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Mesenchymal stem cell therapies for ARDS: translational promise and challenges

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Abstract

Over the past decade, global investigations have rigorously assessed the safety and therapeutic potential of mesenchymal stem cells (MSCs) in managing acute respiratory distress syndrome (ARDS). MSCs, obtained from sources like bone marrow, adipose tissue, and umbilical cord, exert therapeutic effects in ARDS primarily through complex paracrine mechanisms, including anti-inflammatory, immunoregulatory, pro-reparative, antioxidant, antimicrobial, and mitochondrial transfer functions. Preclinical studies have consistently demonstrated significant therapeutic benefits. Clinical trials have further confirmed a favorable safety profile, with no significant infusion-related toxicity or serious adverse events observed even at higher doses (up to 10×10^6 cells/kg) or following multiple administrations. Yet, while some early-phase clinical trials have not conclusively demonstrated a significant reduction in mortality among ARDS patients, multiple studies note diminished inflammatory biomarkers, enhanced markers of endothelial and epithelial repair (e.g., angiopoietin-2), and suggestive benefits in subgroups like younger patients or those receiving higher doses of viable cells. MSC-derived therapies, particularly extracellular vesicles and conditioned medium, represent promising "cell-free" strategies that may overcome limitations associated with live-cell therapy. Despite encouraging progress, clinical translation faces challenges, including optimizing cell sources, preparation, dosing, delivery, and developing robust potency assays. Future research should prioritize large, high-quality randomized trials to confirm efficacy across various ARDS etiologies and clinical phenotypes, evaluate repeat dosing, and explore innovative strategies such as gene modification, cellular preconditioning, and combination therapies. Collectively, MSCs and their derivatives hold substantial potential for ARDS treatment, though their widespread application requires further validation and a deeper understanding of their interactions with the complex ARDS microenvironment.

Keywords Mesenchymal stem cells, Acute respiratory distress syndrome, Cell-free therapies, Translational research, Immunomodulation

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Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by disruption of the alveolar-capillary barrier, pulmonary edema, severe hypoxemia, and reduced lung compliance, precipitated by diverse direct or indirect insults such as pneumonia, sepsis, trauma, or viral infections [1]. Despite improvements in lung-protective ventilation strategies (e.g., low tidal volume ventilation) and supportive therapies (e.g., extracorporeal membrane oxygenation [ECMO] and prone positioning), the mortality rate of ARDS remains high (30% – 40%), and no specific pharmacological treatment has been demonstrated to be effective [2]. Consequently, developing novel therapeutic approaches to improve ARDS outcomes is of critical clinical importance.

Mesenchymal stem cells (MSCs), also referred to as mesenchymal stromal cells, are adult stem cells characterized by their multilineage differentiation potential, self-renewal capability, and potent immunomodulatory functions [3]. They can be isolated from multiple tissues, including bone marrow (BM), adipose tissue (AT), umbilical cord (UC), and placenta (PL) [4]. Over the past decade, researchers worldwide have conducted extensive preclinical and clinical studies to evaluate the safety and efficacy of MSC-based therapies for the treatment of ARDS [5, 6]. Extensive preclinical evidence has demonstrated that MSCs significantly reduce lung injury and improve survival in various ARDS animal models via multiple mechanisms, including anti-inflammatory, anti-apoptotic, epithelial, and endothelial repair, enhanced bacterial clearance, and antioxidant activity [7–11]. These encouraging preclinical findings have propelled clinical translation; early-phase trials suggest MSC administration is safe and potentially improves outcomes in moderate-to-severe ARDS patients [12].

MSC therapy is primarily indicated for moderate-to-severe ARDS caused by diverse etiologies, particularly in critically ill patients with multi-organ failure, with inclusion criteria often based on partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratios (e.g., < 200 mmHg) and inflammatory biomarker levels [5, 10, 12, 13]. Clinical trials typically target the acute phase of ARDS (within 96 h of diagnosis) to maximize the benefit of early intervention in controlling inflammation and lung damage [14]. However, MSC therapy remains investigational, requiring further evidence to confirm its efficacy and safety. Here, we summarize the mechanisms of MSC, their sources and delivery strategies, clinical outcomes, cell-free derivatives, efficacy across ARDS subtypes, and key challenges for future translation.

Therapeutic mechanisms of MSCs in ARDS

The therapeutic mechanisms of MSCs in ARDS are multifaceted and predominantly mediated through paracrine effects rather than long-term engraftment and differentiation at injury sites [15]. The evidence-based mechanistic network centered on MSCs and their therapeutic role in ARDS is depicted in Fig. 1.

Immunomodulation

MSCs respond to inflammatory cues within the damaged microenvironment by releasing a diverse repertoire of soluble mediators and extracellular vesicles (EVs) that modulate both innate and adaptive immune responses. They suppress the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and MIP-2 [16–18], while promoting anti-inflammatory mediators, notably IL-10 [19, 20]. MSCs also shift macrophages from M1 to M2 phenotypes [13, 21, 22], and balance Tregs against Th17 cells to mitigate inflammation [23].

At the signaling level, MSCs exert critical immunomodulatory effects in ARDS by targeting multiple pathways. They significantly attenuate excessive inflammation by inhibiting pro-inflammatory cascades, including the nuclear factor κB (NF-κB) pathway, thereby reducing the production of pro-inflammatory cytokines [24, 25]. MSCs also modulate the receptor for advanced glycation end-products (RAGE) [24] and Toll-like receptor 4 (TLR4) [17, 26], both of which play pivotal roles in amplifying inflammatory responses to tissue damage and pathogens, thus limiting further lung injury. Concurrently, MSCs bolster cellular defense and repair mechanisms. For instance, engagement of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway underpins broad cytoprotective effects through its potent anti-inflammatory and antioxidant actions [17, 25, 27]. These multifaceted actions are complemented by the engagement with the cholinergic anti-inflammatory pathway [28], the secretion of anti-inflammatory mediators like tumor necrosis factor-stimulated gene-6 (TSG-6) [29], and the regulation of soluble TNF receptor 2 (sTNFR2) [30], all contributing to a more balanced immune response and promoting tissue protection in the ARDS lung.

Enhanced alveolar-capillary barrier repair

Beyond immunomodulation, MSCs contribute to alveolar-capillary barrier repair. Studies have shown that MSCs can reduce pulmonary vascular permeability and alleviate pulmonary edema [13, 31], partly through the secretion of growth factors such as angiopoietin-1 (Ang-1) [32], keratinocyte growth factor (KGF) [33], hepatocyte growth factor (HGF) [34], and vascular endothelial growth factor (VEGF) [35]. These factors support the regeneration of alveolar epithelial and endothelial cells, restore barrier integrity, and stabilize the vascular structure. MSCs also possess anti-fibrotic properties, as demonstrated by their ability to reduce collagen deposition and attenuate lung structural abnormalities

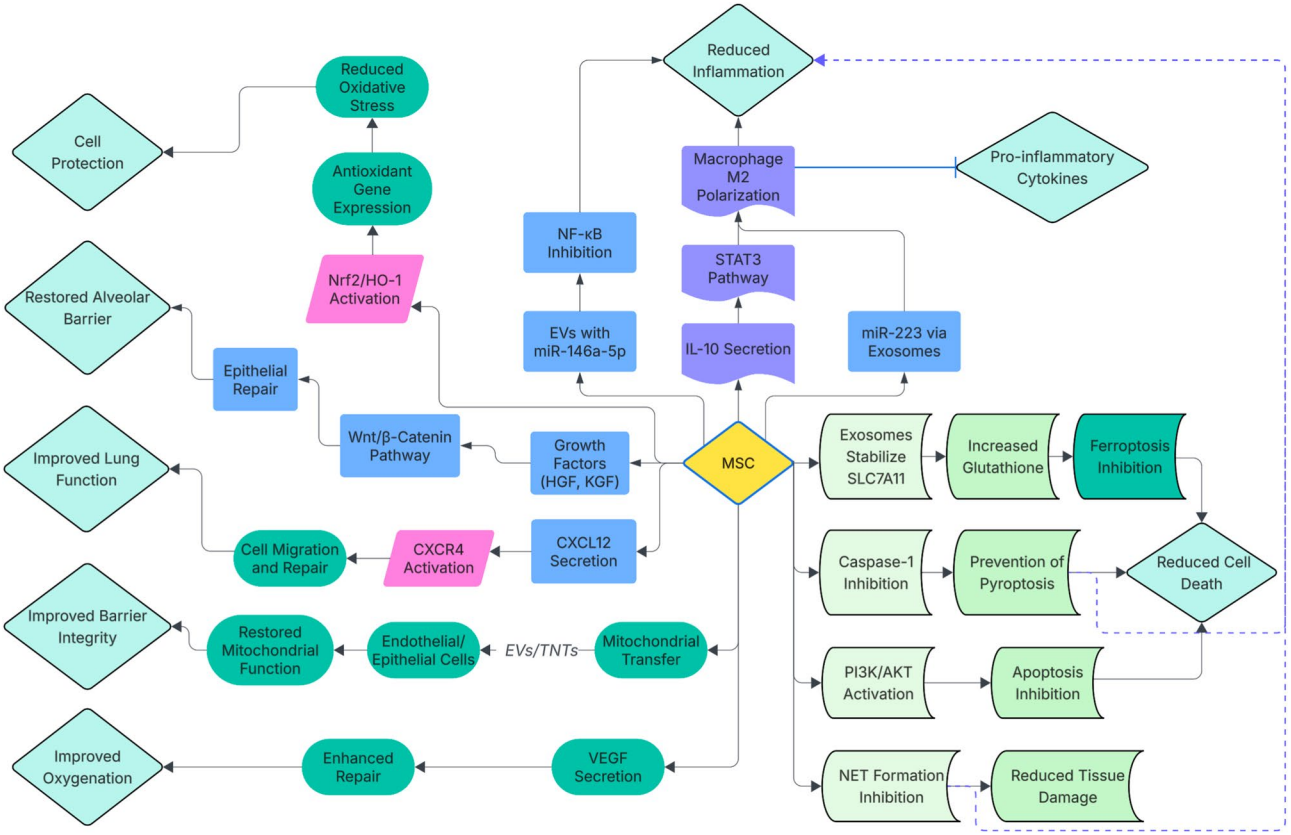

Fig. 1 Illustration of the multifaceted mechanisms by which MSCs exert therapeutic effects in ARDS and ALI. MSCs mediate immunomodulation by interacting with immune cells to attenuate inflammation and promote tissue repair through modulation of epithelial and endothelial cells. They enhance alveolar barrier integrity and cellular function via antioxidant activity, inhibition of ferroptosis, and mitochondrial transfer (via EVs or TNTs). These actions collectively reduce cell death and improve oxygenation in ARDS/ALI. Key molecular mediators include cytokines (e.g., IL-10), chemokines (e.g., CXCL12), microRNAs (e.g., miR-146a-5p), growth factors (e.g., HGF), transcription factors (e.g., STAT3), cell death regulators (e.g., caspase-1), and receptors (e.g., CXCR4) [32, 46, 48, 52, 82, 108, etc]. ARDS: Acute respiratory distress syndrome; ALI: Acute Lung Injury ¨ MSC: Mesenchymal Stem Cell ¨ IL-10:Interleukin-10 ¨ CXCL12:C-X-C Motif Chemokine Ligand 12 ¨ miR-146a-5p: microRNA-146a-5p ¨ HGF: Hepatocyte Growth Factor ¨ STAT3:Signal Transducer and Activator of Transcription 3 ¨ Caspase-1:Cysteine-Aspartate Protease 1 ¨ CXCR4:C-X-C Motif Chemokine Receptor 4

in bleomycin- and paraquat-induced pulmonary fibrosis models [36–38]. Moreover, MSCs safeguard pulmonary cells by inhibiting apoptotic signaling, particularly by regulating the Bax/Bcl-2 balance [39, 40].

Reduced oxidative stress

MSCs alleviate oxidative stress by decreasing the levels of malondialdehyde (MDA) and reactive oxygen species (ROS), and by enhancing the activities of superoxide dismutase (SOD) and glutathione (GSH) [25, 41, 42]. In infectious ARDS, MSCs also promote bacterial clearance, which contributes to reduced pulmonary bacterial burden and improved host defense [43, 44]. Moreover, the Hippo pathway contributes to these antioxidant effects by augmenting MSC antioxidant capabilities [45], further protecting lung tissue.

Mitochondrial transfer

MSCs are capable of transferring functional mitochondria to various injured pulmonary cell types, including alveolar epithelial cells, endothelial cells, and macrophages [46]; this process directly impacts ARDS outcomes through multiple mechanisms [33, 47]. A primary effect of this transfer is the restoration of cellular bioenergetic function. By delivering healthy mitochondria, typically via extracellular vesicles (EVs) [46] or tunneling nanotubes (TNTs) [48], MSCs replenish ATP supplies, enhance oxidative phosphorylation, and improve oxygen consumption rates in recipient cells, all of which are critical for cellular repair and survival in the face of ARDS-induced metabolic stress [49–51]. This bioenergetic rescue is crucial for maintaining alveolar-capillary barrier integrity, a key aspect compromised in ARDS [50, 52].

Beyond direct bioenergetic recovery, mitochondrial transfer also exerts significant anti-apoptotic effects. The provision of functional mitochondria modulates apoptosis-related pathways, such as by increasing anti-apoptotic Bcl-2 levels and preserving mitochondrial membrane potential, thereby protecting lung cells from programmed

cell death [53–55]. For instance, MSC-derived exosomes facilitate mitochondrial transfer to alveolar macrophages, enhancing not only their bioenergetics but also their homeostasis, and phagocytic capacity, while shifting them towards an anti-inflammatory phenotype, all contributing to the resolution of inflammation and tissue repair [46, 48, 53]. Furthermore, mitochondrial transfer to pulmonary endothelial cells can activate metabolic pathways like the TCA cycle, promoting endothelial proliferation, the release of pro-angiogenic factors, and ultimately enhancing vascular regeneration, which is vital for repairing the damaged lung vasculature in ARDS [51, 52].

Other mechanisms

Emerging evidence indicates MSCs may also mitigate lung inflammation and injury by modulating gut microbiota, suggesting a regulatory role via the lung-gut axis [26, 56, 57]. Substantial evidence indicates that MSC engraftment in lung tissue is generally low and short-lived following transplantation [8]. Thus, their therapeutic impact primarily stems from paracrine signaling, involving the secretion of soluble factors like IL-10 and transforming growth factor-beta (TGF-β), alongside EVs, which deliver anti-inflammatory signals, boost macrophage phagocytosis, and promote tissue regeneration [15–17, 58].

Donor age and host microenvironment

The therapeutic effects of MSCs are not only determined by their inherent properties but also critically influenced by donor age and the recipient's inflammatory microenvironment. MSCs derived from younger donors typically demonstrate superior regenerative potential compared to those from aged sources. MSCs from older individuals often exhibit signs of cellular senescence, including shortened telomeres, reduced proliferative capacity, and diminished differentiation potential [59–61]. This age-related decline in MSC "fitness" is also associated with increased oxidative damage, higher levels of reactive oxygen species (ROS), and upregulation of senescence-related genes like p21 and p53 [62]. In addition, senescent MSCs frequently shift toward a pro-inflammatory senescence-associated secretory phenotype (SASP), characterized by reduced secretion of reparative paracrine factors such as HGF and IL-10, and increased release of inflammatory mediators, thereby impairing their immunomodulatory and reparative capacities [63–65].

The host microenvironment also plays a crucial role in regulating MSC function. A highly inflammatory milieu—particularly one with elevated IL-6—elevated IL-6, can compromise MSC immunoregulatory activity by disrupting key intracellular signaling pathways such as STAT3 or NF-κB [64, 66]. Conversely, a less hostile and more balanced immune environment, often observed in younger patients, may facilitate MSC survival, retention, and therapeutic efficacy. This dynamic interplay between donor cell characteristics and recipient immunologic status highlights the importance of considering both intrinsic and extrinsic factors when optimizing MSC-based therapies for ARDS.

MSC sources and their characteristics

MSCs can be sourced from various tissues, with BM-MSCs, AT-MSCs, UC-MSCs, PL-MSCs, and menstrual blood (Menstrual blood-MSC) being commonly studied in preclinical and clinical settings [4]. Each source presents unique advantages and limitations regarding availability, proliferative capacity, immunomodulatory potential, and ethical considerations. A comparative overview of the characteristics and therapeutic features of MSCs from different sources in ARDS is presented in Table 1.

BM-MSCs

BM-MSCs are among the most extensively studied MSC types and are known for their potent immunomodulatory properties [16]. Hao et al. reported that BM-MSCs significantly attenuated LPS-induced pulmonary edema and inflammation, although their effects on reducing alveolar protein leakage were limited [13]. The START clinical trials confirmed that a single intravenous infusion of BM-MSCs at doses up to 10×10^6 cells/kg was well tolerated [67]. Nevertheless, BM-MSCs face challenges, including an invasive harvesting procedure and diminished yield and proliferative capacity with advancing donor age.

AT-MSCs

AT-MSCs can be harvested in large quantities through liposuction; however, they exhibit greater heterogeneity and tend to have shorter pulmonary retention times in ARDS models [68]. Zheng et al. reported that treatment with AD-MSCs resulted in decreased levels of surfactant protein-D (SP-D), yet primary clinical outcomes showed no significant improvement [69].

UC-MSCs

UC-MSCs, sourced from abundant, ethically uncontentious materials (often considered medical waste), exhibit youthful cellular vigor, robust proliferation, and low immunogenicity, rendering them highly appealing for clinical studies [31, 70–72]. Lanzoni et al. reported that treatment with UC-MSCs in patients with COVID-19-associated ARDS led to improved survival and decreased levels of inflammatory cytokines [10]. Both in vitro and animal studies have indicated that UC-MSCs exhibit therapeutic efficacy comparable to BM-MSCs [43].

Table 1 Comparison of MSC sources for ARDS treatment

MSC Source	Yield	Immunogenicity	Clinical Efficacy	Scalability	Reference
BM-MSCs	Moderate; limited by invasive bone marrow aspiration, requires in vitro expansion	Moderate; requires HLA matching to reduce rejection risk	Improves oxygenation and reduces inflammation in ARDS; mixed results in clinical trials (e.g., 28-day mortality 30% vs. 15%, $P = 0.58$)	Low; invasive collection and complex expansion limit large-scale production	[13, 16, 79]
AT-MSCs	High; abundant adipose tissue via liposuction, high cell yield per procedure	Low; minimal rejection risk in allogeneic use	Reduces inflammation and improves lung function in preclinical and early clinical studies	High; minimally invasive, standardized liposuction enables large-scale production	[68, 69]
UC-MSCs	High; umbilical cord tissue readily available, efficient in vitro expansion	Low; suitable for allogeneic therapy due to immune-privileged status	Significantly improves survival in COVID-19 ARDS (91% vs. 42%, $P = 0.015$) and reduces inflammatory cytokines	High; non-invasive, abundant source, supports standardized production	[10, 33, 70]
PL-MSCs	High; plentiful placental tissue, high cell yield per extraction	Low; immune-privileged, low rejection risk	Suppresses inflammation and promotes lung repair in early clinical studies	High; abundant tissue source, feasible for large-scale production	[73–75]

Abbreviations: MSC Mesenchymal Stromal Cells; BM-MSC Bone Marrow-Derived MSCs; AT-MSC Adipose Tissue-Derived MSCs; UC-MSCs Umbilical Cord-Derived MSCs; PL-MSCs Placenta-Derived MSCs; ARDS Acute Respiratory Distress Syndrome; HLA Human Leukocyte Antigen; IV Intravenous; OR Odds Ratio

PL-MSCs

PL-MSCs, which are similarly abundant, highly proliferative, and exhibit low immunogenicity, demonstrate potent anti-inflammatory properties via IL-10/STAT3/NLRP3 axis [73] and are considered suitable for standardized production. Xu et al. demonstrated that PL-MSCs attenuate LPS-induced increases in endothelial permeability and reduce pulmonary injury [74]. A phase I clinical trial in patients with COVID-19-associated ARDS confirmed the safety of intravenous infusion of PL-MSCs; however, no significant differences in therapeutic efficacy were observed compared to the control group [75].

Administration and clinical outcomes

Intravenous (IV) infusion remains the predominant clinical delivery method due to its practicality, yet it encounters a "first-pass effect," where many cells are temporarily sequestered in the pulmonary vasculature before redistribution or clearance [68]. Intratracheal (IT) administration and nebulization allow direct delivery to the lungs, potentially enhancing local therapeutic effects. Numerous preclinical studies affirm their feasibility and efficacy [16, 17, 76, 77], though their clinical safety and effectiveness await further validation. Intrapleural administration has also been investigated and is believed to exert therapeutic effects primarily through paracrine mechanisms [15].

Preclinical studies have explored diverse dosing regimens, whereas clinical trials typically administer doses between 1×10^6 and 10×10^6 cells per kilogram [6, 78], with the START trial confirming IV tolerability up to 10×10^6 cells/kg [79]. However, higher doses may increase the risk of adverse events such as fever and coagulopathy [80, 81]. Most studies favor single doses [69, 79], but some trials have evaluated multiple dosing regimens (e.g., on days 0 and 3, or two to four infusions), demonstrating safety and suggesting possible benefits in survival and pulmonary function [82–86].

The dose-response relationship in MSC therapy for ARDS reveals conflicting evidence. While the START 2a trial (10×10^6 cells/kg) found no mortality reduction (30% vs. 15%, $P = 0.58$), it noted improved oxygenation and reduced endothelial injury with higher viable cell counts [79]. In contrast, Lanzoni et al. (100×10^6 cells, two doses) observed significant survival benefits (91% vs. 42%, $P = 0.015$) [10]. Preclinical data suggest higher doses enhance efficacy [87, 88]. Variability may stem from cell viability [12], host microenvironment (e.g., inflammation, comorbidities) [66], and ARDS heterogeneity. Optimizing cell viability and tailoring dosing strategies to individual patient contexts may improve therapeutic outcomes. Patient-stratified trials are warranted to clarify dosing strategies.

Preclinical evidence suggests that early administration of MSCs—within 24 h after injury—yields superior outcomes compared to delayed administration (e.g., after 48 h), including enhanced anti-inflammatory effects and improved pulmonary retention [68, 80, 88]. In clinical trials, MSC therapy is typically initiated within 48 to 96 h following ARDS diagnosis [79]. Sánchez-Guijo et al. observed a higher rate of extubation in patients who received treatment within 48 h [83]. The optimal timing for MSC intervention—whether during the early inflammatory phase or the later reparative phase—remains unclear and warrants further investigation [89].

Following IV infusion, MSCs primarily localize to the lungs, where they exhibit transient retention [8]. Lung injury has been shown to enhance the homing capacity of MSCs through chemokine-mediated mechanisms [90, 91], though their limited post-transplantation survival

markedly constrains their long-term therapeutic efficacy [92].

Preclinical studies consistently show that MSC therapy lowers mortality in ARDS animal models [11]. Clinical trial outcomes have been heterogeneous. Open-label studies report promising results [82, 85, 93], but rigorous RCTs like START 2a have not confirmed significant mortality reductions [79]. Meta-analyses have suggested that MSC therapy may reduce overall mortality in patients with ARDS, including those with COVID-19-associated ARDS. However, substantial heterogeneity among studies necessitates cautious interpretation [6, 94, 95]. Some studies have reported trends or statistically significant improvements in secondary endpoints [95, 96], including oxygenation and reductions in lung injury and inflammatory biomarkers such as SP-D, Ang-2, and IL-6 [69, 79, 84, 97]. Still, the impact of MSC therapy on ventilator duration and ICU stay remains uncertain [95].

To provide a comprehensive overview of clinical evidence, the key studies evaluating MSC and MSC-derived therapies for ARDS are summarized in Table 2 [10, 12, 30, 69, 75, 79, 84–86, 93, 96–104], highlighting study designs, MSC sources, dosing regimens, primary outcomes, efficacy, and safety profiles.

Cell-free MSC-derived therapies

Concerns regarding live cell transplantation—such as tumorigenicity, alloimmune responses, and embolism risks—as well as standardization challenges, have driven the exploration of cell-free therapies derived from MSC secretions. EVs, including exosomes and microvesicles, are nanosized vesicles that transport proteins, lipids, messenger RNAs (mRNAs), and microRNAs (miRNAs), and play essential roles in intercellular communication [105]. Their advantages encompass low immunogenicity, capacity to traverse biological barriers, absence of proliferative potential (reducing tumorigenic risk), and suitability for standardized production and storage [71, 98, 106]. Preclinical studies demonstrate that MSC-derived EVs can reduce inflammation, vascular permeability, and lung injury in ARDS models, often achieving therapeutic effects comparable to those of whole MSCs [7, 107–109], largely through transferring regulatory molecules like miRNAs (e.g., miR-223-3p [103], miR-27a-5p [104]) and mRNAs (e.g., Ang-1). Furthermore, preconditioning with agents such as interferon-γ (IFN-γ) [58], thrombin [110], or LPS [111], as well as genetic modifications, has been shown to augment EV therapeutic potency. In addition, nebulized administration of EVs has demonstrated superior anti-inflammatory effects in preclinical ARDS models [17, 112].

Clinically, Sengupta et al. demonstrated the safety and preliminary efficacy of ExoFlo™, a BM-MSC-derived EV product, in patients with severe COVID-19 [98]. In a randomized controlled trial, Lightner et al. observed a trend toward reduced mortality at specific dosages [12]. Moreover, Zarrabi et al. reported zero mortality in COVID-19 ARDS patients treated with a combination of MSCs and EVs [80, 84]. These early clinical findings highlight the potential of EV-based therapies, though larger, well-powered trials are warranted to confirm efficacy and safety.

Conditioned medium (CM) encompasses MSC-secreted soluble factors and EVs [25, 105]. Preclinical evidence indicates that CM, containing abundant cytokines (e.g., IL-10), growth factors (e.g., HGF), and EVs, can exert therapeutic effects comparable to MSCs in alleviating lung injury and improving pulmonary function [25, 105, 113, 114]. Similar to EVs, nebulized CM delivery has exhibited promising therapeutic outcomes in preclinical models, suggesting its potential as a noninvasive clinical administration route [76].

While preclinical studies highlight their anti-inflammatory and regenerative potential, direct clinical comparisons with whole MSCs are scarce. Ongoing trials (e.g., NCT03818854) are assessing the safety and efficacy of EVs in ARDS, and may yield crucial insights into their translational potential. Engineered artificial exosomes have shown promise in enhancing ALI treatment [109]. Advances in bioreactor-based culture systems and standardized analytical methods, such as nanoparticle tracking analysis, are being explored to improve reproducibility [115]. Thus, addressing these technical and regulatory hurdles is essential for translating exosome therapies into reliable clinical treatments for ARDS.

Despite their advantages in avoiding risks like embolism and tumorigenicity, MSC-derived exosomes face significant challenges in standardization and batch consistency. Variations in isolation methods (e.g., ultracentrifugation, size-exclusion chromatography), purification protocols, and characterization techniques can lead to inconsistent exosome yield, purity, and potency across batches. Furthermore, regulatory approval is hindered by their novel status and stringent safety requirements. These limitations pose major obstacles to the scalable clinical application of exosome-based therapies.

Efficacy across ARDS subtypes

The heterogeneous nature of ARDS shapes MSC therapeutic responses across its etiologies and immunological profiles. Preclinical models, spanning LPS-induced, bacterial, viral, and ventilator-induced lung injury (VILI), consistently affirm MSC protective effects, albeit with varying degrees of responses [116]. However, the antifibrotic effects of MSCs may differ between pulmonary and extrapulmonary ARDS models [22]. In smoke inhalation ARDS models, concomitant burn injuries may compromise MSC efficacy by diverting their homing to

Table 2 Summary of clinical studies on MSCs and derived therapies for ARDS

First Author (Year)	Study Design	Sample Size Total (Treatment vs. Control)	MSC or Derived Therapy Source	ARDS Etiology	Dose and Administration Frequency	Main Outcomes	Efficacy	Safety
Zheng (2014) [69]	RCT	12 (6 vs. 6)	AD-MSC	ARDS (unspecified, $PaO_2/FiO_2 < 200$)	1×10^6 cells/kg IV, single dose	Safety and lung injury biomarkers	Significant reduction in SP-D (day 5 vs. day 0, $P = 0.027$); Trend toward lower IL-6 ($P = 0.06$)	No infusion toxicities or SAEs; similar AEs in both groups; safe
Matthay (2019) [79]	RCT (Phase 2a START)	60 (40 vs. 20)	BM-MSC	Moderate-to-severe ARDS (Various non-COVID causes)	10×10^6 cells/kg PBW IV, single dose	Safety	28-day mortality 30% (MSC) vs. 15% (Placebo) (OR 2.4, $P = 0.58$); No efficacy difference (adjusted HR 1.43, $P = 0.58$)	No predefined MSC-related AEs; 1 death in MSC group within 24 h (unrelated); safe
Sengupta (2020) [98]	Cohort	24 (Single arm)	BM-MSC-derived EVs	COVID-19 ARDS (Moderate-to-severe)	15 mL IV, single dose	Survival & oxygenation improvement	Survival 83% (17/24 recovered); PaO_2/FiO_2 increase 192% ($P < 0.001$); Reduced CRP ($P < 0.001$), ferritin ($P < 0.001$), D-dimer ($P < 0.05$)	No AEs within 72 h; safe
Hashemian (2021) [85]	Case Series	11 (Single arm)	UC-MSC, 6 cases) / PL-MSC, 5 cases	COVID-19 ARDS (requiring MV)	200×10^6 cells IV, 3 doses (every other day)	Safety and clinical improvement	Clinical survival 6/11; Significant reduction in TNF-α ($P < 0.01$), IL-8 ($P < 0.05$), CRP ($P < 0.01$) in survivors	No SAEs reported 24–48 h post-infusion; safe
Lanzoni (2021) [10]	RCT (Phase 1/2a)	24 (12 vs. 12)	UC-MSC	COVID-19 ARDS	$100 \pm 20 \times 10^6$ cells IV, 2 doses (Day 0 and 3)	Safety (AEs ≤ 6 h; cardiac arrest/death ≤ 24 h post-infusion), Patient survival at 31 days, Time to recovery	Patient survival 91% vs. 42% ($P = 0.015$); SAE-free survival ($P = 0.008$); Time to recovery ($P = 0.03$); Inflammatory cytokines significantly decreased at day 6	No difference in infusion-associated AEs; No SAEs related to UC-MSC; safe
Dilogo (2021) [99]	RCT	40 (20 vs. 20)	UC-MSC	COVID-19 ARDS (Critically ill)	1×10^6 cells/kg IV, single dose	Survival rate, Length of ventilator usage	Survival rate 2.5 times higher in UC-MSC group (50% vs. 20%, $P = 0.047$); Significantly decreased IL-6 in recovered patients ($P = 0.023$)	No AEs reported; safe
Wick (2021) [97]	Nested Cohort (Matthay 2019)	27 (17 vs. 10)	BM-MSC	ARDS (Moderate-to-severe, mixed etiologies (e.g., pneumonia, sepsis))	10×10^6 cells/kg IV, single dose	Airspace biomarker changes	Significantly reduced airspace total protein, Ang-2, IL-6, sTNFR1 vs. placebo; Airspace Ang-2 correlated with fewer VFD ($P = 0.023$)	(Safety reported in parent trial [Matthay 2019]); presumed safe [79]
Kouroupis (2021) [30]	Cohort	24 (from Lanzoni 2021 trial)	UC-MSC	COVID-19 ARDS	$100 \pm 20 \times 10^6$ cells IV, 2 doses (Day 0 and 3)	Plasma TNFα, TNFβ, and sTNFR2 levels at Day 6	Significantly increased sTNFR2; Significantly decreased TNFα and TNFβ in UC-MSC group vs. controls (*P*-values not specified)	(Safety per Lanzoni 2021); presumed safe [10]
Monsel (2022) [100]	RCT (Phase 2b STROMA-CoV-2)	45 (21 vs. 24)	UC-MSC	COVID-19 ARDS (< 96 h)	1×10^6 cells/kg IV, 3 infusions over 5 days	PaO_2/FiO_2 change (Day 0 to Day 7)	No significant difference in PaO_2/FiO_2 change (medians 54.3 vs. 25.3, $P = 0.77$)	SAEs 28.6% (UC-MSC) vs. 25% (Placebo), none related to treatment; safe
Farkhad (2022) [86]	RCT (Phase 1)	20 (10 vs. 10)	UC-MSC	COVID-19 ARDS (Mild-moderate)	1×10^6 cells/kg IV, 3 doses (every other day)	Safety and respiratory function	Significant improvement in SpO_2/FiO_2 ratio; Significant decrease in CRP, IL-6, IFN-γ, TNF-α, IL-17 A ($P < 0.05$)	No serious AEs after cell transplantations; safe

Table 2 (continued)

First Author (Year)	Study Design	Sample Size Total (Treatment vs. Control)	MSC or Derived Therapy Source	ARDS Etiology	Dose and Administration Frequency	Main Outcomes	Efficacy	Safety
Aghayan (2022) [75]	RCT (Phase 1)	20 (10 vs. 10)	PL-MSC	COVID-19 ARDS (ICU patients)	1×10^6 cells/kg IV, single dose	Safety	No significant differences in hospital stay, SpO_2, or other clinical/lab parameters ($P>0.05$)	No AEs observed in PL-MSC group; safe
Grégoire (2022) [87]	Cohort (vs. matched controls)	8 (MSC) vs. 24 (Matched Controls)	BM-MSC	COVID-19 ARDS (Severe, requiring O_2 support)	$1.5\text{-}3\times10^6$ cells/kg IV, 3 infusions (at 3-day intervals)	Safety and survival	Survival at 28 & 60 days: 100% vs. 79.2% ($P=0.025$) & 70.8% ($P=0.0082$); Significantly lower Day-7 D-dimer in MSC group ($P=0.0085$)	No AEs related to MSC infusions; safe
Bowdish (2023) [93]	RCT	222 (112 vs. 110)	Allogeneic MSC (Remestemcel-L)	COVID-19 ARDS (Moderate-to-severe)	2×10^6 cells/kg IV, 2 infusions (Days 0, 4 ± 1)	30-day mortality	30-day mortality 37.5% vs. 42.7% (RR 0.88, $P=0.43$); No significant differences in VFD	No infusion-related toxicities; similar SAEs; safe
Lightner (2023) [12]	RCT (Phase 2)	102 (Placebo vs. 10mL vs. EVs 15mL EVs; $N\approx34$ per arm)	BM-MSC-derived EVs (ExoFlo™)	COVID-19 ARDS (Moderate-to-severe)	Placebo, 10 mL, or 15 mL IV, 2 doses (Days 1 and 4)	All-cause 60-day mortality	Reduced 60-day mortality with 15 mL ExoFlo™ vs. placebo in post hoc subgroup (18–65 yrs, RR 0.385, $P=0.034$); Improved VFD with 15 mL ExoFlo™ (18–65 yrs, $P=0.0455$)	No treatment-related AEs; safe (15 mL dose)
Zarrabi (2023) [84]	RCT	43 (MSC:11, MSC + EV:8 vs. Control:24)	Unspecified source (MSC and MSC-EVs)	COVID-19 ARDS	MSC: 100×10^6 cells IV, 2 doses; or MSC (100×10^6) + EVs (1 dose each)	Mortality, Inflammatory markers	Mortality: MSC 3/11 ($P=0.08$), MSC + EV 0/8 ($P=0.07$) vs. control 8/24; MSC infusion associated with decreased IL-6 ($P=0.015$), TNF-α ($P=0.034$), IFN-γ ($P=0.024$), CRP ($P=0.041$)	No serious AEs; safe
Ichikado (2023) [101]	RCT (Phase 2, ONE-BRIDGE)	30 (20 vs. 10)	BM-derived Multipotent Adult Progenitor Cells	Pneumonia-induced ARDS (with early fibroproliferation)	9.0×10^8 cells IV, single dose	VFDs through day 28	VFDs: 11.6 (Invimestrocel) vs. 6.2 (Standard) (LS mean difference 5.4, $P=0.1397$); Mortality day 180: 26% vs. 43% (numerically lower with Invimestrocel)	No allergic or serious adverse reactions; well tolerated
Gorman (2023) [102]	RCT (REALIST-COVID)	60 (30 vs. 29)	UC-MSC (CD362+)	COVID-19 ARDS (Moderate-to-severe)	400×10^6 cells IV, single dose	Day 7 oxygenation index, Incidence of SAEs	No difference in Day 7 oxygenation index (98.3 vs. 96.6); No differences in secondary outcomes or mortality	SAEs: 6 (ORBCEL-C) vs. 3 (Placebo) (RR 2.9, $P=0.25$), none judged related to treatment; safe

Table 2 (continued)

First Author (Year)	Study Design	Sample Size Total (Treatment vs. Control)	MSC or Derived Therapy Source	ARDS Etiology	Dose and Administration Frequency	Main Outcomes	Efficacy	Safety
Martínez-Muñoz (2024) [103]	RCT	20 (10 vs. 10)	BM-MSC	COVID-19 ARDS (Moderate-to-severe)	1×10^6 cells/kg IV, single dose	Increase in PaO_2/FiO_2 ratio (Day 7)	No significant difference in PaO_2/FiO_2 (83.3 vs. 57.6); WHO score improved at day 7 (50% vs. 0%, $P = 0.033$); Shorter hospital stay (17.5 vs. 28 days, $P = 0.042$)	No infusion or treatment-related SAEs; safe at 1-year follow-up
Sitbon (2024) [104]	RCT (STROMA-CoV-2 long-term)	47 enrolled (19 completed 1-year FU)	UC-MSC	COVID-19 ARDS (from Monsel 2022)	1×10^6 cells/kg IV, 3 doses (over 5 days)	Safety at 6 and 12 months	No significant differences in AEs, lung CT, PFTs, or QoL between groups at 6 & 12 months	No adverse effects observed at 1 year related to UC-MSC; favorable safety profile [100]

Abbreviations: RCT Randomized Controlled Trial; ARDS Acute Respiratory Distress Syndrome; MSC Mesenchymal Stromal Cells; EV Extracellular Vesicles; MAPC Multipotent Adult Progenitor Cells; SAE Serious Adverse Event; VFD Ventilator-Free Days; PBW Predicted Body Weight; IV Intravenous; MV Mechanical Ventilation; PEEP Positive End-Expiratory Pressure; SpO_2/FiO_2 Oxygen Saturation to Fraction of Inspired Oxygen Ratio; PaO_2/FiO_2 Partial Pressure of Oxygen to Fraction of Inspired Oxygen Ratio; CRP C-Reactive Protein; IL-6 Interleukin-6; TNF-α Tumor Necrosis Factor-alpha; IL-8 Interleukin-8; IFN-γ Interferon-gamma; IL-17 A Interleukin-17 A; Ang-2 Angiopoietin-2; sTNFR1 Soluble Tumor Necrosis Factor Receptor 1; sTNFR2 Soluble Tumor Necrosis Factor Receptor 2; SP-D Surfactant Protein-D; RR Relative Risk; HR Hazard Ratio; OR Odds Ratio; LS Least Squares; FU Follow-Up; QoL Quality of Life; PFTs Pulmonary Function Tests; CT Computed Tomography; WHO World Health Organization

cutaneous tissues, thus reducing pulmonary retention [117]. In models of ischemia-reperfusion injury, certain MSC subpopulations—such as multilineage-differentiating stress-enduring (Muse) cells—may exhibit superior therapeutic effects compared to those of conventional MSCs [118].

The COVID-19 pandemic significantly accelerated the clinical investigation of MSC therapy. Multiple RCTs and observational studies confirmed MSC safety, while meta-analyses suggested a potential reduction in mortality among COVID-19 ARDS. However, despite these encouraging findings, robust clinical evidence supporting MSC efficacy in non-COVID-19 ARDS remains limited [6, 94, 95, 119]. Although large-scale RCTs have not consistently achieved significant improvements in primary endpoints [96, 102], MSC safety is well-established, with some positive secondary outcome trends. Factors such as variations in control group treatments, baseline disease severity among enrolled patients, and differences in MSC preparation and administration protocols may help explain the discrepancies observed across clinical trials.

Furthermore, the underlying etiology of ARDS likely plays a crucial role in determining MSC therapeutic efficacy. Most recent clinical trials have focused on COVID-19-associated ARDS, which is characterized by a unique viral-induced endothelial injury and a specific cytokine storm profile. In this context, MSCs have shown promise in improving survival and reducing inflammatory markers in some studies [10, 99]. However, these findings may not be directly generalizable to ARDS from other causes, such as bacterial pneumonia, sepsis, or trauma, which involve different pathogenic mechanisms and immune responses. For instance, the ONE-BRIDGE trial specifically enrolled patients with pneumonia-induced ARDS and, while safe, did not reduce ventilator-free days [101]. This suggests that the therapeutic response to MSCs could be etiology-dependent. Future research must stratify results based on ARDS etiology to identify which patient populations are most likely to benefit and to tailor therapeutic strategies accordingly.

Distinct ARDS immunological phenotypes, including hyperinflammatory and hypoinflammatory subtypes, respond variably to MSC immunomodulatory effects [120]. Adjunctive approaches, such as antioxidant co-administration, have also been shown to amplify MSC therapeutic effects [121], emphasizing the need to tailor therapy to ARDS immunophenotypes.

Subgroup analyses of MSC trials in ARDS suggest that younger patients (aged < 65 years) may derive greater therapeutic benefit [96] possibly owing to their more robust immune responsiveness and intrinsic regenerative capacity [10, 96, 122], which may potentiate the immunomodulatory and reparative effects of MSCs. In addition to age, the host's inflammatory phenotype plays a critical

role in therapeutic response. For instance, a hyperinflammatory pulmonary milieu marked by elevated interleukin-6 (IL-6) levels may attenuate MSC efficacy [66], potentially by overwhelming their immunoregulatory mechanisms. Conversely, patients exhibiting specific cytokine profiles—such as lower baseline IL-6 or distinct soluble tumor necrosis factor receptor 2 (sTNFR2) concentrations—appear to have more favorable clinical outcomes [30]. These beneficial responses may be mediated, at least in part, by enhanced MSC-induced M2 macrophage polarization [20, 21] and expansion of regulatory Tregs [23]. Together, these findings highlight the relevance of age and inflammatory biomarkers (e.g., IL-6, sTNFR2) in patient stratification and support the development of biomarker-guided, personalized MSC therapies for ARDS.

Of note, these differences may be partially explained by age-dependent variations in MSC potency and the host inflammatory microenvironment (see Mechanisms section for details).

Challenges and future directions

Despite their potential, MSC therapies encounter significant barriers to clinical implementation. The short-term safety of MSC therapy is firmly established [6, 67, 69, 79, 83], with one-year follow-up data showing no notable adverse events [104]. However, potential long-term risks—such as immunogenicity, tumorigenicity, and procoagulant effects—warrant ongoing surveillance and systematic evaluation [81].

Long-term safety and risks

MSCs and their derivatives generally exhibit low immunogenicity [53, 123], with AdMSC-derived exosomes and Muse cells specifically noted for lacking tumorigenicity [53, 118]. However, concerns about the potential tumorigenicity of parental MSCs [124] and their incomplete immunological privilege [125] persist, occasionally prompting strategies such as HLA downregulation to evade immune rejection [126]. Despite reassuring short-term findings, dedicated long-term monitoring is still needed to clarify risks such as tumorigenesis and immune responses following MSC therapy in ARDS survivors [125].

Limited follow-up duration remains a recognized challenge in this field. For instance, a systematic review by Kirkham et al. (2022) analyzing RCTs in COVID-19 ARDS reported a median follow-up of only 28 days across the included studies, underscoring the evidence gap for long-term outcomes [94]. Recent long-term follow-up (1–2 years) from clinical trials such as STROMA-CoV-2 and REALIST-COVID in ARDS patients has demonstrated favorable safety profiles for UC-MSCs, with no significant increase in adverse events or mortality compared to placebo [102, 104]. Nevertheless, a critical need remains for extended (e.g., ≥5 years) surveillance protocols within future trials to rigorously assess latent risks like tumorigenesis or chronic immunogenicity. Ongoing post-treatment surveillance will be essential to ensure long-term safety.

Inconsistency among trials and solutions

Inconsistent clinical trial outcomes, particularly concerning mortality, likely stem from variations in study design, patient diversity, and MSC properties. The dose-response relationship remains to be conclusively established and requires validation in larger-scale studies [79]. Key obstacles to clinical translation include non-standardized MSC characterization, culture, post-cryopreservation viability, batch consistency, and potency assays [13, 14, 127, 128]. To enhance efficacy, several strategies have been explored, including enriching functional subsets (e.g., CD362 + MSCs) [102, 129] and improvement of MSC homing and survival within inflamed microenvironments. Epigenetic HLA downregulation has been shown to reduce MSC immunogenicity [126], while gene modification [91, 92] and delivery optimization may help overcome these limitations.

Future directions

Future studies must prioritize refining multiple facets of MSC therapy, including cell source selection, dosing regimens, and administration timing. Advanced cellular engineering strategies also hold considerable promise. For instance, preconditioning approaches such as hypoxia exposure [70], or cytokine stimulation [130] can prime MSCs for enhanced function. Moreover, gene-editing technologies (e.g., CRISPR/Cas9) enable MSC modification to overexpress therapeutic mediators (Nrf2 [131], IL-10 [44], IL-35 [132]) or enhance homing properties via ACE2 [36], ROR2 [90], or AT2R [91], representing a frontier in MSC functional optimization.

In parallel, addressing manufacturing consistency is crucial. The development of controlled manufacturing platforms, such as microcarrier-based microbioreactors, can improve cell yield and standardize critical quality attributes (CQAs) far better than traditional flask cultures [128]. These advanced platforms, along with automated manufacturing systems, generate large, high-quality datasets suitable for artificial intelligence (AI) and machine learning models [133]. AI-based quality control holds transformative potential: for instance, deep learning models can non-invasively predict MSC functional potency and heterogeneity through live-cell microscopy or label-free spectral data [134–136]. This high-throughput, real-time method offers an alternative to conventional destructive assays, enhancing batch selection and therapeutic consistency.

Additionally, combination approaches—such as co-administration with antioxidants or glucocorticoids—warrant further investigation [137–139]. Parallel efforts should be directed toward the development and standardization of MSC-derived extracellular vesicles (EVs) and conditioned medium (CM), which represent promising cell-free alternatives. Priority should be given to conducting large-scale, multicenter RCTs (e.g., NCT03818854) and implementing adaptive clinical trial designs to rigorously assess the efficacy and safety of MSC-based therapies [94, 140].

Furthermore, exploring novel engineering strategies for MSCs, such as tailoring the MSC secretome or enhancing homing capacity, may help overcome translational barriers. Lastly, a critical innovative aspect for future research lies in dissecting the complex interplay between MSCs (or their derivatives) and the recipient's immunophenotype and ARDS etiology. This understanding is paramount for biomarker-guided patient stratification and the realization of precision medicine approaches, enabling more targeted and effective MSC applications in ARDS [121].

Conclusion

MSCs and their derivatives—including EVs and CM—exert multifaceted therapeutic effects in ARDS through mechanisms such as immunomodulation, anti-inflammation, antioxidation, and tissue repair. Accumulating preclinical studies and early-phase clinical trials, particularly those involving COVID-19-associated ARDS, have demonstrated their favorable safety profiles and suggested potential efficacy in specific patient subgroups. Nevertheless, the broad clinical translation of MSC-based therapies faces significant hurdles, including the need for standardized manufacturing, optimization of dosing and administration protocols, and precise patient stratification. To advance the field, high-quality RCTs and precision medicine–oriented strategies will be essential to fully realize the therapeutic potential of MSCs and facilitate their integration into routine clinical practice. Future research should not only focus on refining existing approaches but also on pioneering innovative strategies, such as advanced cell engineering and biomarker-driven personalized therapies, to truly harness the promise of MSCs for ARDS patients.

Supplementary Information

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The original file of Figure 1

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FW conceived the idea and wrote the manuscript. CX and XW made supportive contributions to this work. FW was involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Declarations

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The authors declare that they have no competing interests.

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