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Pathophysiological mechanisms of ARDS: a narrative review from molecular to organ-level perspectives

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Abstract

Background Acute respiratory distress syndrome (ARDS) remains a life-threatening pulmonary condition with persistently high mortality rates despite significant advancements in supportive care. Its complex pathophysiology involves an intricate interplay of molecular and cellular processes, including cytokine storms, oxidative stress, programmed cell death, and disruption of the alveolar-capillary barrier. These mechanisms drive localized lung injury and contribute to systemic inflammatory response syndrome and multiple organ dysfunction syndrome. Unlike prior reviews that primarily focus on isolated mechanisms, this narrative review synthesizes the key pathophysiological processes of ARDS across molecular, cellular, tissue, and organ levels.

Main body By integrating classical theories with recent research advancements, we provide a comprehensive analysis of how inflammatory mediators, metabolic reprogramming, oxidative stress, and immune dysregulation synergistically drive ARDS onset and progression. Furthermore, we critically evaluate current evidence-based therapeutic strategies, such as lung-protective ventilation and prone positioning, while exploring innovative therapies, including stem cell therapy, gene therapy, and immunotherapy. We emphasize the significance of ARDS subtypes and their inherent heterogeneity in guiding the development of personalized treatment strategies.

Conclusions This narrative review provides fresh perspectives for future research, ultimately enhancing patient outcomes and optimizing management approaches in ARDS.

Keywords ARDS, Pathophysiological mechanisms, Cytokine storm, Treatment

Background

Acute respiratory distress syndrome (ARDS) is a critical, life-threatening acute lung injury characterized by non-cardiogenic pulmonary edema and profound hypoxemia, frequently linked to severe infections, trauma, and systemic inflammatory responses [1, 2]. Since its initial description in 1967 [3], the definition and diagnostic criteria of ARDS have undergone multiple refinements [4, 5]. Despite these advances, ARDS remains a notable global health challenge, attributable to its persistently high incidence and mortality rates [6].

Supportive interventions, such as lung-protective ventilation strategies and extracorporeal membrane oxygenation (ECMO), have led to modest improvements in patient outcomes; however, effective targeted therapies remain elusive, with mortality rates persistently ranging from 30 to 40% [6, 7]. The pathogenesis of ARDS is highly complex, with dysregulated inflammation and epithelial

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barrier dysfunction at the core of its pathology [1, 7]. Therefore, a thorough and systematic examination of the pathophysiological mechanisms underlying ARDS is crucial for enhancing clinical outcomes. Given the multifaceted nature of ARDS, a comprehensive analysis spanning multiple biological levels is essential for therapeutic advancements.

Unlike previous reviews that primarily address isolated mechanisms, such as inflammation or oxidative stress, this narrative review adopts a multidimensional approach to analyze the key pathophysiological processes of ARDS from molecular to organ levels. By conducting a nonsystematic literature review, we integrate established theories with cutting-edge research to present a broader perspective on the dynamic heterogeneity and complexity of ARDS.

This review examines inflammatory markers, metabolic reprogramming, oxidative stress, and immune dysregulation, highlighting how these molecular and cellular processes converge to drive organ-level effects. It further elucidates how these interconnected pathways contribute to the onset, progression, and organ dysfunction associated with ARDS through intricate signaling networks. By advancing beyond traditional single-layer research frameworks, this review emphasizes the interplay between molecular mechanisms and organ-level pathophysiological changes, offering a theoretical basis for the future development of personalized therapeutic strategies.

Molecular Battle: cytokines, oxidative stress, and cell death

Cytokine storm: a surge of cytokines and chemokines

A cytokine storm denotes a hyperactive immune response triggered by infection or injury, resulting in the rapid and excessive release of cytokines and chemokines [8]. This phenomenon is particularly pronounced in ARDS, where it plays a central role in driving lung injury and dysfunction [9, 10]. The cytokine storm is characterized by the release of numerous pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), and IL-6 [8]. These cytokines activate signaling pathways such as nuclear factor-κB (NF-κB) [11] and signal transducer and activator of transcription 3 (STAT3) [12], increasing vascular permeability, disrupting the alveolar-capillary barrier, and resulting in pulmonary edema and severe hypoxemia [9].

Chemokines are small signaling proteins that act through G-protein-coupled receptors on cell surfaces, attracting neutrophils and monocytes to the inflammation site and amplifying the inflammatory response [13]. As these immune cells accumulate in the lungs, they release additional inflammatory mediators and reactive oxygen species (ROS) [14], further exacerbating lung tissue damage and vascular permeability. This cascading effect induces localized lung injury and has the potential to trigger systemic inflammatory response syndrome (SIRS), which may progress to multiple organ dysfunction syndrome (MODS), significantly elevating the mortality rate in patients with ARDS.

Oxidative stress: ROS and reactive Nitrogen species (RNS), the Invisible killers

Oxidative stress describes the damage inflicted on tissues and cells resulting from an imbalance between oxidant production and the body's antioxidant defenses [15]. ROS encompass superoxide anion ($O2^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) [16], whereas reactive nitrogen species (RNS) primarily consist of nitric oxide (NO) and peroxynitrite (ONOO-) [17]. In ARDS, the excessive release of ROS and RNS induces oxidative damage to cell membranes and proteins, compromising cellular function and integrity, which results in endothelial and epithelial barrier dysfunction, heightened vascular permeability, and, ultimately, pulmonary edema [18].

Furthermore, ROS activate signaling pathways like NF-κB and mitogen-activated protein kinase (MAPK), exacerbating inflammation and tissue damage [19]. Preclinical studies using murine models indicate that inhibiting ROS cascades reduces pro-inflammatory cytokine production, mitigates lung injury, and improves survival outcomes [20, 21]. However, multiple clinical studies have demonstrated that antioxidants, including N-acetylcysteine and vitamin C, do not cause significant improvements in the prognosis of patients with ARDS [22, 23]. For instance, although vitamin C has been extensively studied for its antioxidant properties, randomized controlled trials (RCTs) have not demonstrated significant clinical efficacy [22].

This lack of efficacy may be attributed to the complexity of oxidative stress mechanisms, which involve not only excessive ROS generation but also the intricate interplay of downstream signaling pathways with inflammation, apoptosis, and other pathological processes [15]. Current evidence suggests that single-agent antioxidant therapies are insufficient to address the multifaceted pathological processes of ARDS. Future research should prioritize multi-targeted or combination strategies to leverage advances in drug delivery technologies and improve clinical outcomes.

Stage of cell death: the conspiracy of apoptosis, necrosis, and Pyroptosis

Cell death is pivotal in the progression of ARDS, primarily mediated through apoptosis, necrosis, and pyroptosis [1]. Apoptosis, a tightly regulated form of programmed cell death, is essential for eliminating damaged or infected cells, thereby preventing the spread of

inflammation; however, excessive apoptosis can impair the lung's reparative capacity [24]. In contrast, necrosis is a non-programmed form of cell death, characterized by the release of cellular contents that further stimulate immune responses, thereby exacerbating inflammation and tissue damage [24, 25].

Pyroptosis, an inflammatory form of programmed cell death, directly damages lung tissue and amplifies the inflammatory response by releasing large amounts of pro-inflammatory mediators [25]. Animal research indicates that the stimulator of interferon genes (STING) agonist diamidobenzimidazole (diABZI) can significantly exacerbate the pathological progression of ARDS by inducing PANoptosis, a synergistic cell death mechanism integrating apoptosis, necrosis, and pyroptosis [26]. The interplay among these cell death mechanisms intensifies lung injury, profoundly influencing the course and prognosis of ARDS.

Cellular War: endothelial and epithelial cells under siege

Endothelial cell disruption: Breakdown of the permeability barrier

Endothelial cells (ECs) form the fundamental architecture of the vascular lining, playing a vital role in maintaining blood vessel integrity and permeability [27]. The extensive network of ECs in the lungs forms an essential interface that supports the complex process of gas exchange and ensures the efficient delivery of oxygen throughout the body [28]. In ARDS, EC injury and dysfunction are crucial in compromising the alveolar-capillary barrier, resulting in severe pathological consequences [1, 7].

ECs may undergo an endothelial-to-mesenchymal transition, a process during which they lose their endothelial identity and acquire mesenchymal traits, leading to increased vascular reactivity, decreased permeability, and promoted fibrosis [27]. Furthermore, oxidative stress, combined with immune cell attacks, can induce apoptosis and necrosis in ECs, further increasing vascular permeability. This cascade results in the leakage of plasma proteins and fluids, ultimately manifesting as pulmonary edema, a condition that exacerbates lung inflammation and tissue damage by facilitating the migration of inflammatory cells and the release of inflammatory mediators [7, 29, 30]. Clinical observational study has identified elevated circulating EC counts in patients with moderate-to-severe ARDS, correlating strongly with disease severity and poor clinical prognosis [29]. Restoring mitochondrial function and reinforcing barrier integrity in ECs are emerging as promising therapeutic strategies to combat ARDS [31].

Struggle of epithelial cells: the fall of the alveolar barrier

Epithelial cells are indispensable components of the alveolar walls, forming a delicate air-blood barrier essential for maintaining alveolar integrity, regulating gas exchange, and defending against external pathogens [32, 33]. Type I alveolar epithelial cells (AEC-I) cover approximately 95% of the alveolar surface, serving a primary role in gas exchange. These cells are connected to adjacent cells via tight and adherens junctions, forming a continuous and effective barrier [33]. Type II alveolar epithelial cells (AEC-II) secrete surfactant to reduce alveolar surface tension and possess stem cell properties, enabling them to differentiate into AEC-I, thus contributing to alveolar repair and lung regeneration [33–35].

Oxidative stress and cytokine storms induce apoptosis and necrosis in epithelial cells, compromising barrier function and resulting in fluid accumulation within the alveoli and the subsequent development of pulmonary edema [1, 36]. Experimental evidence suggests that mitigating epithelial cell apoptosis may improve the clinical course of ARDS [37]. Additionally, mesenchymal stem cells (MSCs), owing to their ability to promote epithelial cell regeneration, show potential as a therapeutic intervention for ARDS [38].

Tissue-Level Transformation: barrier disruption and tissue remodeling

Collapse of the alveolar-capillary barrier: from Protection to Destruction

The alveolar-capillary barrier, comprising the alveolar and capillary endothelium, primarily functions to facilitate gas exchange and maintain a critical separation between blood and alveolar fluid [32, 33]. Under normal conditions, this barrier remains intact due to tight junctions and surfactant secretion, which serve protective functions. In ARDS, however, various pathological factors compromise the integrity of the alveolar-capillary barrier, shifting its role from maintaining homeostasis and protection to exacerbating tissue damage and driving disease progression. Mechanical injuries, such as those induced by mechanical ventilation and elevated airway pressures, directly damage epithelial cells and ECs [1]. Inflammatory mediators, including TNF-α and IL-1β, trigger inflammatory responses that culminate in cellular apoptosis and necrosis [8, 10, 14]. Oxidative stress, mediated by ROS, inflicts oxidative damage on cell membranes and intracellular structures, further compromising barrier function [14, 16, 19]. Simultaneously, immune cells such as neutrophils and macrophages release enzymes and ROS, exacerbating tissue damage [1, 39].

These factors collectively contribute to the breakdown of the alveolar-capillary barrier, resulting in increased permeability and the subsequent formation of pulmonary edema. The loss of alveolar-capillary barrier function

exacerbates pulmonary edema and hypoxemia and profoundly influences ARDS course and prognosis. Future research should focus on elucidating the molecular mechanisms underlying alveolar-capillary barrier injury and repair, as well as on developing novel therapeutic strategies to improve treatment outcomes for patients with ARDS [31, 37].

Tissue remodeling and fibrosis: the Balance between Repair and Fibrosis

During the pathological progression of ARDS, lung tissue repair following injury is frequently accompanied by fibrosis. The balance between tissue remodeling and fibrosis is pivotal in determining the extent of lung function recovery. Effective tissue remodeling can restore normal lung structure and function, whereas excessive fibrosis results in tissue stiffening and impaired function, adversely affecting long-term prognosis [40, 41]. Normal tissue repair relies on the proliferation and differentiation of AEC-II cells, a process that restores the integrity of the alveolar structure and re-establishes normal gas exchange function [35, 42, 43]. However, persistent lung injury and inflammation or an unbalanced repair process causes excessive activation of fibroblasts. This results in the overproduction and deposition of extracellular matrix (ECM), replacing normal lung tissue with connective tissue and forming scar tissue that stiffens the lungs and impairs functionality [44]. Nevertheless, experimental studies in animal models suggest that, despite the potential risk of fibrosis, ECM-based therapies, such as intravascularly infused ECM, may mitigate tissue leakage and promote vascular repair [45]. Therefore, in the treatment of ARDS, maintaining the balance between tissue remodeling and fibrosis is crucial to prevent excessive fibrosis and optimize patient recovery outcomes.

Organ-level impact: the spread of systemic Crisis

SIRS: the systemic reverberation of a local insult

SIRS represents the body's systemic reaction to infection, trauma, or other injuries, manifesting as a widespread inflammatory cascade impacting multiple organ systems [46]. In ARDS, the localized pulmonary inflammatory response can disseminate systemically, precipitating SIRS, which subsequently exacerbates lung injury via an amplified systemic inflammatory response [1]. Locally produced inflammatory mediators, including TNF-α, IL-1β, and IL-6, recruit neutrophils and macrophages to the site of injury for tissue repair and breach the compromised alveolar-capillary barrier, entering the circulation and propagating systemic inflammation [8, 9, 47]. Once these mediators enter the circulatory system, they trigger a constellation of clinical manifestations, including fever, leukocytosis, tachycardia, and tachypnea, which may progress to multi-organ dysfunction characterized by heart failure, acute kidney injury, hepatic insufficiency, and in severe cases, significantly elevated mortality risk [46, 48, 49].

Given the critical role of cytokines in SIRS and ARDS pathogenesis, targeting pro-inflammatory cytokines has emerged as a key therapeutic strategy to mitigate these pathological processes. For instance, the IL-6 inhibitor tocilizumab (TCZ) has demonstrated potential in reducing systemic inflammatory responses and improving clinical outcomes in patients with severe COVID-19, as demonstrated in several RCTs [50, 51]. However, evidence indicates that cytokine-targeted therapies have not significantly improved mortality rates in ARDS. The RECOVERY trial demonstrated that TCZ monotherapy has limited efficacy and may even increase mortality risk in patients not receiving corticosteroid treatment [51]. Similarly, another RCT found TCZ ineffective in improving outcomes in patients with moderate-to-severe ARDS [52].

IL-1β inhibitors have exhibited anti-inflammatory effects in animal models [53], but RCTs and meta-analyses have reported inconsistent clinical efficacy in COVID-19-related ARDS, with significant variability in individual responses [54, 55]. In the same vein, early studies suggested that TNF-α antagonists have the potential to modulate immune responses [56], with animal models demonstrating reduced pulmonary cytokine release and improved respiratory function [57]. However, clinical studies have not confirmed significant improvements in outcomes for patients with ARDS [58, 59]. These findings indicate that, although cytokine-targeted therapies offer theoretical advantages, their clinical efficacy is constrained by patient heterogeneity and the complexity of the disease. Particularly during acute cytokine storms, single-target therapies are insufficient to effectively control the intricate and multifaceted inflammatory cascade. Future research should aim to elucidate the molecular mechanisms underlying SIRS to disrupt its deleterious cascade and improve systemic outcomes in patients with ARDS.

MODS: a multi-systemic crisis

MODS denotes the progressive and systemic failure of multiple organ systems induced by acute pathological insults, constituting a severe and life-threatening complication of ARDS [7, 60]. Persistent cytokine storms and inflammatory mediators drive systemic inflammatory responses, exacerbated by oxidative stress and ongoing cellular injury, which collectively result in endothelial dysfunction, increased vascular permeability, and subsequent microcirculatory collapse [14, 61].

This pathological cascade ultimately impairs the functions of the lungs, cardiovascular system, liver, kidneys, and central nervous system, clinically manifesting as

pulmonary edema, hypoxemia, myocardial depression, acute liver failure, acute kidney injury, and disseminated intravascular coagulation, culminating in a severe and systemic crisis [8, 14, 62, 63]. The onset of MODS signifies the extension of local inflammation and damage on a systemic level, significantly increasing mortality and complicating prognosis [1, 2, 7]. Future research should prioritize identifying the molecular regulatory mechanisms underlying MODS, with the aim of developing novel therapeutic interventions to improve long-term outcomes in affected patients.

Multilayered Regulatory mechanisms: synergistic control of genes, proteins, and metabolism

Genetic orchestration: the dominance of key genes and transcription factors

Genetic and transcriptomic studies have identified significant alterations in the transcription levels of numerous genes associated with ARDS, affecting pathways associated with inflammation, cell survival, apoptosis, and chemotaxis [64, 65]. Specifically, the IL1B gene encoding IL-1β and the TNF gene encoding TNF-α are potent pro-inflammatory cytokines that activate NF-κB and MAPK signaling pathways. This activation promotes the release of inflammatory mediators and amplifies the inflammatory response [66, 67]. The CXCL8 gene encodes the chemokine IL-8, which recruits neutrophils to inflammation sites, exacerbating pulmonary injury [68]. The NFKBIA gene encodes the IκBα protein, which modulates NF-κB activity and, consequently, regulates the inflammatory response [66].

Moreover, the Toll-like receptor (TLR), MAPK, and JAK-STAT signaling pathways are also crucial in ARDS progression. The TLR pathway triggers downstream inflammatory responses through pathogen recognition [69], the MAPK pathway regulates cellular stress responses and apoptosis [70], and the JAK-STAT pathway is instrumental in cell proliferation and immune modulation [71]. The interplay among these genes and signaling pathways collectively drives ARDS pathogenesis. A comprehensive understanding of these mechanisms is critical for developing effective therapeutic strategies. Research focusing on these key genes and signaling pathways elucidates the pathophysiological mechanisms underlying ARDS and provides new targets and insights for clinical intervention [71, 72].

Protein regulation: the balance between enzymes and inhibitory proteins

The balance between enzymes and their inhibitory proteins is crucial in ARDS pathogenesis. Enzymes like matrix metalloproteinases (MMPs), MAPKs, and Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase are instrumental in regulating inflammation, cellular stress, and oxidative stress in ARDS; conversely, inhibitory proteins such as tissue inhibitors of metalloproteinases (TIMPs), protein tyrosine phosphatases (PTPs), and superoxide dismutases are vital for maintaining the balance of these processes [73, 74].

Observational studies have indicated that elevated TIMP-1 levels are associated with poor prognosis in ARDS [75]. The upregulation of MMPs compromises the vascular endothelial barrier by cleaving vascular endothelial cadherin (VE-cadherin), an intercellular adhesion molecule, facilitating inflammatory cell infiltration and degradation of lung tissue architecture [76]. An observational study in pediatric patients suggests that MMPs and their endogenous inhibitors are independently associated with the prognosis of pediatric ARDS [77]. Additionally, MAPK inhibitors have been demonstrated to attenuate the inflammatory response in sepsis-induced ARDS [73]. In-depth research into the interactions and regulatory mechanisms of these enzymes and inhibitory proteins could pave the way for novel therapeutic strategies, including modulating the balance between MMPs and TIMPs or evaluating the activity shifts in MAPKs and PTPs.

Metabolic reprogramming: dynamic regulation of cellular metabolism

Metabolic reprogramming describes the dynamic process through which cells alter their metabolic pathways to adapt to new environmental demands or functional requirements under specific physiological or pathological conditions [78]. Metabolic reprogramming in ARDS leads to profound metabolic shifts in alveolar epithelial cells, ECs, and immune cells, primarily through its impact on mitochondrial function. These shifts serve as adaptive responses to environmental challenges such as inflammation, hypoxia, and oxidative stress [79]. For instance, during the early stages of ARDS, M1 macrophages exacerbate inflammation and tissue damage by releasing pro-inflammatory cytokines, including IL-1β and TNF-α, whereas M2 macrophages dominate the later stages, reducing inflammation and promoting tissue repair [80]. However, ECs often increase fatty acid oxidation to sustain barrier function, though this adaptation can also lead to heightened oxidative stress [81].

These metabolic adjustments are essential for cellular survival under adverse conditions and play pivotal roles in regulating inflammatory responses and immune functions [82]. However, the detrimental consequences of metabolic reprogramming should not be overlooked. For instance, excessive M1 macrophage polarization and ferroptosis induction can worsen tissue damage and inflammation, further exacerbating ARDS [83, 84]. Therefore, a deeper understanding of the mechanisms underlying

metabolic reprogramming in ARDS is crucial for developing novel therapeutic strategies to modulate these metabolic pathways, thereby mitigating disease progression and improving patient outcomes.

Clinical interventions and future perspectives: current strategies and future prospects

Current therapeutic strategies: from mechanical ventilation to ECMO

With a deeper understanding of ARDS pathophysiology, treatment strategies have evolved from basic supportive care to multifaceted, comprehensive interventions [2, 7]. Evidence-based therapies, including low tidal volume ventilation (LTVV), prone positioning, and individualized positive end-expiratory pressure (PEEP) adjustments, now form the cornerstone of ARDS management [85, 86]. These interventions, validated through large-scale RCTs, are the only strategies proven to significantly improve survival in patients with ARDS, establishing the foundation of contemporary clinical practice [87, 88].

LTVV, as standardized in the pivotal ARDSNet trial, limits tidal volume to 6 mL/kg of predicted body weight, effectively reducing ventilator-induced lung injury (VILI) from alveolar overdistension. This strategy significantly improves clinical outcomes and reduces mortality in patients with ARDS [89, 90]. Building on this framework, ultra-protective ventilation (UPV), which further lowers the tidal volume to 4 mL/kg of predicted body weight, has been proposed [91]. Although UPV demonstrates potential in minimizing VILI and facilitating lung recovery in select patients [92], its application poses challenges, including risks of hypercapnia and diaphragmatic dysfunction, necessitating cautious, individualized adjustments [93].

Prone positioning plays an indispensable role in managing moderate-to-severe ARDS by improving ventilation-perfusion matching and reducing intrapulmonary shunting. This intervention enhances the oxygenation index (PaO2/FiO2) and lowers mortality rates [94]. The landmark ROSEVA trial demonstrated significant reductions in 28-day and 90-day mortality (16.0% vs. 32.8% and 23.6% vs. 41.0%, $P < 0.001$) in patients with moderate-to-severe ARDS, alongside improvements in oxygenation and lung function [95]. However, RCTs involving hypoxemic COVID-19 patients (COVID-PRONE and COVI-PRONE trials) showed that awake-prone positioning did not significantly lower intubation rates or mortality [96, 97].

Appropriately adjusting PEEP levels is critical for maintaining functional residual capacity, preventing atelectasis and overdistension, and supporting lung-protective ventilation strategies [7]. Although precise PEEP titration theoretically optimizes lung mechanics and gas exchange, the EPVent-2 trial reported that esophageal pressure-guided PEEP adjustments did not significantly improve clinical outcomes [98]. Similarly, the ART trial revealed that combining lung recruitment maneuvers with high PEEP strategies failed to reduce mortality and instead increased cardiovascular complications [99].

Despite advancements, VILI remains a central challenge in ARDS management, necessitating ongoing optimization of respiratory support [100]. Recent interest has focused on driving pressure and diaphragmatic protection strategies, which hold promise in reducing lung stress and improving outcomes, though further validation through robust clinical trials is needed [101].

For critically ill patients unresponsive to conventional mechanical ventilation, ECMO represents a significant therapeutic advancement [102]. By temporarily replacing lung function, ECMO facilitates lung recovery and improves oxygenation. However, its use is limited by high risks, costs, and the need for strict patient selection criteria and multidisciplinary expertise [103].

Additionally, restrictive fluid management strategies reduce pulmonary edema and, when combined with lung-protective ventilation, enhance patient outcomes [1, 2, 104]. Future research should prioritize high-quality RCTs to explore precision and individualized therapeutic approaches, including multi-target combination therapies and biomarker-driven patient stratification, to address the multifactorial challenges of ARDS.

Innovative approaches: stem cells, gene therapy, and immunotherapy

Beyond traditional ARDS treatment approaches, stem cell therapy, gene therapy, and immunotherapy are emerging as highly promising therapeutic frontiers. These innovative therapies aim to fundamentally improve outcomes for patients with ARDS by facilitating tissue repair, modulating immune responses, and correcting genetic defects.

Stem cell therapy

MSCs are widely regarded as a potential breakthrough in ARDS treatment due to their remarkable immunomodulatory and tissue regenerative capabilities [105–107]. These capabilities underpin their ability to improve ARDS prognosis through multiple mechanisms, including the secretion of anti-inflammatory factors, suppression of alveolar inflammation, reduction of fibrosis, and promotion of alveolar epithelial and vascular endothelial repair [107].

Preliminary clinical trials and observational studies have demonstrated the potential of MSC therapy to enhance survival rates and reduce complications in patients with ARDS [108, 109]. However, a recent RCT indicated that MSC therapy did not significantly improve prognosis in patients with moderate to severe COVID-19-related ARDS [110]. This finding suggests that, despite promising early results, further large-scale, multicenter clinical trials are necessary to comprehensively evaluate the safety and efficacy of MSC therapy and clarify its role in ARDS treatment.

Gene therapy

Gene therapy offers a novel perspective on treating ARDS [111]. Gene editing technologies, such as CRISPR/Cas9, enable direct targeting and repair of gene mutations or regulatory abnormalities associated with ARDS [112]. For instance, genes regulating inflammatory cytokines and oxidative stress responses play critical roles in ARDS progression. Gene therapy can mitigate lung injury by precisely modulating the expression of these genes [111]. Additionally, gene transfer techniques that enhance the expression of anti-inflammatory or antioxidant genes present a new avenue for ARDS treatment [113].

Immunotherapy

Dysregulation of the immune response often leads to exacerbated inflammation and subsequent tissue injury in ARDS [1]. Cytokine storms are a common pathological feature of ARDS [8], and immune checkpoint inhibitors and cytokine antagonists can effectively suppress these excessive inflammatory responses, thereby mitigating lung injury [114, 115].

Funda Terzi et al. found that the cytokine IL-6 inhibitor TCZ downregulates the expression of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8, effectively preventing cytokine storms and exerting antioxidant effects [116]. Further RCTs have demonstrated that TCZ improves clinical outcomes in patients with severe COVID-19 [50]. However, the RECOVERY trial indicated that the use of TCZ alone might be associated with an increased risk of mortality in patients who have not received corticosteroid treatment [51]. Moreover, although anti-cytokine therapies such as IL-1β inhibitors and anti-TNF agents have shown promising effects in animal models, including reducing pulmonary inflammation and alleviating lung injury [53, 56], clinical trials and RCTs have largely yielded disappointing results [55, 58]. Notably, employing invariant natural killer T (iNKT) cell therapy to activate the innate and adaptive immune systems and regulate the inflammatory response offers an additional therapeutic strategy for improving clinical outcomes in patients with ARDS [117].

Challenges in clinical translation of emerging therapies

Despite the promising potential of stem cell therapy, gene therapy, and immunotherapy for treating ARDS, their clinical translation faces several critical challenges that demand further investigation and resolution.

Safety concerns Ensuring the safety of emerging therapies is paramount for their clinical application. Stem cell therapy carries risks such as immune rejection and tumor formation, including teratoma development, due to the self-renewal and pluripotent capabilities of stem cells [118]. Gene therapy involves the introduction of exogenous genes or gene editing, which may result in off-target effects, leading to unintended mutations in non-target genes or the activation of oncogenes [119, 120]. Immunotherapy, conversely, poses risks of cytokine release syndrome or autoimmune responses, potentially resulting in severe adverse events [121].

Ethical and Regulatory considerations Advanced gene-editing technologies (e.g., CRISPR/Cas9) and the use of certain stem cell sources (e.g., embryonic stem cells) present complex ethical and legal challenges [122]. For example, the announcement in 2018 by a Chinese scientist regarding the birth of gene-edited twins ignited global ethical debates and regulatory discussions [123]. The lack of international consensus on these issues underscores the urgent need for comprehensive ethical guidelines and robust regulatory frameworks to guide research and clinical applications.

Cost and accessibility The substantial costs associated with developing, producing, and implementing these emerging therapies remain significant barriers to accessibility. For example, stem cell culture, gene delivery vector production, and advanced delivery systems demand specialized expertise and substantial investments [124]. Consequently, these treatments often become prohibitively expensive, limiting patient access and imposing additional strain on healthcare systems [125]. Addressing these cost-related barriers is essential to ensure equitable access and sustainable integration into clinical practice.

Technical feasibility and standardization Challenges in large-scale production, quality control, and standardization impede the widespread adoption of these therapies [125, 126]. Stem cell products require stringent measures to ensure purity, potency, and stability; gene

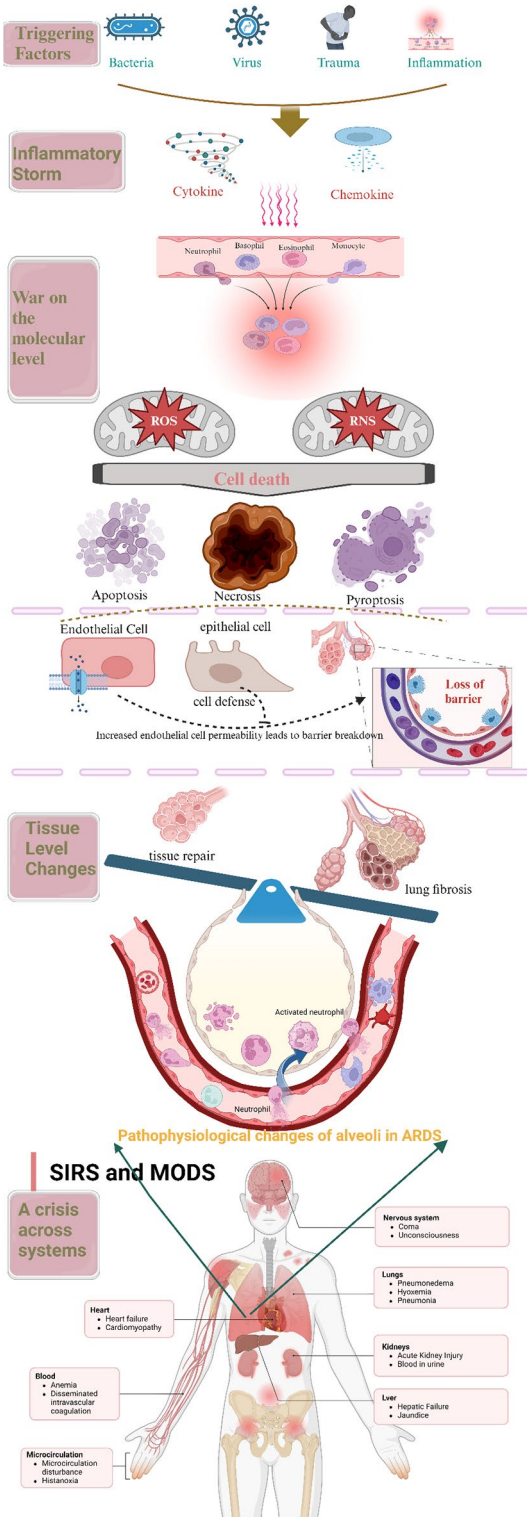

Fig. 1 Pathophysiological Mechanisms of ARDS: From Molecular to Organ-Level Insights. **Molecular Level**: Initiating factors such as infection and trauma lead to the accumulation of inflammatory cells, triggering an intense cytokine storm and oxidative stress, which in turn produce a large quantity of pro-inflammatory cytokines, as well as ROS and RNS. **Cellular Level**: These oxidative stress products induce necrosis and apoptosis, damaging endothelial and alveolar epithelial cells, which subsequently disrupt the alveolar-capillary barrier, leading to pulmonary edema and impaired gas exchange. **Tissue Level**: The breakdown of the alveolar-capillary barrier, coupled with an imbalance between tissue remodeling and fibrosis, exacerbates lung injury. **Organ Level**: Ultimately, the spread of localized inflammation can lead to SIRS and MODS. *ROS: Reactive oxygen species, RNS: Reactive nitrogen species, SIRS: Systemic inflammatory response syndrome, MODS: Multiple organ dysfunction syndrome

therapies need optimized vector delivery and expression control; and immunotherapies demand precise modulation of response intensity [127]. The absence of standardized protocols across these domains compromises the consistency of therapeutic efficacy and safety. Establishing uniform guidelines and scalable production processes is crucial for advancing these therapies toward routine clinical use.

Conclusions

ARDS is a complex and highly heterogeneous disorder, characterized by multi-level pathophysiological mechanisms spanning from molecular dysregulation to organ dysfunction (Fig. 1). Although significant progress has been made in ARDS management through numerous RCTs in recent years (Table 1), with strategies such as LTVV and prone positioning proven to significantly improve patient outcomes, other approaches (e.g., high PEEP and recruitment maneuvers) have failed to improve prognosis. Additionally, the efficacy of pharmacological interventions remains inconsistent, highlighting the marked heterogeneity in patient responses. Emerging therapies, including stem cell therapy, gene therapy, and immunotherapy, offer new directions for ARDS treatment. However, their clinical translation requires validation through large-scale clinical trials. Future research should leverage multi-omics technologies and artificial intelligence to elucidate the molecular mechanisms and clinical heterogeneity of ARDS, thereby providing a scientific foundation for the development of precise and individualized therapeutic strategies.

Table 1 Summary and Analysis of Key RCTs in ARDS

RCT	Patients	Intervention Group vs. Control Group	Primary Outcomes/Measures	Results	Conclusion	Limitations	Underlying Mechanisms
ARDS Network(2000)[89]	861	Low tidal volume (6 mL/kg) vs. high tidal volume (12 mL/kg)	Mortality, ventilator-free days at 28 days	Significantly reduced mortality (31.0% vs. 39.8%, $P=0.007$); more ventilator-free days (12 ± 11 vs. 10 ± 11 days, $P=0.007$)	Low tidal volume ventilation significantly reduces mortality, proving to be an effective lung-protective strategy	Focused only on mechanically ventilated patients; subgroup data not analyzed	Low tidal volume reduces alveolar overdistension and stretch injury, lowering inflammatory response
ALVEOLI TRIAL (2004) [128]	549	High PEEP (12–24 cm H_2O) vs. low PEEP (5–12 cm H_2O)	Mortality before hospital discharge	No significant difference in mortality (24.9% vs. 27.5%, $P=0.48$)	High PEEP does not improve mortality or organ dysfunction-free days	Did not include lung recruitment strategies, possibly underestimating PEEP's effects	High PEEP reduces repetitive alveolar collapse but may increase overdistension risk
PROSEVA TRIAL (2013) [95]	446	Prone positioning vs. supine positioning	Mortality at 28 and 90 days	Significantly lower 28-day mortality (16.0% vs. 32.8%, $P<0.001$); significantly lower 90-day mortality (23.6% vs. 41.0%, $P<0.001$)	Prone positioning significantly reduces mortality, improving outcomes in severe ARDS	Focused only on severe ARDS; not applicable to mild or moderate ARDS	Prone positioning improves ventilation-perfusion matching, reducing regional overdistension and inflammation
ART (ARDS Network) Study (2017) [99]	1010	Lung recruitment + high PEEP vs. conventional low PEEP	Mortality at 28 days and 6 months, incidence of pneumothorax	28-day mortality 55.3% vs. 49.3% ($P=0.07$); higher incidence of pneumothorax ($P=0.03$)	High PEEP does not significantly improve mortality but increases pneumothorax risk	High pneumothorax incidence impacts safety	Recruitment improves oxygenation but may increase stretch injury
EOLIA-ECMO Study (2018) [102]	249	Early ECMO vs. conventional ventilation with potential ECMOECMO	60-day all-cause mortality, treatment failure rates	No significant reduction in mortality (35% vs. 46%, $P=0.09$; RR 0.76; 95% CI 0.55–1.04); lower treatment failure rates (35% vs. 57%, $P<0.001$)	ECMO shows potential advantages for patients with severe ARDS	Control group crossover to ECMO diluted effects	ECMO reduces ventilator dependence, protecting lung function
CITRIS-ALI (2019) [22]	167	Vitamin C vs. placebo	Modified SOFA score, CRP levels	No significant difference in primary endpoints, but reduced mortality (29.8% vs. 46.3%, $P=0.03$)	Vitamin C may reduce mortality; further studies are needed	Secondary endpoints require cautious interpretation	Vitamin C reduces oxidative stress and inflammation, improving microcirculation
CoDEX TRIAL (2020) [129]	299	Dexamethasone vs. standard care	Ventilator-free days at 28 days, all-cause mortality	Increased ventilator-free days (6.6 vs. 4.0 days, $P=0.04$); no significant reduction in mortality	Dexamethasone improves short-term ventilation outcomes but does not significantly reduce mortality	Small sample size; limited to COVID-19 ARDS; long-term effects unvalidated	Suppresses inflammation, improves oxygenation
RECOVERY TRIAL (2021) [51]	4116	Tocilizumab + dexamethasone vs. standard care	28-day all-cause mortality	Lower mortality (31% vs. 35%, $P=0.0028$)	Tocilizumab further reduces mortality when combined with dexamethasone	Heterogeneity among patients may impact results	Blocks IL-6 activity, reducing cytokine storm and inflammation

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ECs	Endothelial cells
ECM	Extracellular matrix
ECMO	Extracorporeal membrane oxygenation
IL	Interleukin
LTVV	Low tidal volume ventilation
MMPs	Matrix metalloproteinases
MSCs	Mesenchymal stem cells
MAPK	Mitogen-activated protein kinase
MODS	Multiple organ dysfunction syndrome
NF-κB	Nuclear factor-κB
PEEP	Positive end-expiratory pressure
PTPs	Protein tyrosine phosphatases
RCTs	Randomized controlled trials
RNS	Reactive Nitrogen Species
ROS	Reactive oxygen species
STAT	Signal transducer and activator of transcription
SIRS	Systemic inflammatory response syndrome
TIMPs	Tissue inhibitors of metalloproteinases
TCZ	Tocilizumab
TNF-α	Tumor necrosis factor-α
AEC-I	Type I alveolar epithelial cells
AEC-II	Type II alveolar epithelial cells
UPV	Ultra-protective ventilation
VILI	Ventilator-induced lung injury

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Author contributions
JYL conceived and designed the study. QQQ is responsible for literature review and analysis and KHZ performed references collection, analysis and writing original draft. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

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References

1. Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. Lancet. 2022;400(10358):1145–56.
2. Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. Lancet. 2022;400(10358):1157–70.
3. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
4. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33.
5. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, et al. A New Global Definition of Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2024;209(1):37–47.
6. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of Care, and mortality for patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 countries. JAMA. 2016;315(8):788–800.
7. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet. 2021;398(10300):622–37.
8. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255–73.
9. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Signal Transduct Target Ther. 2021;6(1):255.
10. De Virgiliis F, Di Giovanni S. Lung innervation in the eye of a cytokine storm: neuroimmune interactions and COVID-19. Nat Rev Neurol. 2020;16(11):645–52.
11. Attiq A, Yao LJ, Afzal S, Khan MA. The triumvirate of NF-κB, inflammation and cytokine storm in COVID-19. Int Immunopharmacol. 2021;101:108255. Pt B).
12. Zanders L, Kny M, Hahn A, Schmidt S, Wundersitz S, Todiras M, et al. Sepsis induces interleukin 6, gp130/JAK2/STAT3, and muscle wasting. J Cachexia Sarcopenia Muscle. 2022;13(1):713–27.
13. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. Febs j. 2018;285(16):2944–71.
14. Lim EY, Lee SY, Shin HS, Kim GD. Reactive oxygen species and strategies for antioxidant intervention in Acute Respiratory Distress Syndrome. Antioxid (Basel). 2023;12(11).
15. Forman HJ, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. Nat Rev Drug Discov. 2021;20(9):689–709.
16. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat Rev Mol Cell Biol. 2020;21(7):363–83.
17. Kwon N, Kim D, Swamy KMK, Yoon J. Metal-coordinated fluorescent and luminescent probes for reactive oxygen species (ROS) and reactive nitrogen species (RNS). Coord Chem Rev. 2021;427:213581.
18. Kellner M, Noonepalle S, Lu Q, Srivastava A, Zemskov E, Black SM. ROS Signaling in the pathogenesis of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Adv Exp Med Biol. 2017;967:105–37.
19. Tirunavalli SK, Gourishetti K, Kotipalli RSS, Kuncha M, Kathirvel M, Kaur R, et al. Dehydrozingerone ameliorates Lipopolysaccharide induced acute respiratory distress syndrome by inhibiting cytokine storm, oxidative stress via modulating the MAPK/NF-κB pathway. Phytomedicine. 2021;92:153729.
20. Zhai Z, Ouyang W, Yao Y, Zhang Y, Zhang H, Xu F, et al. Dexamethasone-loaded ROS-responsive poly(thioketal) nanoparticles suppress inflammation and oxidative stress of acute lung injury. Bioact Mater. 2022;14:430–42.
21. Yin M, Lei D, Liu Y, Qin T, Gao H, Lv W, et al. NIR triggered polydopamine coated cerium dioxide nanozyme for ameliorating acute lung injury via enhanced ROS scavenging. J Nanobiotechnol. 2024;22(1):321.
22. Fowler AA 3rd, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of Vitamin C Infusion on Organ failure and biomarkers of inflammation and vascular Injury in patients with Sepsis and severe Acute Respiratory failure: the CITRIS-ALI randomized clinical trial. JAMA. 2019;322(13):1261–70.
23. Taher A, Lashgari M, Sedighi L, Rahimi-Bashar F, Poorolajal J, Mehrpooya M. A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID19-associated acute respiratory distress syndrome. Pharmacol Rep. 2021;73(6):1650–9.
24. Sauler M, Bazan IS, Lee PJ. Cell death in the lung: the apoptosis-necroptosis Axis. Annu Rev Physiol. 2019;81:375–402.
25. Nagata S, Tanaka M. Programmed cell death and the immune system. Nat Rev Immunol. 2017;17(5):333–40.
26. Messaoud-Nacer Y, Culerier E, Rose S, Maillet I, Rouxel N, Briault S, et al. STING agonist diABZI induces PANoptosis and DNA mediated acute respiratory distress syndrome (ARDS). Cell Death Dis. 2022;13(3):269.
27. Dejana E, Lampugnani MG. Endothelial cell transitions. Science. 2018;362(6416):746–7.
28. Millar FR, Summers C, Griffiths MJ, Toshner MR, Proudfoot AG. The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities. Thorax. 2016;71(5):462–73.
29. Moussa MD, Santonocito C, Fagnoul D, Donadello K, Pradier O, Gaussem P, et al. Evaluation of endothelial damage in sepsis-related ARDS using circulating endothelial cells. Intensive Care Med. 2015;41(2):231–8.

30. Borek I, Birnhuber A, Voelkel NF, Marsh LM, Kwapiszewska G. The vascular perspective on acute and chronic lung disease. J Clin Invest. 2023;133(16).
31. Dutra Silva J, Su Y, Calfee CS, Delucchi KL, Weiss D, McAuley DF et al. Mesenchymal stromal cell extracellular vesicles rescue mitochondrial dysfunction and improve barrier integrity in clinically relevant models of ARDS. Eur Respir J. 2021;58(1).
32. Whitsett JA, Alenghat T. Respiratory epithelial cells orchestrate pulmonary innate immunity. Nat Immunol. 2015;16(1):27–35.
33. Weibel ER. On the tricks alveolar epithelial cells play to make a good lung. Am J Respir Crit Care Med. 2015;191(5):504–13.
34. John AE, Joseph C, Jenkins G, Tatler AL. COVID-19 and pulmonary fibrosis: a potential role for lung epithelial cells and fibroblasts. Immunol Rev. 2021;302(1):228–40.
35. Liberti DC, Kremp MM, Liberti WA 3rd, Penkala IJ, Li S, Zhou S, et al. Alveolar epithelial cell fate is maintained in a spatially restricted manner to promote lung regeneration after acute injury. Cell Rep. 2021;35(6):109092.
36. Tojo K, Yamamoto N, Tamada N, Mihara T, Abe M, Nishii M, et al. Early alveolar epithelial cell necrosis is a potential driver of COVID-19-induced acute respiratory distress syndrome. iScience. 2023;26(1):105748.
37. Cui Y, Wang X, Lin F, Li W, Zhao Y, Zhu F, et al. MiR-29a-3p improves Acute Lung Injury by reducing alveolar epithelial cell PANoptosis. Aging Dis. 2022;13(3):899–909.
38. Qin H, Zhao A. Mesenchymal stem cell therapy for acute respiratory distress syndrome: from basic to clinics. Protein Cell. 2020;11(10):707–22.
39. Wang K, Wang M, Liao X, Gao S, Hua J, Wu X, et al. Locally organised and activated Fth1(hi) neutrophils aggravate inflammation of acute lung injury in an IL-10-dependent manner. Nat Commun. 2022;13(1):7703.
40. Michalski JE, Kurche JS, Schwartz DA. From ARDS to pulmonary fibrosis: the next phase of the COVID-19 pandemic? Transl Res. 2022;241:13–24.
41. Burnham EL, Janssen WJ, Riches DW, Moss M, Downey GP. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. Eur Respir J. 2014;43(1):276–85.
42. Barkauskas CE, Cronce MJ, Rackley CR, Bowie EJ, Keene DR, Stripp BR, et al. Type 2 alveolar cells are stem cells in adult lung. J Clin Invest. 2013;123(7):3025–36.
43. Desai TJ, Brownfield DG, Krasnow MA. Alveolar progenitor and stem cells in lung development, renewal and cancer. Nature. 2014;507(7491):190–4.
44. Herrera J, Henke CA, Bitterman PB. Extracellular matrix as a driver of progressive fibrosis. J Clin Invest. 2018;128(1):45–53.
45. Spang MT, Middleton R, Diaz M, Hunter J, Mesfin J, Banka A, et al. Intravascularly infused extracellular matrix as a biomaterial for targeting and treating inflamed tissues. Nat Biomed Eng. 2023;7(2):94–109.
46. Kaukonen KM, Bailey M, Bellomo R. Systemic inflammatory response syndrome criteria for severe Sepsis. N Engl J Med. 2015;373(9):881.
47. Yamashita M, Niisato M, Kawasaki Y, Karaman S, Robciuc MR, Shibata Y et al. VEGF-C/VEGFR-3 signalling in macrophages ameliorates acute lung injury. Eur Respir J. 2022;59(4).
48. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol. 2021;17(11):751–64.
49. Zhang H, Dhalla NS. The role of pro-inflammatory cytokines in the Pathogenesis of Cardiovascular Disease. Int J Mol Sci. 2024;25(2).
50. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.
51. Tocilizumab in patients. Admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.
52. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021;9(5):511–21.
53. Wang X, Chen S, Zhao L, Shi X. Protective effect of combination of anakinra and MCC950 against acute lung injury is achieved through suppression of the NF-κB-mediated-MAPK and NLRP3-caspase pathways. Int Immunopharmacol. 2021;97:107506.
54. Declercq J, Van Damme KFA, De Leeuw E, Maes B, Bosteels C, Tavernier SJ, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. Lancet Respir Med. 2021;9(12):1427–38.
55. Ao G, Wang Y, Li T, Tran C, Yang Q. The effect of canakinumab on clinical outcomes in patients with COVID-19: a meta-analysis. J Infect. 2022;84(6):834–72.
56. Ramasamy S, Subbian S. Critical determinants of Cytokine Storm and Type I Interferon Response in COVID-19 pathogenesis. Clin Microbiol Rev. 2021;34(3).
57. Morris DR, Ansar M, Ivanciuc T, Qu Y, Casola A, Garofalo RP. Selective blockade of TNFR1 improves clinical disease and Bronchoconstriction in experimental RSV infection. Viruses. 2020;12(10).
58. Fakharian A, Barati S, Mirenayat M, Rezaei M, Haseli S, Torkaman P, et al. Evaluation of adalimumab effects in managing severe cases of COVID-19: a randomized controlled trial. Int Immunopharmacol. 2021;99:107961.
59. Fisher BA, Veenith T, Slade D, Gaskell C, Rowland M, Whitehouse T, et al. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. Lancet Respir Med. 2022;10(3):255–66.
60. Marshall JC, Deutschman CS. The multiple organ dysfunction syndrome: syndrome, Metaphor, and Unsolved Clinical Challenge. Crit Care Med. 2021;49(9):1402–13.
61. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020;46(6):1105–8.
62. Gando S, Fujishima S, Saitoh D, Shiraishi A, Yamakawa K, Kushimoto S, et al. The significance of disseminated intravascular coagulation on multiple organ dysfunction during the early stage of acute respiratory distress syndrome. Thromb Res. 2020;191:15–21.
63. Del Sorbo L, Slutsky AS. Acute respiratory distress syndrome and multiple organ failure. Curr Opin Crit Care. 2011;17(1):1–6.
64. Lu J, Chen Y, Zhou K, Ling Y, Qin Q, Lu W, et al. Immune characteristics of kidney transplant recipients with acute respiratory distress syndrome induced by COVID-19 at single-cell resolution. Respir Res. 2024;25(1):34.
65. Cao S, Li H, Xin J, Jin Z, Zhang Z, Li J, et al. Identification of genetic profile and biomarkers involved in acute respiratory distress syndrome. Intensive Care Med. 2024;50(1):46–55.
66. Lu W, Ji R. Identification of significant alteration genes, pathways and TFs induced by LPS in ARDS via bioinformatical analysis. BMC Infect Dis. 2021;21(1):852.
67. Tung YT, Wei CH, Yen CC, Lee PY, Ware LB, Huang HE, et al. Aspirin attenuates Hyperoxia-Induced Acute Respiratory Distress Syndrome (ARDS) by suppressing pulmonary inflammation via the NF-κB signaling pathway. Front Pharmacol. 2021;12:793107.
68. Kaiser R, Leunig A, Pekayvaz K, Popp O, Joppich M, Polewka V et al. Self-sustaining IL-8 loops drive a prothrombotic neutrophil phenotype in severe COVID-19. JCI Insight. 2021;6(18).
69. Wu G, Xu G, Chen DW, Gao WX, Xiong JQ, Shen HY, et al. Hypoxia exacerbates inflammatory Acute Lung Injury via the toll-like receptor 4 signaling pathway. Front Immunol. 2018;9:1667.
70. Roy RK, Sharma U, Wasson MK, Jain A, Hassan MI, Prakash H. Macrophage activation syndrome and COVID 19: impact of MAPK driven Immune-Epigenetic Programming by SARS-Cov-2. Front Immunol. 2021;12:763313.
71. Zhang Y, Gao Z, Jiang F, Yan H, Yang B, He Q, et al. JAK-STAT signaling as an ARDS therapeutic target: Status and future trends. Biochem Pharmacol. 2023;208:115382.
72. Bagheri B, Torabi M, Salarian S. Toll-like receptor 4 in Acute Respiratory Distress Syndrome: good time to target? J Cell Mol Anesth. 2020;5(4):246–50.
73. Fang W, Cai SX, Wang CL, Sun XX, Li K, Yan XW, et al. Modulation of mitogen–activated protein kinase attenuates sepsis–induced acute lung injury in acute respiratory distress syndrome rats. Mol Med Rep. 2017;16(6):9652–8.
74. Almuntashiri S, Jones TW, Wang X, Sikora A, Zhang D. Plasma TIMP-1 as a sex-specific biomarker for acute lung injury. Biol Sex Differ. 2022;13(1):70.
75. Hästbacka J, Linko R, Tervahartiala T, Varpula T, Hovilehto S, Parviainen I, et al. Serum MMP-8 and TIMP-1 in critically ill patients with acute respiratory failure: TIMP-1 is associated with increased 90-day mortality. Anesth Analg. 2014;118(4):790–8.
76. de Almeida LGN, Thode H, Eslambolchi Y, Chopra S, Young D, Gill S, et al. Matrix metalloproteinases: from Molecular mechanisms to Physiology, Pathophysiology, and Pharmacology. Pharmacol Rev. 2022;74(3):712–68.
77. Zinter MS, Delucchi KL, Kong MY, Orwoll BE, Spicer AS, Lim MJ, et al. Early plasma Matrix Metalloproteinase profiles. A novel pathway in Pediatric Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2019;199(2):181–9.
78. Xia L, Oyang L, Lin J, Tan S, Han Y, Wu N, et al. The cancer metabolic reprogramming and immune response. Mol Cancer. 2021;20(1):28.

79. Robinson MJ, Krasnodembskaya AD. Therapeutic targeting of metabolic alterations in acute respiratory distress syndrome. Eur Respir Rev. 2020;29(156).
80. Wang L, Wang D, Zhang T, Ma Y, Tong X, Fan H. The role of immunometabolism in macrophage polarization and its impact on acute lung injury/acute respiratory distress syndrome. Front Immunol. 2023;14:1117548.
81. Luo Z, Yao J, Wang Z, Xu J. Mitochondria in endothelial cells angiogenesis and function: current understanding and future perspectives. J Transl Med. 2023;21(1):441.
82. Kelly B, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015;25(7):771–84.
83. Yang Y, Ma Y, Li Q, Ling Y, Zhou Y, Chu K, et al. STAT6 inhibits ferroptosis and alleviates acute lung injury via regulating P53/SLC7A11 pathway. Cell Death Dis. 2022;13(6):530.
84. Wang Z, Wang Z. The role of macrophages polarization in sepsis-induced acute lung injury. Front Immunol. 2023;14:1209438.
85. Venkatesan P. Updated ESICM guidelines on ARDS. Lancet Respir Med. 2024;12(1):16–8.
86. Gattinoni L, Citerio G, Slutsky AS. Back to the future: ARDS guidelines, evidence, and opinions. Intensive Care Med. 2023;49(10):1226–8.
87. Robba C, Bonatti G, Battaglini D, Rocco PRM, Pelosi P. Mechanical ventilation in patients with acute ischaemic stroke: from pathophysiology to clinical practice. Crit Care. 2019;23(1):388.
88. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med. 2006;32(1):24–33.
89. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8.
90. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299(6):637–45.
91. Gattinoni L. Ultra-protective ventilation and hypoxemia. Crit Care. 2016;20(1):130.
92. Rozencwajg S, Guihot A, Franchineau G, Lescroat M, Bréchot N, Hékimian G, et al. Ultra-protective ventilation reduces Biotrauma in patients on venovenous extracorporeal membrane oxygenation for severe Acute Respiratory Distress Syndrome. Crit Care Med. 2019;47(11):1505–12.
93. Costa EL, Amato MB. Ultra-protective tidal volume: how low should we go? Crit Care. 2013;17(2):127.
94. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med. 2020;46(12):2385–96.
95. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159–68.
96. Fralick M, Colacci M, Munshi L, Venus K, Fidler L, Hussein H, et al. Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ. 2022;376:e068585.
97. Alhazzani W, Parhar KKS, Weatherald J, Al Duhailib Z, Alshahrani M, Al-Fares A, et al. Effect of Awake Prone Positioning on Endotracheal Intubation in patients with COVID-19 and Acute Respiratory failure: a Randomized Clinical Trial. JAMA. 2022;327(21):2104–13.
98. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with Acute Respiratory Distress Syndrome: a Randomized Clinical Trial. JAMA. 2019;321(9):846–57.
99. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with Acute Respiratory Distress Syndrome: a Randomized Clinical Trial. JAMA. 2017;318(14):1335–45.
100. Albert RK. Constant Vt ventilation and surfactant dysfunction: an overlooked cause of ventilator-induced Lung Injury. Am J Respir Crit Care Med. 2022;205(2):152–60.
101. Goligher EC, Dres M, Patel BK, Sahetya SK, Beitler JR, Telias I, et al. Lung- and diaphragm-protective ventilation. Am J Respir Crit Care Med. 2020;202(7):950–61.
102. Mi MY, Matthay MA, Morris AH. Extracorporeal membrane oxygenation for severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018;379(9):884–7.
103. Combes A, Schmidt M, Hodgson CL, Fan E, Ferguson ND, Fraser JF, et al. Extracorporeal life support for adults with acute respiratory distress syndrome. Intensive Care Med. 2020;46(12):2464–76.
104. Wiener C, Albert RK. ECMO and prone position in patients with severe ARDS. JAMA. 2024;331(14):1232.
105. Hoang DM, Pham PT, Bach TQ, Ngo ATL, Nguyen QT, Phan TTK, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Ther. 2022;7(1):272.
106. Weiss DJ. Cell-based therapies for acute respiratory distress syndrome. Lancet Respir Med. 2019;7(2):105–6.
107. Zhang H, Slutsky AS. Enhancing the efficacy of mesenchymal stromal cells in COVID-19-related Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2023;208(3):222–4.
108. Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med. 2015;3(1):24–32.
109. Hashemian SR, Aliannejad R, Zarrabi M, Soleimani M, Vosough M, Hosseini SE, et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series. Stem Cell Res Ther. 2021;12(1):91.
110. Bowdish ME, Barkauskas CE, Overbey JR, Gottlieb RL, Osman K, Duggal A, et al. A randomized trial of mesenchymal stromal cells for moderate to severe Acute Respiratory Distress Syndrome from COVID-19. Am J Respir Crit Care Med. 2023;207(3):261–70.
111. Liu J, Dean DA. Gene Therapy for Acute Respiratory Distress Syndrome. Front Physiol. 2021;12:786255.
112. Bai Y, Liu Y, Su Z, Ma Y, Ren C, Zhao R, et al. Gene editing as a promising approach for respiratory diseases. J Med Genet. 2018;55(3):143–9.
113. Bisserier M, Sun XQ, Fazal S, Turnbull IC, Bonnet S, Hadri L. Novel insights into the therapeutic potential of lung-targeted gene transfer in the most common respiratory diseases. Cells. 2022;11(6).
114. Wang M, Zhai X, Li J, Guan J, Xu S, Li Y, et al. The role of cytokines in Predicting the response and adverse events related to Immune Checkpoint inhibitors. Front Immunol. 2021;12:670391.
115. Meng L, Wu H, Wu J, Ding P, He J, Sang M, et al. Mechanisms of immune checkpoint inhibitors: insights into the regulation of circular RNAS involved in cancer hallmarks. Cell Death Dis. 2024;15(1):3.
116. Huang M, Yu Y, Tang X, Dong R, Li X, Li F, et al. 3-Hydroxybutyrate ameliorates sepsis-associated acute lung injury by promoting autophagy through the activation of GPR109α in macrophages. Biochem Pharmacol. 2023;213:115632.
117. Hammond TC, Purbhoo MA, Kadel S, Ritz J, Nikiforow S, Daley H, et al. A phase 1/2 clinical trial of invariant natural killer T cell therapy in moderate-severe acute respiratory distress syndrome. Nat Commun. 2024;15(1):974.
118. Ben-David U, Benvenisty N. The tumorigenicity of human embryonic and induced pluripotent stem cells. Nat Rev Cancer. 2011;11(4):268–77.
119. Zhu M, Xu R, Yuan J, Wang J, Ren X, Cong T et al. Tracking-seq reveals the heterogeneity of off-target effects in CRISPR-Cas9-mediated genome editing. Nat Biotechnol. 2024.
120. Manghwar H, Li B, Ding X, Hussain A, Lindsey K, Zhang X, et al. CRISPR/Cas Systems in Genome Editing: methodologies and tools for sgRNA Design, off-target evaluation, and strategies to Mitigate Off-Target effects. Adv Sci (Weinh). 2020;7(6):1902312.
121. Dougan M, Luoma AM, Dougan SK, Wucherpfennig KW. Understanding and treating the inflammatory adverse events of cancer immunotherapy. Cell. 2021;184(6):1575–88.
122. Peng YJ, Huang X, Zhou Q. Ethical and policy considerations for human embryo and stem cell research in China. Cell Stem Cell. 2020;27(4):511–4.
123. Cyranoski D. The CRISPR-baby scandal: what's next for human gene-editing. Nature. 2019;566(7745):440–2.
124. Potnis KC, Di M, Isufi I, Gowda L, Seropian SE, Foss FM, et al. Cost-effectiveness of chimeric antigen receptor T-cell therapy in adults with relapsed or refractory follicular lymphoma. Blood Adv. 2023;7(5):801–10.
125. Patel A, Bagai J, Dickerson DA, Muncy K, Baer BM, Long N, et al. Evaluation of cost drivers and cost-efficacy of autologous hematopoietic transplant and chimeric Antigen receptor T-Cell therapy in high-Grade B Cell Lymphoma from a Healthcare Firm Perspective. Blood. 2022;140(Supplement 1):13082–4.
126. Dai X, Mei Y, Cai D, Han W. Standardizing CAR-T therapy: getting it scaled up. Biotechnol Adv. 2019;37(1):239–45.
127. Wang JH, Gessler DJ, Zhan W, Gallagher TL, Gao G. Adeno-associated virus as a delivery vector for gene therapy of human diseases. Signal Transduct Target Ther. 2024;9(1):78.

128. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351(4):327–36.
129. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and Ventilator-Free in patients with moderate or severe Acute Respiratory Distress Syndrome and COVID-19: the CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307–16.

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