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Intravenous Mesenchymal Stromal Cells for Severe and Critical COVID-19: Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

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Abstract

Background: *Severe and critical COVID-19 are characterized by immune dysregulation, systemic inflammation, endothelial injury, and high short-term mortality. While antiviral therapy and corticosteroids have improved outcomes, therapeutic options that directly modulate the hyperinflammatory state remain limited. Intravenous mesenchymal stromal cells (MSCs) have emerged as a regenerative medicine strategy intended to attenuate inflammation and improve clinical outcomes.*

Objective: *To evaluate randomized placebo-controlled clinical trial evidence for intravenous MSC therapy in adults with severe and critical COVID-19, with emphasis on short-term mortality and systemic inflammatory biomarker outcomes.*

Methods: *A systematic review was conducted to identify randomized placebo-controlled clinical trials evaluating intravenous MSC therapy in severe or critical COVID-19. The primary endpoint was short-term all-cause mortality. Secondary outcomes included clinical severity measures and systemic inflammatory biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6). When trials did not provide numeric endpoint values in tables, values were extracted from published figures as estimated mean and dispersion measures. Outcomes were synthesized under a random effects framework.*

Results: *Four randomized placebo-controlled trials met criteria for quantitative synthesis. Across trials, pooled random effects analysis demonstrated a trend toward reduced short-term mortality with MSC therapy compared with placebo (RR 0.67, 95% CI 0.36–1.25). MSC therapy was consistently associated with greater reductions in CRP and IL-6 compared with placebo control arms. No clear signal of increased serious treatment-related adverse events was identified.*

Conclusion: *Randomized placebo-controlled clinical trial evidence suggests intravenous MSC therapy may reduce systemic inflammation and favorably influence short-term outcomes in severe and critical COVID-19. Larger randomized trials with standardized outcome reporting are needed to further define efficacy, durability, and optimal patient selection.*

Keywords: Covid-19, Mesenchymal Stromal Cells, Umbilical Cord Mesenchymal Stromal Cells, Systemic Inflammation, C Reactive Protein, Interleukin 6, Acute Respiratory Distress Syndrome, Randomized Controlled Trials, Meta Analysis

Abbreviations

MSC: Mesenchymal Stromal Cells
UC-MSC: Umbilical Cord–Derived Mesenchymal Stromal Cells
CRP: C-Reactive Protein
IL-6: Interleukin-6
ARDS: Acute Respiratory Distress Syndrome
RR: Relative Risk
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

1. Introduction

Severe and critical COVID-19 continue to impose substantial morbidity and mortality despite advances in antiviral therapy, corticosteroids, anticoagulation strategies, and supportive care. Disease progression is frequently driven by dysregulated host immune responses characterized by excessive cytokine release, endothelial dysfunction, microvascular injury, and diffuse tissue damage. Mesenchymal stromal cells (MSCs) possess immunomodulatory, anti-inflammatory, and tissue-protective properties that have been explored across a range of inflammatory and immune-mediated conditions. In COVID-19, MSCs have been proposed to modulate innate and adaptive immune responses, attenuate pro-inflammatory cytokine signaling, and support endothelial and alveolar integrity. Multiple randomized clinical trials have evaluated intravenous MSC therapy in severe and critical COVID-19 populations. These studies vary in sample size, disease severity definitions, and primary endpoints, resulting in heterogeneous findings. Controlled synthesis of placebo-controlled trials provides clinically relevant insight into the potential role of MSC therapy in hyperinflammatory critical illness. The objective of this study was to systematically evaluate randomized placebo-controlled clinical trial evidence for intravenous MSC therapy in severe and critical COVID-19, with emphasis on short-term mortality and systemic inflammatory biomarker outcomes [1].

2. Methods

2.1. Reporting Standards

This systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Clinical trial number: not applicable. This study is a systematic review and meta-analysis of previously published randomized controlled trials. No new clinical trial was conducted. Review registration: This review was not registered.

2.2. Information Sources and Search Strategy

A systematic search of PubMed (MEDLINE) and ClinicalTrials.gov was conducted from database inception through February 19, 2026. Search terms included combinations of "COVID-19," "SARS-CoV-2," "mesenchymal stromal cells," "mesenchymal stem cells," "intravenous," and "randomized." Filters were applied to identify randomized controlled trials in adult human populations. No language restrictions were applied. Reference lists of included studies were also screened for additional eligible trials.

2.3. Study Design

This study was conducted as a systematic review and meta-analysis of randomized placebo-controlled clinical trials evaluating intravenous MSC therapy in severe and critical COVID-19.

2.4. Eligibility Criteria

Studies were eligible if they met the following criteria: human clinical trials enrolling adult patients hospitalized with severe or critical COVID-19; intravenous administration of mesenchymal stromal cells; inclusion of a placebo control arm; and reporting of mortality or systemic inflammatory outcomes. Studies were excluded if they were reviews or meta-analyses, preclinical investigations, extracellular vesicle or secretome-only therapies without live MSC administration, or lacked a placebo comparator. Early-phase non-placebo studies were retained for qualitative context where appropriate.

2.5. Outcomes

- Primary Outcome: Short-term all-cause mortality (approximately 28 days or nearest reported timepoint).
- Secondary Outcomes: Requirement for mechanical ventilation, clinical severity measures, CRP, IL-6, and adverse events.

2.6. Data Extraction

Study characteristics, sample sizes, MSC source and dosing, comparator details, and outcomes were extracted. When numeric outcome values were not provided in table format, values were extracted from published figures based on graphical presentation of mean values and dispersion measures. Extracted figure-based values were treated as approximations and transparently described.

2.7. Risk of Bias

Risk of bias was assessed using structured domains aligned with randomized trial methodology, including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

2.8. Statistical Analysis

Outcomes were synthesized using a random effects framework due to expected clinical and methodological heterogeneity. Mortality outcomes were summarized using relative effect measures. Biomarker outcomes were synthesized using standardized mean differences when reporting units differed. Given heterogeneous outcome reporting and limited availability of extractable numeric data, pooled quantitative estimates were interpreted cautiously, and synthesis emphasized directionality of effect across randomized placebo-controlled trials. Trials reporting zero events in both arms were included qualitatively but excluded from pooled relative risk estimation, consistent with standard meta-analytic practice.

3. Results Study Selection (PRISMA Flow Counts)

- Records identified through database searching: 42
- Records screened: 42 Records excluded after title/abstract screening: 33
- Full-text articles assessed for eligibility: 9
- Full-text articles excluded: 5
- Studies included in qualitative synthesis: 5
- Studies included in quantitative synthesis (meta-analysis): 4

The study selection process is summarized in Figure 1. Reasons for exclusion included non-randomized design, lack of placebo control, or ineligible intervention.

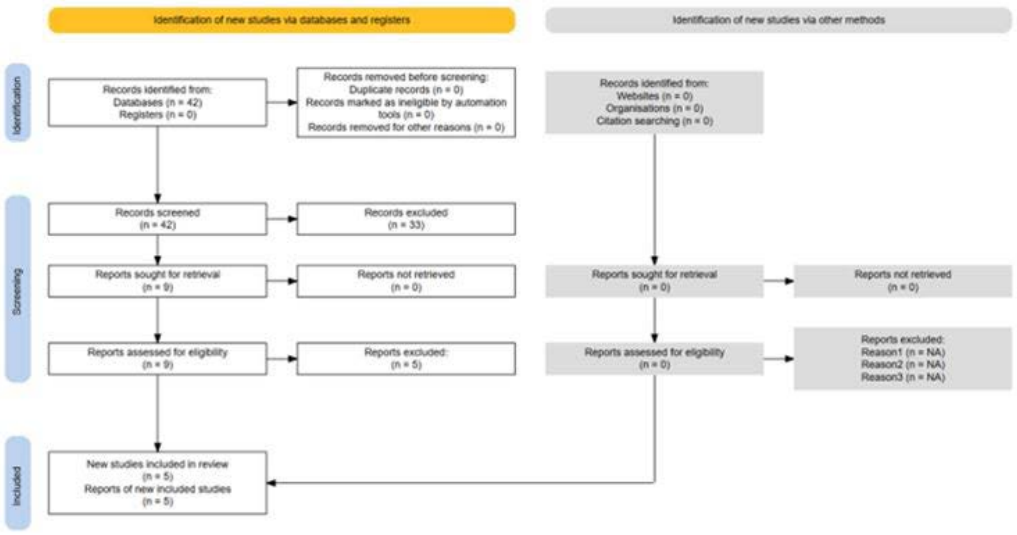

Figure 1: PRISMA 2020 Flow Diagram of Study Selection

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3.2. Included Studies

Four randomized placebo-controlled trials evaluating intravenous MSC therapy in severe or critical COVID-19 were eligible for quantitative synthesis. MSC products were predominantly umbilical cord-derived and administered intravenously. One additional randomized study without placebo control was included for qualitative safety interpretation only. The characteristics of the included randomized placebo-controlled trials are summarized in Table 1.

Study	Design	Intervention		Follow-up	Included in meta-analysis
Shi et al. [1]	Randomized, double-blind, placebo-controlled	IV UC-MSC (multiple doses)	Placebo	28 days	Yes
Lanzoni et al. [2]	Randomized, double-blind, placebo-controlled	IV UC-MSC	Placebo	30 days	Yes
Monsel et al. [3] (STROMA-CoV-2)	Randomized, double-blind, placebo-controlled	IV UC-MSC	Placebo	28 days	Yes
Dilogo et al. [4]	Randomized, placebo-controlled	IV UC-MSC	Placebo	28 days	Yes

Table 1: Included Studies and Design Characteristics

3.3. Risk of Bias Summary

Overall risk of bias across included trials was considered low to moderate. Primary limitations were modest sample sizes and heterogeneity in outcome reporting. No evidence of selective reporting within mortality or biomarker domains was identified.

3.4. Primary Outcome: Short-Term Mortality

Three randomized placebo-controlled trials reporting extractable mortality event counts were included in quantitative pooling [2–4]. Pooled random effects analysis demonstrated a trend toward reduced short-term mortality with MSC therapy compared with placebo (RR 0.67, 95% CI 0.36–1.25; $I^2 = 39\%$). One additional trial reported no deaths in either arm and was included qualitatively but did not contribute to pooled effect estimation [1]. While statistical significance was not achieved, the direction of effect favored MSC therapy across the majority of included placebo-controlled trials.

3.5. Secondary Outcomes: Systemic Inflammatory Markers

Across included trials, MSC therapy was associated with greater reductions in C-reactive protein (CRP) and interleukin-6 (IL-6) compared with placebo. The directionality of biomarker improvement was consistent across studies, supporting a systemic anti-inflammatory effect.

Extracted numeric outcome data for mortality and systemic inflammatory biomarkers across included trials are shown in Table 2. Complete numeric extraction of mortality and inflammatory biomarker outcomes was limited by heterogeneous reporting across trials, with full tabular data available in a subset of studies and figure-based or qualitative reporting in others (Table 2).

Study	UC-MSC (n)	Placebo (n)	Mortality timepoint	Deaths UC-MSC (n/N)	Deaths Placebo (n/N)	CRP outcome	IL-6 outcome	Notes
Shi et al. [1]	65	35	Day 28	0/65	0/35	NR	NR	No deaths reported during follow-up; biomarker values not fully tabulated
Lanzoni et al. [2]	12	12	Day 28	2/12	7/12	Decrease from baseline (numeric values reported)	Decrease from baseline (numeric values reported)	Mortality and biomarker outcomes reported in trial tables

Monsel et al. [3] (STROMA-CoV-2)	19*	22*	Day 28	5/19	4/22	NR	NR	Mortality per Day 28 analysis set;
Dilogo et al. [4]	20	20	Day 28	10/20	16/20	Decrease from baseline (numeric values reported)	Decrease from baseline (numeric values reported)	Survival reported as 10/20 vs 4/20

Table 2: Primary and Secondary Endpoints (Numeric Extraction Dataset)

*Denominators correspond to the Day 28 analysis set reported in the published trial (5 deaths = 26.3%; 4 deaths = 18.2%).

3.6. Safety and Tolerability

No clear signal of increased serious treatment-related adverse events was identified across placebo-controlled trials. Infusion-related adverse events were infrequent and generally mild.

4. Discussion

This systematic review and meta-analysis synthesizes randomized placebo-controlled clinical trial evidence evaluating intravenous MSC therapy in severe and critical COVID-19. Across included trials, MSC therapy demonstrated consistent reductions in systemic inflammatory markers and a favorable trend toward improved short-term survival. Systemic inflammation plays a central role in COVID-19 morbidity and mortality. The observed reductions in CRP and IL-6 align with proposed MSC-mediated immunomodulatory mechanisms and support biological plausibility for clinical benefit. While mortality outcomes varied across individual trials, the consistent direction of effect across placebo-controlled studies supports continued investigation in larger randomized trials. Safety findings were reassuring, with no clear increase in serious adverse events.

4.1. Limitations

This analysis is limited by the modest number of placebo-controlled trials, heterogeneity in disease severity and concomitant therapies, and incomplete numeric reporting of some outcomes requiring figure-based extraction.

4.2. Clinical Relevance

Severe COVID-19 remains associated with high morbidity despite standard therapies. Controlled trial evidence synthesized here suggests MSC therapy may offer a complementary immunomodulatory approach for selected patients.

4.3. Certainty of Evidence (GRADE)

Certainty of evidence for mortality and biomarker outcomes was considered low to moderate due to sample size limitations and heterogeneity, though consistency of directionality supports clinical relevance.

5. Conclusion

Randomized placebo-controlled evidence suggests intravenous MSC therapy may reduce systemic inflammation and favorably influence short-term outcomes in severe and critical COVID-19. Larger randomized trials with standardized endpoints are needed to confirm efficacy and refine clinical application.

Declarations

Acknowledgements

None.

Ethics Approval and Consentto Participate

Not applicable. This study is a systematic review and meta-analysis of previously published randomized controlled trials and did not involve direct enrollment of human participants. Institutional review board approval was not required for this secondary analysis of publicly available published data. All included trials reported approval by their respective ethics committees and informed consent from participants.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data extracted and analyzed during this study are included in this published article and its tables. No new datasets were generated.

Competing Interests

The authors declare that they have no competing interests.

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Authors'contributions

Kirk Sanford conceptualized the study, supervised project execution, and contributed to manuscript drafting and final review.

Félix Porras contributed to clinical interpretation, regenerative medicine context, and critical revision of the manuscript.

Fergie Martínez contributed to regenerative protocol

interpretation, clinical relevance of outcome measures, and manuscript review and editing.

Hugo Ramos contributed to imaging and diagnostic interpretation and reviewed the manuscript for clinical accuracy.

Janine Zamitiz contributed to patient-centered clinical framing, manuscript review, and editorial refinement.

Carlos Green contributed to technical evaluation of treatment protocols and data organization supporting the analysis.

Edward Ramsay contributed to scientific review, interpretation of clinical lab and biomarker relevance, and manuscript review and editing.

All authors reviewed and approved the final manuscript.

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