TNF-alpha inflammatory marker level|Pulmonary symptoms
NCT04491240 Russian Federation *Completed	Covid19|SARS-CoV-2 PNEUMONIA| COVID-19	Drug: EXO 1 inhalation Drug: EXO 2 inhalation	Drug: Placebo inhalation	Number of Participants With Non-serious and Serious Adverse Events During Trial|Number of Participants With Non-serious and Serious Adverse During Inhalation Procedure|Time to Clinical Recovery (TTCR)|SpO2 Concentration|C-reactive Protein|Lactic Acid Dehydrogenase (LDH)
NCT04333368 France	Severe Acute Respiratory Syndrome Coronavirus 2|Severe Acute Respiratory Distress Syndrome	Biological: Umbilical cord Wharton's jelly-derived MSC	NaCl 0.9%	Respiratory efficacy evaluated by the increase in PaO2/FiO2 ratio from baseline to day 7 in the experimental group compared with the placebo group|Lung injury score|Oxygenation index|In-hospital mortality|Mortality|Ventilator-free days|Number of days between randomization and the first day the patient meets weaning criteria o Number of days between randomization and the first day the patient meets PaO2/FiO2 > 200 (out of a prone positioning session)|Cumulative use of sedatives|Cumulative duration of use of sedatives|Cumulative duration of use of neuromuscular blocking agents (other than used for intubation)|Cumulative use of neuromuscular blocking agents (other than used for intubation)|ICU-acquired weakness and delirium|Treatment-induced toxicity rate and adverse events up to day 28|Quality of life at one year (EQ5D-3L quality of life questionnaire)|Measurements of plasmatic cytokines (IL1, IL6, IL8, TNF-alpha, IL10, TGF-beta, sRAGE, Ang2) level|Anti-HLA antibodies plasmatic dosage
NCT04299152	Severe Acute Respiratory Syndrome (SARS) Pneumonia	Combination Product: Stem Cell Educator-Treated Mononuclear Cells Apheresis	Conventional treatment	Determine the number of Covid-19 patients who were unable to complete SCE Therapy|Examine the percentage of activated T cells after SCE therapy by flow cytometry|Assess the percentage of Th17 cells after SCE therapy by flow cytometry|Chest imaging changes by computed tomography (CT) scan of the chest|Quantification of the SARS-CoV-2 viral load by real time RT-PCR

Study ID Location	Population / Setting	Intervention/s	Control	Outcomes
NCT04466098 United States	COVID-19 Pneumonia with Acute Respiratory Distress Syndrome, Moderate or Severe	Biological: Mesenchymal stromal cells	Placebo	Incidence of grade 3-5 infusional toxicities and predefined hemodynamic or respiratory adverse events related to the infusion of MSC|Incidence of a reduction in one or more biomarkers of inflammation by day 7|Trend changes in PaO2:FiO2 ratio|Trend changes in Mean Airway Pressure|Trend changes in peak pressure|Trend changes in plateau pressure|Trend changes in Positive end-expiratory airway pressure (PEEP)|Incidence of mortality|Number of ICU-free days|Number of days alive and ventilator free composite score 3|Change in acute lung injury (ALI) score 2|Incidence of serious adverse events|Number of days alive off supplemental oxygen
NCT04445220 United States	COVID-19 with acute kidney injury and receiving or planned to receive renal replacement therapy in < 24 hours	Biological: SBI-101 (Extracorporeal Mesenchymal Stromal Cell Therapy)	Standard of care	Safety and tolerability as measured by incidence of IP-related serious adverse events
ChiCTR2000029580 China	COVID-19	Ruxolitinib combined with mesenchymal stem cell	Routine treatment	Safety
ChiCTR2000030088 China	COVID-19 with respiratory failure	IV injection of Wharton's Jelly mesenchymal stem cells (1×10^6/kg), cell suspension volume: 40ml	IV 40ml saline	Nucleic acid test via throat secretion Ground glass on CT scan
ChiCTR2000030173 China	COVID-19	Umbilical cord mesenchymal stem cells	Conventional treatment	Pulmonary function Chest radiograph Chest CT scan findings
ChiCTR2000030138	COVID-19 pneumonia	Intravenous injection of human umbilical cord mesenchymal stem cells (UC-MSC)	Placebo + routine treatment	Clinical index