

[Home](#) » [Browse Articles](#)

# You searched for Hanestya Oky Hermawan

[ARTICLES](#) [FACULTY REVIEWS](#) [DOCUMENTS](#) [POSTERS](#) [SLIDES](#)FILTERS 

1-2 of 2 ARTICLES

SYSTEMATIC REVIEW  metrics 

## Mesenchymal stem cell therapy efficacy in COVID-19 patients: A systematic review and meta-analysis [version 1; peer review: 1 approved]

Andrianto Andrianto, Desak Ketut Sekar Cempaka Putri, Makhyan Jibril Al Farabi, Teuku Yusrizal, Hanestya Oky Hermawan

 PEER REVIEWER *Ali Golchin*

FUNDER Indonesian Endowment Fund for Education (LPDP)

PUBLISHED 22 Sep 2021

RESEARCH ARTICLE  metrics

AWAITING PEER REVIEW

## Acute effects of cigarette smoke on Endothelial Nitric Oxide synthase, vascular cell adhesion molecule 1 and aortic intima media thickness [version 1; peer review: awaiting peer review]

Meity Ardiana, Anwar Santoso, Hanestya Oky Hermawan, Ricardo Adrian Nugraha, Budi Susetyo Pikir, I. Gde Rurus Suryawan

 PEER REVIEWERS *Invited*

PUBLISHED 18 May 2021



The F1000Research website uses cookies. By continuing to browse the site, you are agreeing to our use of cookies. [Find out more >](#)

## PUBLISH YOUR RESEARCH



### ARTICLES

We publish a wide range of article types in science, engineering, medicine, social sciences and humanities, with no editorial biases.

**[SUBMIT AN ARTICLE \(/FOR-AUTHORS/PUBLISH-YOUR-RESEARCH\)](#)**

See [guidelines](#) and [policies](#).

An innovative open access publishing platform offering rapid publication and open peer review, whilst supporting data deposition and sharing.

[BROWSE](#)

[BLOG](#)

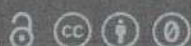
[GATEWAYS](#)

[CONTACT](#)

[COLLECTIONS](#)

[RSS](#)

[HOW IT WORKS](#)



Follow us



[Home](#) » [Advisory Board](#)

## Advisory Board

The Advisory Board of F1000Research comprises a large group of leading experts across biology and medicine. They do not act as Editors in the traditional sense (they do not handle manuscripts or make decisions to accept or reject a paper), but they provide strategic input on the direction we should take with F1000Research. They occasionally advise us on issues arising with specific articles, and many members of the board also review for us.

[A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [R](#) [S](#) [T](#) [U](#) [V](#) [W](#) [X](#) [Y](#) [Z](#)

**B**

- Ian Beales
- Nelson Bennett
- Avri Ben-Ze'ev
- Benedikt Berninger
- Eric Beyer
- Azra Bihorac
- Daniel Bikle
- Kevin J Black
- Cheflakkan Selvanesan Blesson
- Erin Aiello Bowles
- Bruce Brew

**C**

- David Catcheside
- Andrew Chalmers
- Tak Mao Chan
- Karen Chapman
- Declan Chard
- Walter Chazin
- Jonathan Chernoff
- Cheng-Ming Chiang
- Ryan Chisholm
- Wei-Sheng Chong
- Sandra Citi
- Vitaly Citovsky
- Tim Clark
- James Coker
- Giuseppe Colloca
- William Colmers
- Jason Crawford
- David Criddle

**D**

- Ira Daar
- Linda Dagi
- Blossom Damania
- Eric Dannaoui
- Vinicio de Jesus Perez
- Sharon DeMorrow
- Gonzalo G de Polavieja
- Saskia de Wildt
- Harriet de Wit
- Eleftherios P Diamandis
- Phedias Diamandis
- Betty Diamond
- J Alan Diehl
- Petya Dimitrova
- Annette Dolphin
- Lucy Donaldson



**E**  
Sharyn Endow  
Markus Engstler  
Sam Enna  
Erim Erdem

**F**  
Alastair Ferguson  
Gerardo Ferrara  
Richard Festenstein  
Thomas Finger  
Céline Fiset  
Heike Fölsch  
Steven Frank  
Bernd Fritzsche

**G**  
Gus Gazzard  
Jozef Gécz  
Robert Gerlai  
Ivan Gerling  
Carole Gobie  
Richard Gomer  
Andrew Goryachev  
John Greenspan  
Guy Griebel  
W Sue Griffin  
Elizabeth Grove  
Jaime Grutzendler  
Wei Guo

**H**  
Adam Hartman  
Johannes Hell  
Winston Hide  
Stephen Hoffman  
Stephen Holgate  
Thorsten Hoppe  
Wolfgang Huber  
Arthur Hurwitz

**I**  
Radu Iliescu  
Robert Insall  
Harry Ischiropoulos

**J**  
Jan Jakobsson  
Guilhem Janbon  
Michael Joannidis  
Norman Johnson  
Etienne Joly

**K**  
Dieter Kabelitz  
Wael Kafienah  
Chaya Kaicheim  
Lynn Kamerlin  
Mikhail Kazachkov  
Johannes S Kern  
Jean-Pierre Kinet  
Edward Kipreos  
Fenella Kirkham  
Gordon Klein  
Alisa Koch

## L

Eileen Lafer  
Hans Lassmann  
Mario Lebediker  
John Lee  
Laurel Lenz  
Simon Levin  
Stefan Linder  
Ton Lisman  
Creighton M Litton  
Hartmut Lode  
Theresa Lu  
Robyn Lucas  
Ben Lugtenberg  
Paul Lyons

## M

Roberto Maggi  
Martin Marinus  
M Rashad Massoud  
Jocelyn McDonald  
Robert McPeak  
Anthony Means  
Julien Mendlewicz  
Arthur Mercurio  
Ralph Mistlberger  
Ali Mobasheri  
David Moher  
Randall Moon  
Carlos Morel  
Dimitrios Morikis  
Nicola Mulder

## N

Corey Nislow

## O

Chiadi Onyike

## P

Leonid Padyukov  
Eleftherios Paschalis  
Graham Pawelec  
Ming Pei  
Giampaolo Perna  
Stephen Pinfeld  
Michel Pohl  
Simon Portsmouth  
David Potter  
Chaim Putterman

## R

Adam Ratner  
Ana Reeber  
Victor Reus  
José Luis Riechmann  
Karin Romisch  
Vincent Rotello  
Barry Rouse  
Gloria Rudenko  
James Russell

## S

Philippe Saas  
Paul R Sanberg



Wend, Senior

Michael Sendtner  
Andrew D Sherrocks  
Nilabh Shastri  
Kazim Sheikh  
Andrew Shennan  
Xiao Shifu  
Chiara Simonelli  
Helmy Siragy  
Cassian Sitaru  
Richard Smith  
H Peter Soyer  
Pamela Stanley  
Christoph Stein  
Carly Stevens  
Charles Stevens  
Bruno Stieger

T

Paul-Peter Tak  
Paul Terry  
Igor Tetko  
Jacques Thibodeau  
Jakub Tolar  
Peter Tonellato  
Francis Tsai  
Takeshi Taubata  
Tom Tullius  
Burkhard Tümmler

U

Hisashi Umemori  
Shiro Urayama  
Vladimir Uversky

V

Hans van Beek  
Hans van Bokhoven  
Martin van den Berg  
Peter Van Endert  
Dirk van Helden  
Chandra Verma  
Jan Vermorken  
David Voehringer

W

Claire Walczak  
Nick Ward  
Peter Wark  
Stephen Waxman  
Alan Wein  
Tom Woodcock  
Long-Jun Wu  
Jeremy C Wyatt  
Kevan Wylie

X

Yongbiao Xue

Y

Michael B Yaffe  
Kenneth Yamada  
Helen Yap  
Dorothy Yuan



The F1000Research website uses cookies. By continuing to browse the site, you are agreeing to our use of cookies. [Find out more >](#)



# F1000Research

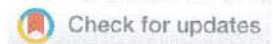
An innovative open access publishing platform offering rapid publication and open peer review, whilst supporting data deposition and sharing.

- BROWSE
- BLOG
- GATEWAYS
- CONTACT
- COLLECTIONS
- RSS
- HOW IT WORKS



Follow us   

© 2012-2022 F1000 Research Ltd. ISSN 2046-1402 | [Legal](#) | [Partner of HINARI](#) · [CrossRef](#) · [ORCID](#) · [FAIRSharing](#)



## SYSTEMATIC REVIEW

# Mesenchymal stem cell therapy efficacy in COVID-19 patients: A systematic review and meta-analysis [version 1; peer review: 1 approved]

Andrianto Andrianto , Desak Ketut Sekar Cempaka Putri ,  
Makhyan Jibril Al Farabi , Teuku Yusrizal , Hanestya Oky Hermawan

Department of Cardiology and Vascular Medicine, Universitas Airlangga, Soetomo General Hospital, Surabaya, 60825, Indonesia

**V1** First published: 22 Sep 2021, 10:956  
<https://doi.org/10.12688/f1000research.53825.1>  
Latest published: 22 Sep 2021, 10:956  
<https://doi.org/10.12688/f1000research.53825.1>

## Abstract

**Objective:** To evaluate mesenchymal stem cell (MSC) administration safety and efficacy in COVID-19 patients.

**Methods:** We conducted a literature search on PubMed/MEDLINE, medRxiv, EBSCOhost/CINAHL, ProQuest, and Scopus with keywords adjusted to each search engine's specifications on February 12, 2021. Interventional studies that reviewed MSC efficacy (mortality, hospitalization duration, need for mechanical ventilators, and inflammation markers) and/or safety (adverse events) in COVID-19 patients who were 18 years old or more were included in this study. Study eligibility, data extraction, and study quality assessment were conducted independently by each author.

**Results:** A total of five studies of moderate to high quality with a total of 193 patients were included. One of the three randomized studies included did not apply blinding to either participants or medical professionals. Pooled OR (Odd Ratio) for mortality risk, adverse events incidence, and use of mechanical ventilators for patients on MSC therapy were 0.13 [95% CI: 0.02, 0.68], 0.91 [95% CI: 0.45, 1.86], and 0.42 [95% CI: 0.12, 1.47], respectively. Pooled mean difference for hospitalization duration in the MSC group versus the control was -3.54 [CI 95%: -4.68, -2.40] with 7% heterogeneity. All studies agreed that there was an increase of pro-inflammatory cytokines and a decrease of anti-inflammatory markers that were statistically different in the MSC group.

**Conclusion:** Mesenchymal stem cell administration to COVID-19 patients is safe and effective in reducing mortality and hospitalization duration. Furthermore, a decrease of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines were observed.

## Keywords

COVID-19, efficacy, safety, mesenchymal stem cell.

## Open Peer Review

Approval Status 


1

version 1

22 Sep 2021



[view](#)

1. **Ali Golchin** , Urmia University of Medical Sciences, Urmia, Iran

Any reports and responses or comments on the article can be found at the end of the article.



**Corresponding authors:** Andrianto Andrianto ([andrianto@fk.unair.ac.id](mailto:andrianto@fk.unair.ac.id)), Desak Ketut Sekar Cempaka Putri ([desak.fkua@hotmail.com](mailto:desak.fkua@hotmail.com)), Makhyani Jibril Al Farabi ([m.farabi.17@ucl.ac.uk](mailto:m.farabi.17@ucl.ac.uk))

**Author roles:** **Andrianto A:** Conceptualization, Formal Analysis, Methodology, Validation, Visualization; **Cempaka Putri DKS:** Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Al Farabi MJ:** Investigation, Methodology, Software, Validation, Visualization, Writing – Review & Editing; **Yusrizal T:** Data Curation, Funding Acquisition, Software, Supervision; **Hermawan HO:** Validation, Visualization, Writing – Original Draft Preparation

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work was supported by the Indonesian Endowment Fund for Education (Lembaga Pengelola Dana Pendidikan Republik Indonesia).

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2021 Andrianto A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Andrianto A, Cempaka Putri DKS, Al Farabi MJ *et al.* **Mesenchymal stem cell therapy efficacy in COVID-19 patients: A systematic review and meta-analysis [version 1; peer review: 1 approved]** F1000Research 2021, 10:956 <https://doi.org/10.12688/f1000research.53825.1>

**First published:** 22 Sep 2021, 10:956 <https://doi.org/10.12688/f1000research.53825.1>

## Introduction

Coronavirus disease 2019 (COVID-19) is a new disease that resembles pneumonia. As of August 2021, more than 200 million people worldwide have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the virus that causes COVID-19, and more than four million people have died.<sup>1</sup> In Indonesia alone, COVID-19 has reached almost four million cases (as of August 2021) with more than 120,000 deaths.<sup>2</sup>

Besides fever, cough, and shortness of breath that are typical of pneumonia, COVID-19 has various clinical manifestations ranging from sore throat, fatigue, dizziness, myalgia, chest pain, rhinitis, neurological manifestations, conjunctivitis, anorexia, diarrhea, skin manifestations such as rashes and urticaria, and some are even asymptomatic.<sup>3–5</sup> Therefore, COVID-19 is also known as “the great imitator”. It is interesting that COVID-19 is less severe in children than in adults, while the elderly and people with comorbidities such as hypertension, obesity, diabetes mellitus, cardiovascular disease, malignancies, and other chronic diseases, tend to have more severe symptoms and have a higher mortality rate.<sup>3,6,7</sup>

Even though it has a mortality rate that is not too high (case fatality rate of 2-3%), deaths from COVID-19 should not be underestimated.<sup>3</sup> Various types of treatment for COVID-19 have been observed in trials such as various antivirals, dexamethasone, anti-inflammatory drugs, and even convalescent plasma therapy. However, most of these treatments have not proved effective and only the drug, remdesivir, has been shown to be effective and approved by the FDA (US Food and Drug Administration). Therefore, currently the majority of COVID-19 patients are treated symptomatically.<sup>8</sup> Although the majority of patients have mild symptoms and recover without the use of mechanical ventilation, severe respiratory distress may occur in some patients, which can result in mortality.<sup>9</sup> Therefore, various studies are still being conducted to find other potential treatments in COVID-19 management, one of which is stem cell therapy.

Mesenchymal stem cells (MSCs) are a type of multipotent stem cells in adults that can be found in various autologous and allogeneic sources, which have high proliferative abilities and can differentiate into various lineages. Several studies have shown that MSCs have immunomodulatory abilities that might help modulate proliferation, activation, and function of a wide variety of immune cells, both innate and adaptive cells. MSCs were previously used in graft vs host disease management and several immunological diseases caused by viruses such as HIV, chronic hepatitis B, and acute lung injury caused by influenza virus.<sup>9</sup>

Excessive inflammatory reaction is found in COVID-19 patients due to the production of inflammatory factors including cytokines, chemokines, and reactive immune cells that cause cytokine storms. MSCs administration is thought to reduce immune reactions in COVID-19 patients, therefore preventing cytokine storms from occurring in the immune system and triggering endogenous repair. After intravenous injection is given, the trapped population of mesenchymal stem cells in the lungs functions to reduce inflammation by releasing anti-inflammatory mediators, improve lung microenvironment by releasing antimicrobial peptides, protect alveolar epithelial cells, prevent pulmonary fibrosis, and improve pulmonary dysfunction and pneumonia due to COVID-19.<sup>10,11</sup>

There are many advantages that MSCs have compared to other therapies, 1) mesenchymal stem cells can be extracted from various tissues such as bone marrow, adipose tissue, umbilical cord, dental pulp, menstrual blood, buccal fat tissue etc; 2) these stem cells are multipotent; 3) mesenchymal stem cells can be stored for repetitive use; and 4) there have been no studies showing adverse events of allogeneic stem cells.<sup>10</sup>

Many studies have been conducted globally on the efficacy of MSCs against COVID-19. A case report from China by Liang *et al.*,<sup>12</sup> reported a 65-year-old woman infected with SARS-CoV-2 who showed improvement in vital signs, blood and immune profiles, and CT scan results after MSC administration from umbilical cord. A randomized controlled trial conducted in the United States by Lanzoni *et al.*,<sup>13</sup> reported that COVID-19 patients who were given stem cell therapy experienced significant symptom improvement compared to the control group and no adverse event was reported. However, one study reported a high incidence of adverse events.<sup>14</sup> These controversial findings prompted the authors to conduct a systematic review and meta-analysis of MSC safety and efficacy in COVID-19 patients.

## Methods

### Eligibility criteria

We included interventional studies with/without randomization and blinding. Each study must've reported evidence of ethical clearance by the local research ethics committee. Only articles in English with a full manuscript available were included. The type of intervention was MSC administration, without any restrictions on cell seeding/harvesting method and MSC dose. There were no restrictions on the patient's social status, ethnicity, race, or nationality. The expected comparisons were administration of a standard therapy regimen according to local health protocols, placebo, or MSC vehicle.

We excluded studies that included patients with: 1) age under 18 years (pediatric patients); 2) multiorgan failure at the start of study; or 3) inherited/acquired immunity disorder. Each study reported at least one of these variables: mortality rates, adverse events, need for ventilators, treatment duration, time for clinical improvement, and changes in inflammatory markers. Case reports or case series studies were also excluded from this systematic review. Mortality was defined as deaths that occurred during hospitalization. Adverse events were evaluated within six hours of MSC administration, which included urticaria, palpitations, and pulmonary edema. Cardiac arrest within 24 hours after MSC administration was also considered as an adverse event.

### Literature search

A systematic literature search of (Pubmed/MEDLINE, EBSCO/CINAHL, ProQuest, and Scopus from 1 January 2020 to 20 February 2021) was performed using the search strategy outlined in Table 1.<sup>15</sup> Additional records were retrieved from Google Scholar. Duplicate articles were removed after the initial search. Two authors independently screened the title and abstract of the articles. Articles that passed the screening were assessed in full text based on the eligibility criteria. Disagreements were resolved by discussion with the senior author. This study was conducted following the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>16</sup>

### Selection of studies

We assessed the suitability of each study that appeared in the search engines by title and abstract. All appropriate articles were input in our database and duplicated using Zotero 5.0 (RRID:SCR\_013784) citation manager application. All authors conducted an independent assessment of the eligibility of all studies. At this stage, the article eligibility assessment was conducted based on the full text of the assessed article. Any discrepancies that occurred were resolved by discussion.

### Data extraction and management

All authors extracted the data independently. We developed a data extraction sheet that was referred to by the Cochrane Consumers and Communication Review Group.<sup>15,17</sup> Some of the data we extracted included study design, age, number of participants, comorbidities, type of intervention, and all of the previously mentioned outcomes. Numerical representations were preferred over graphs to avoid misinterpretation/estimation. However, graphic presentation in each article was not a reason to exclude an article.

This meta-analysis compared MSC safety and efficacy in COVID-19 patients against primary (mortality) and secondary (adverse events, treatment duration, need for mechanical ventilation) clinical outcomes. For treatment duration, the input data are numerical, therefore we used the mean difference from each study to be processed in this meta-analysis. We used a 2 × 2 format to assess mortality, side effects, and need for mechanical ventilation outcomes, therefore OR (Odd Ratio)

**Table 1. Search strategy and literature search results in databases using listed keywords.**

Database	Keywords	Hit	Selected	Comments
MEDLINE	(((COVID-19[MeSH Terms]) OR (COVID-19[Title/Abstract])) OR (2019-nCoV [Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (Coronavirus disease [Title/Abstract]) AND (clinicaltrial [Filter]) AND (((mesenchymal stem cell) OR (mesenchymal stromal cell)) OR (mesenchymal stem (stromal) cell)) OR (mesenchymal stem cells) OR (mesenchymal stromal cells) OR (mesenchymal stem (stromal) cells) AND (clinicaltrial [Filter])) Filters: Clinical Trial	4	3	1 did not fit PICO
ProQuest	(mesenchymal stem cells OR stromal cell OR cell transplantation OR cells transplantation) AND (COVID-19 OR 2019-nCoV OR SARS-CoV-2) Filter: Article AND (Case Study OR Report OR Evidence Based Healthcare)	39	0	23 did not fit PICO 16 literature reviews
CINAHL	(((mesenchymal stem cell) OR (mesenchymal stromal cell)) OR (mesenchymal stem (stromal) cell)) OR (mesenchymal stem cells) OR (mesenchymal stromal cells) OR (mesenchymal stem (stromal) cells) AND (COVID-19 OR coronavirus disease)	18	1	12 literature reviews 5 did not fit PICO
Scopus	TITLE-ABS-KEY (stem cells OR stem cell OR cell transplantation OR cells transplantation) AND TITLE-ABS-KEY (COVID-19 OR 2019-nCoV OR SARS-CoV-2) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (EXACTKEYWORD, "COVID-19"))	74	2	61 literature reviews 10 did not fit 1 was not a clinical study

were obtained from each study. We compiled all the outcomes from each study by considering their weight, using the RevMan 5.0 (RRID:SCR\_003581) application. Studies with high heterogeneity were analyzed using the DerSimonian and Laird random-effects model and Mantel-Haenszel fixed effect model was used if heterogeneity was low.

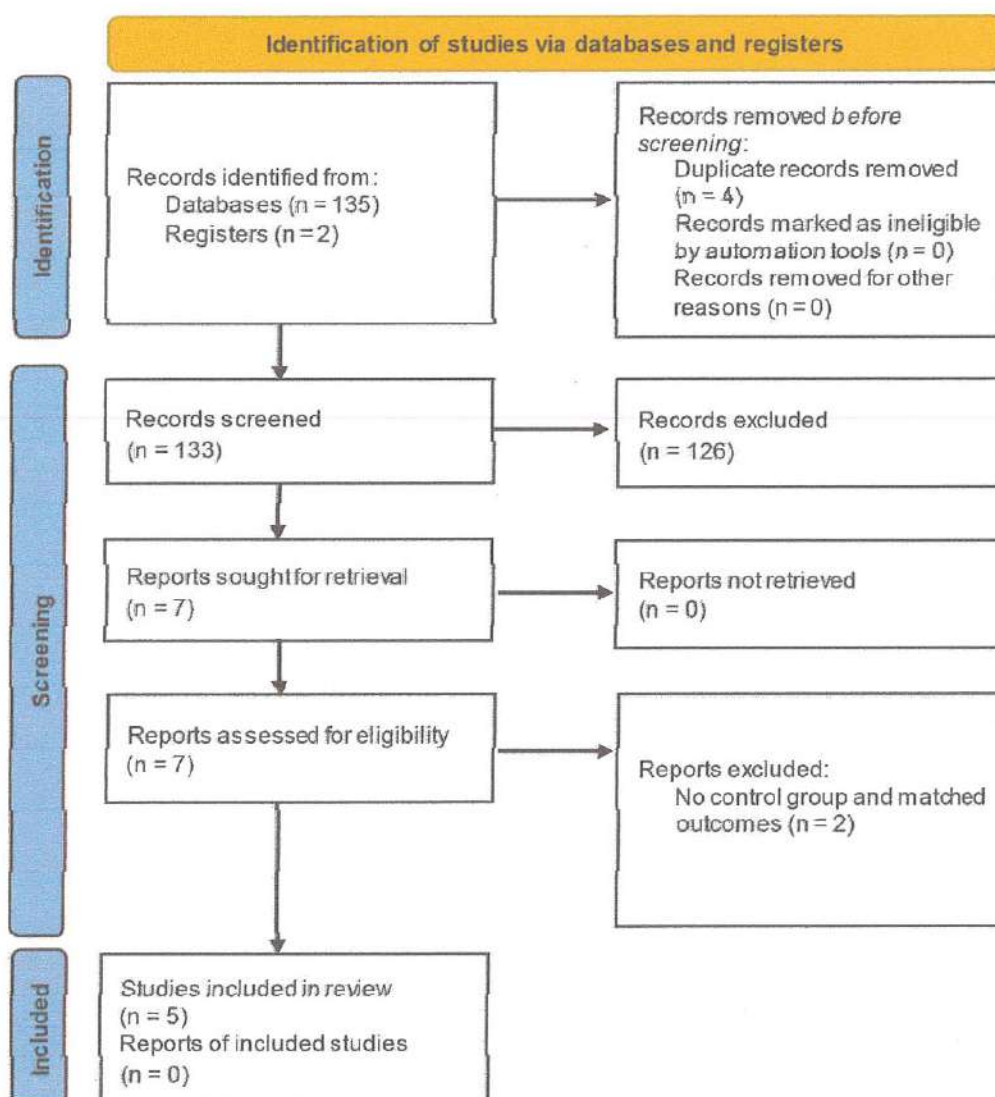
### Study quality assessment

Quality assessment was conducted by two independent reviewers (A and B). If there were differences in bias assessment results, a senior reviewer (C) was involved in making the final decision. Bias risk assessment in this study used the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool and the revised Cochrane risk-of-bias (RoB) tool for randomized trials.<sup>18</sup> The RoB instrument was used to assess the quality of interventional randomized studies with/without blinding.<sup>18</sup> The ROBINS-I instrument was used to assess bias risk in interventional studies without randomization, according to Cochrane recommendations. The ROBINS-I tool used low, moderate, and serious as terminologies for risk stratification of the assessed studies.<sup>18</sup>

## Results

### Literature search

There were 137 articles that appeared in the initial search of the entire electronic database. Checking for duplicated articles was conducted using Zotero 5.0 (RRID:SCR\_013784) citation manager application, where 133 articles were



**Figure 1.** Flow diagram of the literature search according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA). Five studies were included from 137 results of the literature search.

**Table 2. Characteristics of studies consisting of sample size, age, comorbidities, type of intervention, and outcomes.**

Authors	Design	N	Age	Comorbidities	Intervention	Outcomes
Lanzoni et al., 2021, <sup>20</sup>	Randomized and double-blind interventional study	12 (I) 12 (C)	58.58 ± 15.93 (I) 58.83 ± 11.61 (K)	Diabetes (45.83%); hypertension (66.67%)	IV infusion of 100 ± 20 × 10 <sup>5</sup> umbilical cord-derived mesenchymal stem cells	Adverse events, mortality, inflammation markers
Leng et al., <sup>18</sup> 2020.	Interventional study without randomization	7 (I) 3 (C)	57 ± 7.75 (I) 65 ± 16.46 (K)	NR	Mesenchymal stem cells infusions*	Adverse events, mortality, inflammation markers
Meng et al., <sup>14</sup> 2020.	Interventional study without randomization	9 (I) 9 (C)	45.11 ± 10.13 (I) 49.55 ± 10.06 (K)	NR	Umbilical cord-derived mesenchymal stem cells infusions*	Adverse events, treatment duration, need for ventilator Inflammation markers
Shi et al., <sup>19</sup> 2020.	Randomized and double-blind interventional study	65 (I) 35 (C)	60.72 ± 9.14 (I) 59.94 ± 7.79 (K)	Diabetes (17%); hypertension (27%)*	Umbilical cord-derived mesenchymal stem cells infusions*	Adverse events, mortality, need for ventilator
Shu et al., <sup>21</sup> 2020.	Randomized and non-blinded interventional study (open label)	12 (I) 29 (C)	61.00 ± 17.87 (I) 57.86 ± 15.79 (K)	Diabetes (19.51%); hypertension (21.95%)*	2 × 10 <sup>6</sup> Umbilical cord-derived mesenchymal stem cells/kg	Adverse events, mortality, treatment duration, need for ventilator Inflammation markers

Description: I: intervention (MSC); C: control (placebo or only MSC vehicle); NR: not reported.

\*Dosage was not reported.

\*\*Patient distribution was not significantly different between groups.

**Table 3. Summary of outcomes measurement for each study.**

Authors	Adverse events	Mortality	Need for ventilator	Treatment duration	Study quality
Lanzoni et al., 2021, <sup>20</sup>	0.18 [0.02, 1.95]	0.07 [0.01, 0.75]	Not reported	Not reported	Good
Leng et al., 2020. <sup>18</sup>	None*	0.11 [0.00, 3.70]	Not reported	Not reported	Moderate
Meng et al., 2020. <sup>14</sup>	10.23 [0.45, 233.23]	Not reported	0.16 [0.01, 1.83]	-2.75 [-4.62, -0.88]	Good
Shi et al., 2020. <sup>19</sup>	0.88 [0.38, 2.03]	None*	2.80 [0.13, 59.86]	Not reported	Good
Shu et al., 2020. <sup>21</sup>	None*	0.30 [0.01, 6.32]	0.29 [0.03, 2.62]	-4.00 [-5.44, -2.56]	Moderate

Description: Data were presented as OR [95% CI, min-max] or mean difference ± SD.

\*Outcome did not occur between groups.

found free from duplication. We screened articles based on title and abstract suitability, and only seven articles matched. Two articles were excluded because they did not use controls (comparators) and did not report outcomes that matched the outcomes set in this meta-analysis. The PRISMA flow diagram detailing the literature search can be seen in [Figure 1](#).

### Study characteristics

We included five interventional studies with a total of 193 participants. Two out of the five studies did not apply randomization. One of the three randomized studies did not apply blinding to either participants or medical professionals. MSCs were taken from human umbilical cord, except for *Leng et al.*, who did not specify the MSC origin used.<sup>19</sup> *Shi et al.*, administered MSC therapy at a dose of  $2 \times 10^6$  cells/kg,<sup>20</sup> while *Lanzoni et al.*, used a fixed dose of  $100 \pm 20 \times 10^6$  cells.<sup>21</sup> The other three studies did not mention the MSC dose administered explicitly.

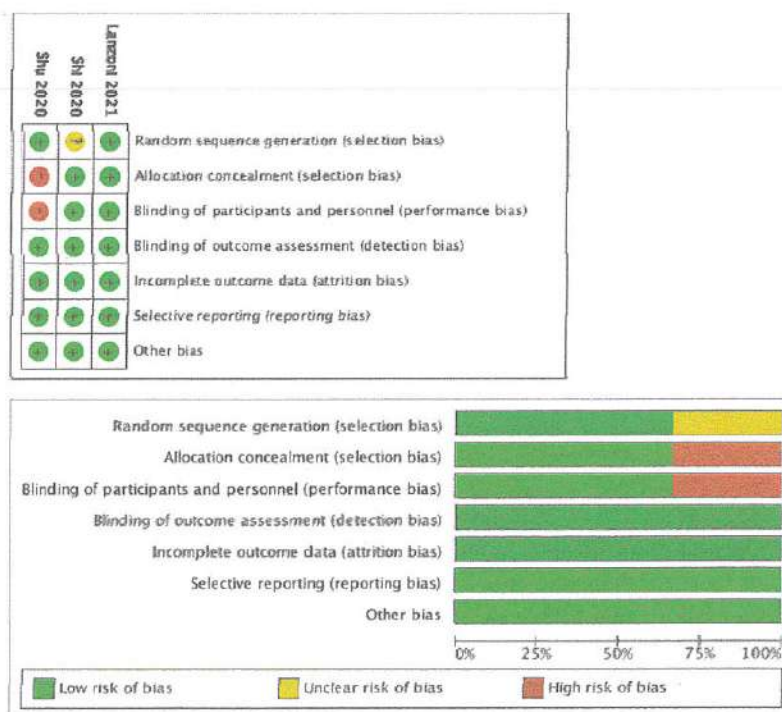
All studies excluded pediatric patients. The mean age of participants across the studies was over 45 years. *Meng et al.*, and *Leng et al.*, excluded patients with comorbidities.<sup>14,19</sup> The other three studies included comorbid patients, with a distribution/proportion that did not differ significantly between groups. The study characteristics and outcomes reported for each study can be seen in [Tables 2](#) and [3](#).

### Bias risk assessment

Study quality assessment based on risk of bias using the RoB and ROBINS-I tools showed that the included studies were of moderate to good quality ([Figure 2](#) and [Table 4](#)). A study by *Leng et al.*, had moderate quality because there was no difference in the analysis of group characteristics.<sup>19</sup> This might lead to confounding bias. Furthermore, a study by *Shu et al.*, did not apply blinding, thus triggering performance bias, detection bias, and attrition bias.<sup>21</sup>

### Mortality

Four out of five studies reported mortality within 28 days after MSC therapy. *Lanzoni et al.*, reported mortality incidence in one in 11 patients treated with MSC, and seven in 12 patients who were given standard therapy.<sup>21</sup> This led to a statistically significant difference in patient mortality rates between groups, with an OR of 0.07 [CI 95%: 0.01, 0.75]. *Leng et al.*, and *Shu et al.*, did not report any mortality in the intervention group.<sup>18,21</sup> Meanwhile, *Shi et al.*, did not report any mortality in two groups.<sup>19</sup>



**Figure 2.** Bias risk assessment used the revised Cochrane risk-of-bias (RoB) tool for randomized trials. Results showed that a study by *Shu et al.*, did not apply blinding of the subject and personnel, thus triggering performance bias, detection bias, and attrition bias.

**Table 4.** Bias risk assessment result using the ROBINS-I Tools.

Studies	Pre-intervention		Inter-vention		Post-intervention			Overall risk of bias
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
Leng et al., <sup>18</sup> 2020.	Mod	Mod	Low	Low	Low	Low	Low	Mod*
Meng et al., <sup>14</sup> 2020.	Low	Low	Low	Low	Low	Low	Low	Low

Description:

\*Mod: moderate- A study by Leng et al., 2020<sup>18</sup> had moderate quality because there was no difference in the analysis of group characteristics. This might lead to confounding bias.

Compilation of the study findings was conducted using a forest plot. The pooled OR for mortality risk for patients with MSC therapy was 0.13 [95% CI: 0.02, 0.68]. This value was obtained by the Mantel-Haenszel fixed effect model method because the heterogeneity was 0% and p value for heterogeneity was 0.76 (Figure 3).

### Adverse events

Adverse event is a parameter that could represent the safety of a product. The adverse events referred to were urticaria, palpitations, or pulmonary edema (within six hours) and/or cardiac arrest (within 24 hours) after MSC administration or placebo or MSC vehicle (without MSC). All studies reported this parameter in their articles. None of these studies reported a significant difference in adverse event incidence between groups. Meng *et al.*, and Shu *et al.*, found no adverse events in either group.<sup>14,21</sup>

With the Mantel-Haenszel fixed effect model method, it was found that the pooled OR for the MSC group that experienced adverse events was 0.91 [CI 95%: 0.45, 1.86], with a heterogeneity value of 51% (Figure 4).

### Need for a mechanical ventilator

The need for a mechanical ventilator could represent the respiratory distress severity of a patient. In this systematic review, three out of five studies reported the need for a mechanical ventilator post-MSC therapy during the treatment period. None of the three studies reported a significant difference in the number of mechanical ventilators needed between groups. Only Shi *et al.*, reported a higher percentage of mechanical ventilator use in the MSC group.<sup>19</sup>

In this study, pooled OR for the MSC group that required a mechanical ventilator during treatment was 0.42 [95% CI: 0.12, 1.47]. This figure was obtained by Mantel-Haenszel fixed effect model, with a heterogeneity of 0% (Figure 5).

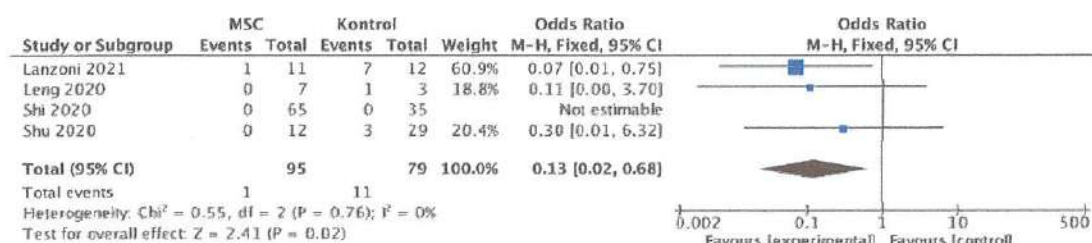


Figure 3. The forest plot of mortality outcome shows lower mortality risk in patients with MSC therapy with OR 0.13 [95% CI: 0.02, 0.68].

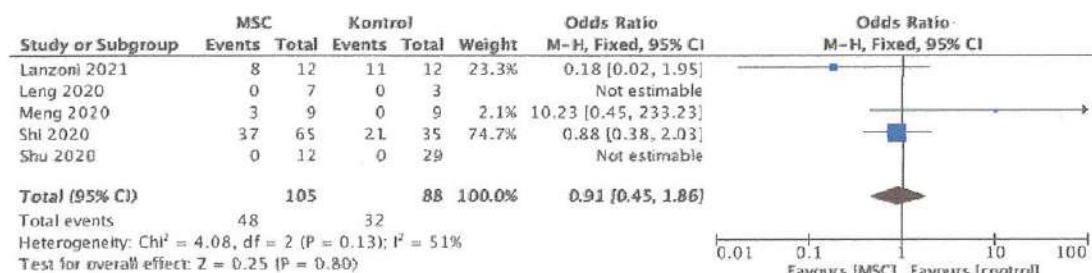


Figure 4. The forest plot shows that MSC therapy causes no significant adverse events compared to the control (OR 0.91 [95% CI: 0.45, 1.86]).

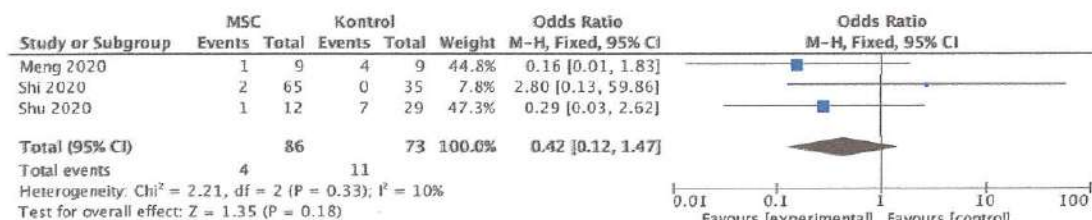
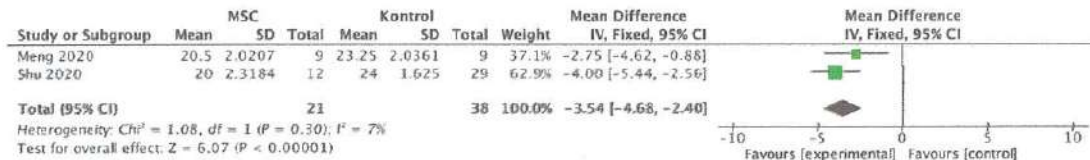


Figure 5. The forest plot shows a lower need for mechanical ventilator in patients with MSC therapy with OR 0.42 [95% CI: 0.12, 1.47].





**Figure 6.** The forest plot shows a shorter hospitalization duration in patients with MSC therapy with OR  $-3.54$  [95% CI:  $-4.68$ ,  $-2.40$ ].

### Treatment duration

There were only two studies reporting hospitalization duration. Meng *et al.* reported that the mean hospitalization duration in patients on MSC therapy was  $20.5 \pm 2.0207$  days, and  $23.25 \pm 2.0361$  days for patients without MSC administration.<sup>14</sup> Shu *et al.*, also agreed that the mean hospitalization duration in patients on MSC therapy was shorter than patients who received standard therapy, with a mean difference of  $4.00 [-5.44, -2.56]$  days.<sup>21</sup> The results of meta-analysis using the Mantel-Haenszel fixed effect model method found that the pooled mean difference was  $-3.54$  [CI 95%:  $-4.68, -2.40$ ] with 7% heterogeneity (Figure 6).

### Inflammation markers

Leng *et al.*, found a significantly greater increase in the IL-10 ratio and decrease in TNF- $\alpha$  in the intervention group compared to the control group within 10 days post-MSC administration.<sup>18</sup> Meng *et al.*, reported a significant reduction in IL-6 levels in patients receiving MSC therapy.<sup>14</sup> Changes in IL-6 levels were not found to be significant in patients on standard therapy. Lanzoni *et al.*, found a significant decrease in various inflammatory markers at six days post-MSC administration.<sup>20</sup> Inflammation markers that were found to be significantly decreased were TNF- $\alpha$ , IL-2, IL-6, and IL-7. There was no significant decrease in these inflammatory markers in the control group. Shu *et al.*, reported significantly lower levels of CRP and IL-6 in the MSC group compared to the control group at days three and seven post-MSC administration.<sup>21</sup> On the same day, oxygenation index and lymphocyte count were found to be significantly higher in the MSC group.<sup>21</sup>

### Heterogeneity and risk of publication bias

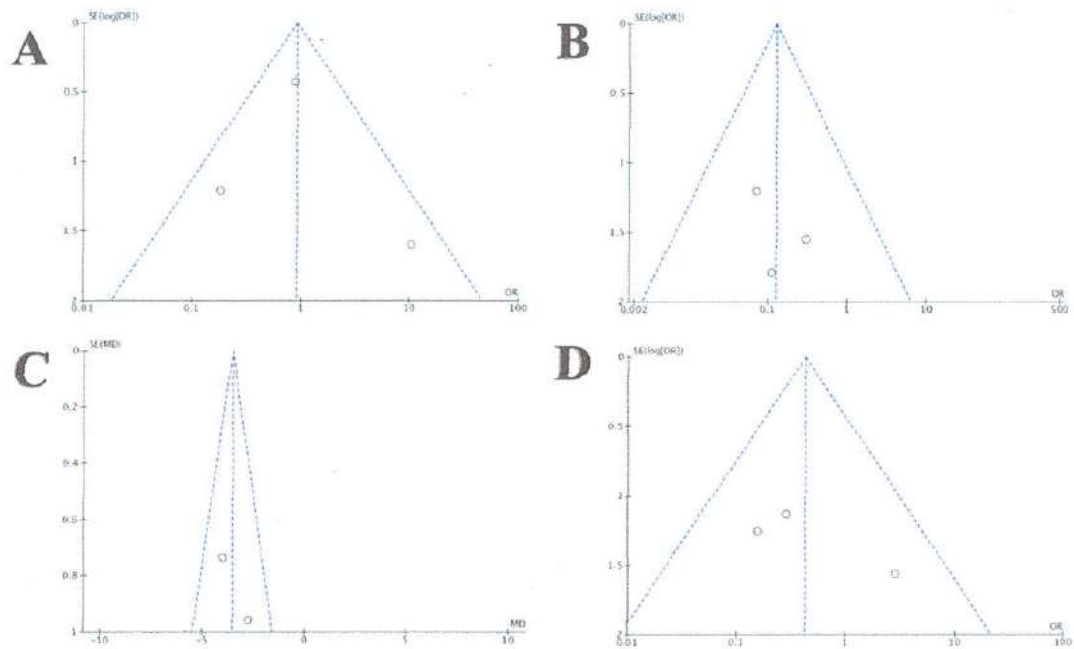
This systematic review and meta-analysis included five interventional studies. We assessed the heterogeneity of each outcome with the parameter  $I^2$  value in percent (%). Heterogeneity was noted to be quite low in all outcomes, except for the side effect outcome, which had moderate heterogeneity (51%). Moderate heterogeneity of side effects may result from different definitions or types of side effect reported in each study. Using a funnel plot, we noted that there was no significant risk of publication bias in all outcomes (Figure 7). The studies are evenly distributed in the right and left areas of the triangle forming a symmetrical funnel plot.

### Discussion

This meta-analysis attempted to compare MSC administration safety and efficacy in COVID-19 patients, which were assessed by mortality, adverse events, treatment duration, need for mechanical ventilators, and inflammation markers. To answer the formulated clinical questions, we used five interventional studies, two of which did not apply randomization. For the most part, the studies included in this meta-analysis reported that MSC was effective and safe to be given to COVID-19 patients.

We found that MSC administration was successful in reducing hospitalization duration and significantly reduced mortality risk. The decrease in hospitalization duration was certainly related to disease resolution. At hematological level, we also found a significantly greater increase in IL-10 ratio and decrease in TNF- $\alpha$  in MSC treated patients within 10 days post-MSC administration.<sup>19</sup> IL-10 is an anti-inflammatory mediator that counteracts TNF- $\alpha$  action. Increased IL-10 and decreased TNF- $\alpha$  levels indicate cytokine storm resolution. Significant decrease in TNF- $\alpha$ , IL-2, IL-6, and IL-7 levels in MSC treated patients was also reported in studies that were included in this systematic review.<sup>21–23</sup>

COVID-19 pathogenesis could not be separated from immunity dysregulation, which manifests as a cytokine storm. COVID-19 triggers immunity dysregulation by triggering pro-inflammatory cytokine production cascade activation, mainly IFN-I.<sup>24</sup> Other cytokines such as IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), MCP-1, MIP-1 $\alpha$ , interferon gamma-induced protein-10 (IP-10), IFN- $\gamma$ , TNF- $\alpha$ , and hepatocyte growth factor (HGF) have also been shown to be increased in COVID-19 patients, resulting in cytokine storms and a worsening of the patient's condition.<sup>25</sup> This systematic review indicates that MSC administration plays a role in improving COVID-19 patient's condition through improvement of immunological status by decreasing pro-inflammatory cytokines.



**Figure 7. Publication bias risk assessment with funnel plot for outcomes: mortality (A); side effects (B); duration of hospitalization (C); and the need for a mechanical ventilator (D).**

Findings regarding MSC's role in restoring immunological control in COVID-19 patients are supported by several studies that have proven beneficial effects. MSCs were shown to reduce TNF- $\alpha$ , IL-1 and IL-6 through hepatocyte growth factor (HGF), prostaglandin-E2 (PGE2), lipoxin A4-stimulated gene 6-protein (LXA4), TNF (TSG-6) release and suppression of inflammatory T-cell proliferation by indoleamine 2,3-dioxygenase expression, transition of Th1 and Th17 responses to Th2, and monocyte and mature myeloid dendritic cell inhibition.<sup>26</sup>

Treatment with MSCs is a therapeutic strategy to stop the uncontrolled inflammatory cascade and, at the same time, reduce post-COVID-19 pulmonary fibrosis and abnormal lung function, decrease ground-glass opacification (GGO) and infiltrate zones in patients post-MS administration. This indicates that MSC therapy does not only improve patient's immunological status, but also plays a role in structural improvement and prevention of lung damage in COVID-19 patients.<sup>27,28</sup> These findings are supported by an *in vivo* study, which found that MSCs interfere with pulmonary fibrosis activation pathways resulting in pulmonary protective effects against damage/injury.<sup>29</sup>

Evidence that MSCs play a role in the immunomodulation process and lung structural repair supports the results that we found in this meta-analysis and systematic review, where MSCs effectively reduce mortality risk and reduce hospitalization duration. MSCs modulate oxidative stress, suppress systemic inflammation, and reduce lung damage progression.<sup>30</sup>

In addition, this meta-analysis also found that MSCs are safe to administer to COVID-19 patients. We noted no significant difference in adverse events incidence between groups. MSCs are a heterogeneous population of non-hematopoietic multipotent stromal cells with a specific cell surface expression pattern, low alloreactivity (expression of major histocompatibility complex (MHC)-I, MHC-II, and low co-stimulation molecules), and have the ability to differentiate tissues from favorable mesodermal lineage.<sup>31</sup> Through these mechanisms, the body's resistance to MSC administration will be minimal. This confirms the findings of this meta-analysis that there are no adverse events in patients after MSC administration, and MSCs are safe to administer to COVID-19 patients.

From our knowledge, there has been no meta-analysis or systematic review addressing the clinical questions explored in this article. Apart from the clinical questions that were successfully answered through this meta-analysis, there are several limitations that need to be underlined. First, the exclusion criteria were not applied for the MSC's type of source and seeding methods. Second, all comorbid patients were included. Patients with degenerative or malignant diseases were perceived to have different immunological responses, which might affect MSC therapy efficacy. Third, some studies

have low quality or a fairly high bias risk, especially those that did not apply blinding to their studies. In addition, the number of participants in each study and overall is still considered insufficient.

## Conclusion

Giving MSCs to COVID-19 patients is safe and effective in reducing mortality and hospitalization duration. Clinical improvement in patients occurred through cytokine storm resolution, which was characterized by decreased pro-inflammatory cytokines and increased anti-inflammatory suppression in patients.

## Data availability

### Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

## Reporting guidelines

Figshare: PRISMA checklist for 'Mesenchymal stem cell therapy efficacy in COVID-19 patients: A systematic review and meta-analysis', <https://doi.org/10.6084/m9.figshare.16602203.v1>.<sup>16</sup>

Data are available under the terms of the [Creative Commons Attribution 4.0 International license \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/).

## Acknowledgment

This work was supported by Indonesian Endowment Fund for Education (LPDP) Republic of Indonesia.

## References

- Dong E, Du H, Gardner L: **An interactive web-based dashboard to track COVID-19 in real time.** *The Lancet Infectious Diseases.* 2020 May; **20**(5): 533–534.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Megasari NLA, Utsumi T, Yamani LN, et al.: **Seroepidemiological study of SARS-CoV-2 infection in East Java, Indonesia.** *PLoS ONE.* 2021 May; **16**(5): e0251234.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Singhal T: **A Review of Coronavirus Disease-2019 (COVID-19).** *Indian J Pediatr.* 2020; **87**(4): 281–286.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shi V, Hsiao JL, Shi YY: **COVID-19 skin manifestations: the new great imitator?** *Dermatol Online J.* 2020 Nov; **15**: 26(11).  
[PubMed Abstract](#)
- da Rosa MR, Francelino Silva Junior LC, Santos Santana FM, et al.: **Clinical manifestations of COVID-19 in the general population: systematic review.** *Wien Klin Wochenschr.* 2020 Nov 26; 1–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yuki K, Fujlogi M, Koutsogiannaki S: **COVID-19 pathophysiology: A review.** *Clin Immunol.* 2020 Jun; **215**: 108427.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Zhou Y, Yang Q, Chi J, et al.: **Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis.** *Int J Infect Dis.* 2020 Oct 1; **99**: 47–56.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Beigel JH, Tomashek KM, Dodd LE, et al.: **Remdesivir for the treatment of Covid-19.** *N Eng J Med.* 2020 Oct; **383**(19): 1813–1826.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Choudhery MS, Harris DT: **Stem cell therapy for COVID-19: Possibilities and challenges.** *Cell Biol Int.* 2020; **44**(11): 2182–2191.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Goldin A, Seyedjafari E, Ardeshiryajimi A: **Mesenchymal Stem Cell Therapy for COVID-19: Present or Future.** *Stem Cell Rev Rep.* 2020 Apr; **13**: 1–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rajarshi K, Chatterjee A, Ray S: **Combating COVID-19 with mesenchymal stem cell therapy.** *Biotechnol Rep.* 2020 Jun 1; **26**: e00467.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liang B, Chen J, Li T, et al.: **Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells.** *Medicine (Baltimore).* 2020 Jul 31; **99**(31).  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lanzoni G, Linetsky E, Correa 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 May; **10**(5): 560–573.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Meng F, Xu R, Wang S, et al.: **Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial.** *Signal Transduct Target Ther.* 2020 Aug 27; **5**(1): 1–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lefebvre C, Manheimer E, Glanville J: **Searching for Studies.** In: *Cochrane Handbook for Systematic Reviews of Interventions.* John Wiley & Sons, Ltd; 2008. p. 95–150.
- Andrianto A, Sari DKSC, Farabi MJA, et al.: **Mesenchymal stem cell therapy efficacy in COVID-19 patients: A systematic review and meta-analysis.** *Figshare.* 2021; [Publisher Full Text](#)
- Ryan R, Hill S: **Supporting implementation of Cochrane methods in complex communication reviews: resources developed and lessons learned for editorial practice and policy.** *Health Res Policy Syst.* 2019 Mar 28; **17**(1): 32.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Higgins J, Green S: **Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.** *The Cochrane Collaboration.*; 2011 [cited 2020 May 7].  
[Reference Source](#)
- 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 Apr; **11**(2): 216–228.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shi L, Huang H, Lu X, et al.: **Treatment with human umbilical cord-derived mesenchymal stem cells for COVID-19 patients with lung damage: a randomised, double-blind, placebo-controlled phase 2 trial.** *medRxiv.* 2020 Oct 21; 2020.10.15.20213553.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shu L, Niu C, Li R, et al.: **Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells.** *Stem Cell Res Ther.* 2020 Aug 18; **11**(1): 361.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lanzoni G, Linetsky E, Correa 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 Jan; 5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Sun P, Qie S, Liu Z, *et al.*: **Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis.** *J Med Virol.* 2020; 92(6): 612–617.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Guo Y-R, Cao Q-D, Hong Z-S, *et al.*: **The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status.** *Mil Med Res.* 2020 Mar; 13: 7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. Tahaghoghi-Hajghorbani S, Zafari P, Masoumi E, *et al.*: **The role of dysregulated immune responses in COVID-19 pathogenesis.** *Virus Res.* 2020 Dec; 290: 198197.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Monguió-Tortajada M, Bayes-Genis A, Rosell A, *et al.*: **Are mesenchymal stem cells and derived extracellular vesicles valuable to halt the COVID-19 inflammatory cascade? Current evidence and future perspectives.** *Thorax.* 2021 Feb 1; 76(2): 196–200.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Thille AW, Esteban A, Fernández-Segoviano P, *et al.*: **Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a prospective cohort study of clinical autopsies.** *Lancet Respir Med.* 2013 Jul 1; 1(5): 395–401.  
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Zhang Y, Ding J, Ren S, *et al.*: **Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia.** *Stem Cell Res Ther.* 2020 May 27; 11(1): 207.  
[Publisher Full Text](#)
29. McIntyre LA, Moher D, Fergusson DA, *et al.*: **Efficacy of Mesenchymal Stromal Cell Therapy for Acute Lung Injury In Preclinical Animal Models: A Systematic Review.** *PLoS One.* 2016; 11(1): e0147170.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. 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.* 2019 Feb 1; 7(2): 154–162.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Daminici M, Le Blanc K, Mueller I, *et al.*: **Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement.** *Cytotherapy.* 2006; 8(4): 315–317.  
[PubMed Abstract](#) | [Publisher Full Text](#)

# Open Peer Review

Current Peer Review Status: 

Version 1

Reviewer Report 21 January 2022

<https://doi.org/10.5256/f1000research.57248.r97905>

© 2022 Golchin A. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Ali Golchin 

Department of Clinical Biochemistry and Applied Cell Science, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

This paper is a comprehensive and good systematic study. The authors have tried to consider all protocols and guidelines of systematic reviews and meta-analyses. Their conclusion is based on their results and real; however, it is possible that from Feb 2021 published new clinical reports about MSC therapy in COVID-19 patients. Moreover, it was expected in discussion and conclusion different issues of Mesenchymal stem cell therapy such as cost-utility, source limitations, personalized medicine aspects, etc. These issues make the most challenging aspects of stem cell therapy in different diseases, especially COVID-19 patients.

## References

1. Basiri A, Mansouri F, Azari A, Ranjbarvan P et al (2021) Stem cell therapy potency in personalizing severe COVID-19 treatment. *Stem Cell Rev Rep* 17:193-213. <https://doi.org/10.1007/s12015-020-10110-w>

## References

1. Basiri A, Mansouri F, Azari A, Ranjbarvan P, et al.: Stem Cell Therapy Potency in Personalizing Severe COVID-19 Treatment. *Stem Cell Rev Rep.* 17 (1): 193-213 [PubMed Abstract](#) | [Publisher Full Text](#)

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Yes

**Is the statistical analysis and its interpretation appropriate?**

Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Stem cell research, Cell-based therapy

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**

# Source details

## F1000Research

Open Access ⓘ

Scopus coverage years: from 2012 to Present

Publisher: Taylor & Francis

E-ISSN: 2046-1402

Subject area: [Pharmacology, Toxicology and Pharmaceutics: General Pharmacology, Toxicology and Pharmaceutics](#)

[Biochemistry, Genetics and Molecular Biology: General Biochemistry, Genetics and Molecular Biology](#)

View all ▾

Source type: Journal

CiteScore 2020

4.4 ⓘ

SJR 2020

1.099 ⓘ

SNIP 2020

0.921 ⓘ

[View all documents >](#)

[Set document alert](#)

[Save to source list](#) [Source Homepage](#)

[CiteScore](#) [CiteScore rank & trend](#) [Scopus content coverage](#)

### Improved CiteScore methodology



CiteScore 2020 counts the citations received in 2017-2020 to articles, reviews, conference papers, book chapters and data papers published in 2017-2020, and divides this by the number of publications published in 2017-2020. [Learn more >](#)

CiteScore 2020 ▾

$$4.4 = \frac{13,426 \text{ Citations } 2017 - 2020}{3,027 \text{ Documents } 2017 - 2020}$$

Calculated on 05 May, 2021

CiteScoreTracker 2021 ⓘ

$$4.9 = \frac{14,958 \text{ Citations to date}}{3,026 \text{ Documents to date}}$$

Last updated on 06 March, 2022 - Updated monthly

### CiteScore rank 2020 ⓘ

Category	Rank	Percentile
Pharmacology, Toxicology and Pharmaceutics	#13/67	81st
General Pharmacology, Toxicology and Pharmaceutics		
Biochemistry, Genetics and Molecular Biology	#60/204	70th

[View CiteScore methodology >](#) [CiteScore FAQ >](#) [Add CiteScore to your site ↗](#)

SCIMAGO INSTITUTIONS RANKINGS

**SJR** Scimago Journal & Country Rank

Enter Journal Title, ISSN or Publisher Name

Home Journal Rankings Country Rankings Viz Tools Help About Us

## F1000Research

### COUNTRY

United Kingdom



### SUBJECT AREA AND CATEGORY

- Biochemistry, Genetics and Molecular Biology
  - Biochemistry, Genetics and Molecular Biology (miscellaneous)
- Immunology and Microbiology
  - Immunology and Microbiology (miscellaneous)
- Medicine
  - Medicine (miscellaneous)
- Pharmacology, Toxicology and Pharmaceutics
  - Pharmacology, Toxicology and Pharmaceutics (miscellaneous)

### PUBLISHER

### H-INDEX

# 60

### PUBLICATION TYPE

Journals

### ISSN

20461402

### COVERAGE

2012-2020

### INFORMATION

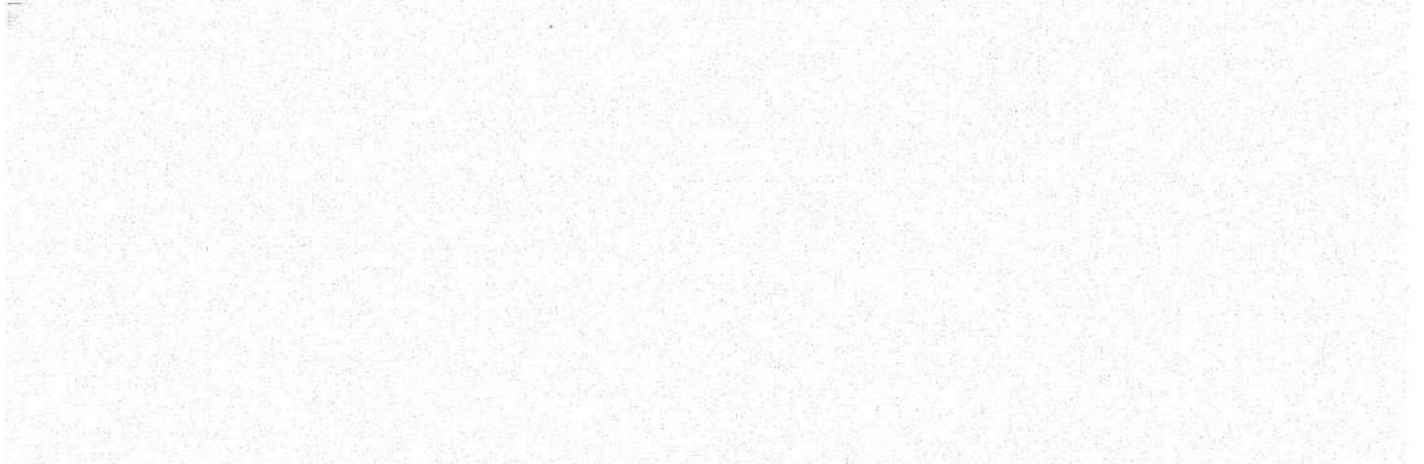
- [Homepage](#)
- [How to publish in this journal](#)
- [research@f1000.com](mailto:research@f1000.com)

### SCOPE

F1000Research publishes articles and other research outputs reporting basic scientific, scholarly, translational and clinical research across the physical and life sciences, engineering, medicine, social sciences and humanities. F1000Research is a scholarly publication platform set up for the scientific, scholarly and medical research community, each article has at least one author who is a qualified researcher, scholar or clinician actively working in their speciality and who has made a key contribution to the article. Articles must be original (not duplications). All research is suitable irrespective of the perceived level of interest or novelty; we welcome confirmatory and negative results, as well as null studies. F1000Research publishes different type of research, including clinical trials, systematic reviews, software tools, method articles, and many others. Reviews and Opinion articles providing a balanced and comprehensive overview of the latest discoveries in a particular field, or presenting a personal perspective on recent developments, are also welcome. See the full list of article types we accept for more information.

[Join the conversation about this journal](#)

### Quantiles





**FIND SIMILAR JOURNALS**

<b>Advances in Experimental Medicine and Biology</b> 1756 <b>79%</b> similarity	<b>EBioMedicine</b> 4467 <b>78%</b> similarity	<b>Science Translational Medicine</b> 1234 <b>73%</b> similarity	<b>Frontiers of Medicine</b> 1234 <b>73%</b> similarity	<b>Journal of Biomedical Science</b> 1234 <b>71%</b> similarity
--	---	---	--	--

**SJR**

2013 2014 2015 2016 2017 2018 2019 2020

**Total Documents**

2012 2014 2016 2018 2020

**Citations per document**

2012 2014 2016 2018 2020

Cites / Doc. (4 years)  
 Cites / Doc. (3 years)  
 Cites / Doc. (2 years)

**Total Cites** **Self-Cites**

2012 2013 2014 2015 2016 2017 2018 2019 2020

**External Cites per Doc** **Cites per Doc**

2012 2013 2014 2015 2016 2017 2018 2019 2020

**% International Collaboration**

2012 2013 2014 2015 2016 2017 2018 2019 2020

**Citable documents** **Non citable documents**

2012 2013 2014 2015 2016 2017 2018 2019 2020

**Cited documents** **Uncited documents**

2012 2013 2014 2015 2016 2017 2018 2019 2020

**F1000Research**

Q1 Medicine (miscellaneous) 2021 (Jan-Jun)

SJR 2020 1.1

powered by scopus.com

Show this widget in your own website

Just copy the code below and paste within your html code.

<a href="https://www.scimagojr.com">https://www.scimagojr.com</a>

**SCImago Graphica**

Explore, visually communicate and make sense of data with our new free tool.

[Get it](#)

Metrics based on Scopus® data as of April 2021

**H** hany akeel naji 6 months ago

I have been waiting about one year for my article to publish or review but till now nothing happened.

[reply](#)

**Melanie Ortiz** 5 months ago SCImago Team

Dear Hany,

Thank you for contacting us.

Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff, so they could inform you more deeply.

Best Regards, SCImago Team

**A** alemu 12 months ago

Background: Nowadays, people die due to metabolic aging than chronological age worldwide. Unhealthy lifestyle behaviors may be long-term risk factors for chronic circumstances and its effect on quality of life is not routinely examined.

Objective: To investigate the association between health-related quality of life and unhealthy lifestyles behaviors among middle aged urban residents in West Ethiopia.

Methods: This cross-sectional study was conducted on 266 adults. Data were collected using health promoting questionnaires for lifestyle behaviors and EQ-5D of health-related quality of life.