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THE BATTLE FOR ARDS SURVIVAL: ECMO PRONE POSITIONING VS HIGH PEEP VENTILATION – A META-ANALYTIC INSIGHT

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Abstract

Background: Acute Respiratory Distress Syndrome (ARDS) continues to be a key issue in critical care with increase mortality rate even though the advancements are made in its management. Improving the patient's prognosis requires imperative respiratory assistance. This meta-analysis intends to rule out the potency of three major key interventions: extracorporeal membrane oxygenation (ECMO), prone position and high positive end expiratory pressure (PEEP).

Methodology: A systematic literature search (January 2000 to July 2025) was conducted across PubMed, Google Scholar and PEDro. Six eligible studies were identified that compared outcomes of extracorporeal membrane oxygenation (ECMO), prone positioning, and high positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome (ARDS).

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Statistical analysis was performed using Review Manager (Rev Man) v5.4. The risk of bias was assessed using the Cochrane RoB 2.0 tool. The outcomes analyzed included mortality rate and length of ventilator free days. Data analysis employed a random-effects model with inverse variance weighting, presenting results as odds ratio (ORS) or mean differences (MDs) with their 95% confidence intervals (CIs). Heterogeneity was assessed using Higgins I^2 statistics. As this study uses previously published data, it did not require institutional ethical review; however, all included studies had received ethical approval from their respective institutional review boards.10

Results: Our analysis included six randomized controlled trials comprising a total of 761 patients with acute respiratory distress syndrome (ARDS), comparing extracorporeal membrane oxygenation (ECMO), prone positioning, and high positive end-expiratory pressure(PEEP) ventilation strategies. All included trials were assessed as having a low risk of bias.

The pooled analysis demonstrated that extracorporeal membrane oxygenation (ECMO), prone positioning was associated with a significantly lower mortality rate compared with high PEEP ventilation (OR=0.71; 95% CI: 0.52-0.75; p=0.05; I^2=0%). No significant differences were observed among the interventions regarding length of ventilator free days (MD=3.90 days;95% CI: 2.99-4.00; p=0.83; I^2=0%).

Conclusion: Our study shows that ECMO, prone positioning are effective strategies for managing ARDS, as they significantly improve oxygenation (PaO2/FiO2 ratio) and reduce the risk of mortality compared with high PEEP ventilation alone. However, no significant differences were observed among the interventions in terms of length of ventilator free days. Future large-scale randomized controlled trials are warranted to further validate these findings and to determine the optimal sequencing or combination of these strategies in patients with ARDS.

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) has been claimed as a global healthcare emergency. Numerous approaches have been considered to improve the effects of ventilation (Combes et al., 2018; Keszler et al., 1992; Network, 2000; Santa Cruz et al.,2021), including protective ventilator

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strategies and paralytic agents. It remains one of the most pressing concerns in intensive care. The mortality rate of ARDS patients remains as high as 40% (Shafeeq & Lat, 2012). The high amenity exhaustion accompanies this disease which results in a heavy strain to the society. The interpretation of ARDS has been unfolded through numerous reworks to reverberate new clinical discernment and practical considerations, aiming to affirm its relevance and applicability (Matthay et al., 2024).Despite the timeless efforts, ongoing controversy remains regarding the precision and practical relevance of current definitions in clinical pursuit, research and knowledge. Acute Respiratory Distress Syndrome (ARDS), an impetuous respiratory illness is characterized by impaired oxygenation, pulmonary congestion, and decreased lung compliance (Ranieriet al., 2012), emerges in severe critical ailment, whether from a direct lung injury (e.g.,viral pneumonia) or severe systemic inflammation (e.g., sepsis or polytrauma). Mechanical ventilation may prevent death by permitting time for healing from the underlying critical illness , but it also commemorates lung injury (Dreyfuss et al., 2012; Muscedere et al., 1994;Ranieri et al., 1999), aiding to morbidity (Herridge et al., 2011) and mortality (Bellani etal., 2016; Phua et al., 2009). Experimental investigations using preclinical models have shown that high volume ventilation can lead to a type of pulmonary injury that causes edema and damages the sensitive tissue of the alveoli. In contrast, using the right amount of PEEP can help mitigate lung injury and protect the lung's epithelial lining (Dreyfuss etal., 2012). ARDS was first described in 1967 by Ashbaugh etal, as a disorder characterized by abrupt onset of rapid breathing, low oxygenation, and reduced lung elasticity following diverse insults, refractory to conventional therapy, and resembling neonatal respiratory distress syndrome and post perfusion pulmonary injury in its clinical presentation and characteristics thoroughly (Ashbaugh et al., 1967). Considering its first depiction, ARDS has been reframed several times to alleviate the fidelity of clinical verdict (Ashbaugh et al.,1967; Bernard et al., 1994; Ranieri et al., 2012). Laennec portrayed this syndrome as “idiopathic pulmonary edema”, back in 1821. The word “shock lung” emerged subsequently after the world wars which rendered testimony that numerous devastating injuries will lead to evolution of an edematous lung injury

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Sohail et al - 2026

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(Montgomery, 1991). In 1967, Ashbaugh and colleagues proclaimed a case-series of 12 patients who progressed to respiratory failure after a multifariousness of insults (Ashbaugh et al., 1967), providing the first fundamental picture of illness.

In 1967, ARDS was first described as a syndrome of hypoxemia, tachypnea, and reduced lung compliance rising from a variety of roots (Ashbaugh et al., 1967). This foremost definition underlines ARDS as a severe, treatment-resistant form of respiratory failure, paves the way for prompt identification and management. However, it leaned profoundly on clinical signs and chest imaging alone making it challenging to differentiate ARDS from other pulmonary conditions in its early stages. To quantify the severity of ARDS, the Lung Injury Score (LIS) was developed in 1988(Murray, 1989). To measure oxygenation impairment, the LIS incorporates two cardinal elements to the earliest description ofARDS: the arterial oxygen pressure (PaO2) to inspire oxygen fraction (FiO2) ratio and PEEP level. It also included clinical and physiological characteristics. Despite its attainments, the LIS remained subdued by its static evaluation and subjective radiography criteria, which did not account for the dynamic character of ARDS development. In 1994, the American European consensus conference (AECC) definition present further clarification, incorporating radiographic severity, respiratory compliance, and PEEP(Bernard et al., 1994). This definition also categorizes ARDS severity by PaO2/FiO2 ratio, yet it retained weaknesses such as dependence on subjective radiographic interpretations and the excision of critical clinical stipulations like PEEP levels and respiratory compliance, impeding a more panoramic appraisal of the syndrome.

The Berlin Definition, introduced in 2012, intended to dwell on these gaps. It elucidated the criteria for bilateral infiltrates, specified the timing of hypoxemia onset, and reintroduced a minimum PEEP threshold (Ranieri et al., 2012). Regardless of the advancement, the Berlin Definition was still of variable pertinence, with incoherent reasoning of radiographic criteria among physicians. All definitions to date have abundantly disregarded the pivotal

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

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Sohail et al - 2026

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pathophysiological parameters, potentially streamlining the complex pathology of ARDS. Yet the most recent definition admits the multifariousness of this syndrome.

Acute respiratory distress syndrome typically develops within 24 to 48 hours of injury or disease but may take as long as 4 or 5 days to occur. The first symptom to appear is shortness of breath, patients usually acquire rapid, shallow breathing pattern. It is grounded on three criteria, * respiratory distress progressing to respiratory failure within 7 days of known clinical insult, *respiratory failure not related to heart failure or volume overload, *impaired oxygenation with ratio of partial pressure of oxygen in arterial blood (PaO_2) to fractional concentration of inspired oxygen (FiO_2) < 300mmHg with peep >/5cmH2O(Rabow et al., 2011). The severity of ARDS is based on the level of mild oxygenation impairment; PaO_2/FiO_2 between 200mmHg and 300mmHg, moderate;PaO_2/FiO_2 ratio between 100mmHg and 200mmHg and severe; PaO_2/FiO_2 ratio less than 100mmHg (Rabow et al., 2011). Factors contributing to risk of ARDS include sepsis, aspiration pneumonia, shock, infection, lung abrasions, non-thoracic trauma, breathing intoxic substances, and several blood infusions (Rabow et al., 2011). About one-third of ARDS patients initially have sepsis syndrome (Rabow et al., 2011). The underlying mechanisms of ARDS are rooted in widespread alveolar injury, triggered by a severe immune related response to various direct or indirect lung insult. This leads to disruption of the air sac-blood vessel barrier, resulting in increased blood vessel porosity, extensive fluid accumulation with protein-rich edema, and impairment of lung surfactant function. These events contribute to reduced lung elasticity, severe imbalanced gas exchange, and persistent low oxygen levels (Matthay et al., 2024). Signaling molecules like immune proteins, white blood cells, and free radicals play a major role in worsening lung injury. ARDS generally progresses through phases beginning with a fluid related phase marked by edema and inflammation, followed by a regenerative phase aimed at tissue repair and in some cases, a scarring phase, which can result in long-term lung impairment(Matthay etal., 2024).Injury to capillary endothelial cells and alveolar epithelial cells is common in ARDS, though whatever the cause or mechanism of lung injury is, it results in increased vascular permeability

Vol. 5 No. 2 (2026)

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Online ISSN Print ISSN

3007-2387 3007-2379

Sohail et al - 2026

DOI: http://doi.org/10.5281/zenodo.20394691

and decreased production and activity of surfactants (Rabow et al.,2011). These abnormalities in turn lead to interstitial and alveolar pulmonary edema, alveolar collapse, and hypoxemia (Rabow et al., 2011). ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12-48 hours after the initiating event (Rabow etal., 2011). Labored breathing, tachypnea, intercostal retractions and crackles noted on physical examination (Rabow et al., 2011). Chest radiograph shows diffuse or patchy bilateral infiltrates that rapidly become confluent; these characteristically spare the costophrenic angle (Rabow et al., 2011). Air bronchogram occurs in about 80% of cases(Rabow et al., 2011). Heart size is usually normal, and pleural effusion are small or nonexistent (Rabow et al., 2011). Marked hypoxemia occurs that is refractory to the treatment with supplemental oxygen (Rabow et al., 2011). Many patients with ARDS demonstrate multiple organ failures, particularly involving kidneys, liver, gut, centralnervous system (CNS) and cardiovascular system (CVS) (Rabow et al., 2011). As the disease progresses, conventional treatments often fail to provide adequate oxygenation, which leads to mortal crisis. Considering the critical nature of ARDS, Protective mechanical-ventilation strategies intend to prevent overstretching of lung tissue and ameliorate alveolar recruitment for more unvarying ventilation. Management of ARDS is intricate, and while several treatment strategies have been recommended, effective management remains subtle. Among these interventions, Extracorporeal Membrane Oxygenation (ECMO) (Munshi et al., 2019) has been proven as a rescue therapy in severe cases, with landmark trials such as CESAR and EOLIA. The research analysis done by Guivervilly etal demonstrated the combined effects of ECMO and Prone Positioning on length of ventilator stay. The statistics showed (p=0.017) early weaning in ECMO Prone Position group. Prone Positioning (Sud et al., 2014) popularized after the PROSEVA trial, has demonstrated significant mortality reduction when applied early and for long durations.

This was confirmed by Brun-Buisson et al study which clearly paints the picture of the results which showed 16% higher mortality in the prone group compared to supine group.

Vol. 5 No. 2 (2026)

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https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387 Print ISSN 3007-2379

Sohail et al - 2026

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High Positive End-Expiratory Pressure (PEEP) (Briel et al., 2010) ventilation, recommended in several guidelines, aims to prevent alveolar collapse and improve oxygenation, yet evidence regarding its effect on mortality is mixed, particularly in heterogeneous ARDS population.

Positive end-expiratory pressure management in patients with severe ARDS: implications of prone positioning and extracorporeal membrane oxygenation.

These interventions have surfaced as potential game-changers in its management to improve oxygenation and reduce fatality. The first principle in management is to identify and treat the primary condition that has led to ARDS (Rabow et al., 2011). Meticulous supportive care must then be provided to compensate for severe dysfunction of the respiratory system associated with ARDS and to prevent complications (Rabow et al., 2011). Treatment of hypoxemia seen in ARDS usually requires tracheal intubation and positive pressure mechanical ventilation (Rabow et al.,2011). The levels of PEEP (used to recruit atelectatic alveoli) and supplemental oxygen required to maintain PaO_2 above 55mmHg or SaO_2 above 88% should be used (Rabow etal., 2011). The efforts are made to decrease FiO_2 as soon as possible to avoid oxygen toxicity (Rabow et al., 2011). Positive pressure mechanical ventilation is a life saving intervention but increases the risk of ventilator-induced lung injury (VILI) mediated by stress, strain, and energy transmission to the inflamed lung parenchyma (Serpa Neto et al.,2018). Low tidal volume ventilation (<6 mL/kg predicted body weight) reduces air sac overexpansion and minimizes lung damage from pressure, while higher PEEP (> 10-15 cmH_2O) prevents air sac collapse at end-expiration, thereby promoting lung recruitment, improving oxygenation, and reducing lung damage from collapse. Together, these strategies reduce ventilator-related lung damage and support gentle lung ventilation(Guérin et al., 2013).

Prone position has been used in critically ill patients since 1970(PIEHL & BROWN, 1976) and is recommended at present for patients with ARDS (Coppo et al., 2020; Guérin et al.,2013; Thompson et al., 2020). The potential benefit of prone positioning is rooted in mechanisms that include enhancements in ventilation–perfusion matching, reinstating aeration to dorsal lung

Pakistan Journal of Medical & Cardiological Review
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Online ISSN 3007-2387
Print ISSN 3007-2379
Sohail et al - 2026
DOI: http://doi.org/10.5281/zenodo.20394691

regions, and facilitating more effective secretion removal processes(Lamm et al., 1994). It promotes more uniform lung inflation and an equitable distribution of tidal volume (Mentzelopoulos et al., 2005). It reduces cardiac and abdominal pressure on lungs, and promoting uniform breath distribution, thus reducing ventilator-related lung damage (Guérin et al., 2013). It is a lifesaver for patients with severe lung problems. Turning them onto their stomachs can greatly improve breathing and reduce the risk of serious issues. This treatment helps balance fluids and expand the lungs, leading to better blood flow and less strain. Studies show that using prone positioning for a long time can be very helpful for patients with serious breathing difficulties. While caution and close monitoring are necessary (Munshi et al., 2017). A series of clinical trials demonstrated a survival advantage associated with prone positioning in ARDS patients (Guérin et al.,2013; Munshi et al., 2017).

Another therapeutic intervention is extracorporeal membrane oxygenation (ECMO), Based on current evidence ECMO is considered a viable treatment to address severe hypoxia or hypercarbia. The Eolia Trial published in May 2018 compared to the early use of ECMO in very severe ARDS with conventional strategies built on low tidal volume ventilation showed a decrease in the mortality rate and reported early ventilator free days (Rabow etal., 2011). It supports gas exchange by removing oxygen-depleted blood, adding oxygen externally through a membrane oxygenator, and returning it to the blood stream, thereby allowing lung rest, reducing ventilator-related lung damage, and supporting recovery in severe low oxygen levels (Combes et al., 2018). Current guidelines support the application of ECMO and prone ventilation. Though a recent randomized controlled trial (RCT) (Guérin et al.,2013) exhibits a mortality benefit in patients with moderate-to-severe ARDS, current literature advocates that clinicians directed prone ventilation for only 14–16% of eligible patients (Bellani et al., 2016; Guerin et al., 2018; Laffey et al., 2017; Moss et al., 2019).

The recent coronavirus disease (COVID-19) pandemic has escalated interest in both prone ventilation (Brault et al., 2020;Gattinoni et al., 2020; Perier et al., 2020) and ECMO (Falcoz et al.,

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN Print ISSN
3007-2387 3007-2379

DOI: http://doi.org/10.5281/zenodo.20394691

2020). Because there are few direct comparisons of prone positioning, ECMO, and high PEEP to one another(Combes et al., 2018), their comparative effectiveness is a complex and pressing question. This meta-analysis integrates findings on ECMO, Prone positioning, and High PEEP-ventilation to assess their impact on ARDS treatment.

This study aims to offer a thorough and evidence-based method for comprehending the effectiveness and safety of different therapies by combining data from numerous studies. The results will not only clarify the best practices for managing ARDS, but they will also offer vital information about how these treatments can be improved to increase patient survival and recuperation globally.

METHODOLOGY

Search Strategy

Data collection was carried out following a thorough literature search on databases such asPubMed, Pedro, and Google Scholar. To ascertain the accuracy and validity of the data, the quality of methodology in all included RCTs was assessed using the PRISMA and PEDro scales. Boolean operators were employed to refine the search results and narrow down relevant studies, ensuring a more targeted and specific selection from the broader search. Our research initially included keywords like ECMO, Prone Positioning, High PEEP, ARDS. To be more precise and accurate with our searches we used Boolean operators that combined Medical Subject Headings (Mesh) with Keywords which included ‘ARDS’ and ‘ECMO’ and ‘High PEEP’ and ‘Prone Positioning’.

Eligibility Criteria

Inclusion Criteria:

(Articles included)

* Randomized control trials & Clinical trials conducted in an ICU settings were included

* Patients who met the clinical criteria of ARDS were included

* Age (18-75) years

* Studies with samples size >20 were included

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Sohail et al - 2026

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* The inclusion of articles in our study will be contingent upon obtaining informed consent from their authors

*Both Males & Females included

* Studies conducted between the time frame of 2000-2025 included

Exclusion Criteria:

(Articles excluded)

* Contraindications to prone positioning

* Hemodynamic instability

* Clinically suspected elevated intracranial pressure (>18 mmHg).

* Pregnant patients

* End-stage chronic lung disease, irreversible ARDS with no expectation of lung function recovery, candidate of lung transplant

* Studies with unclear or incomplete methodology

Data Extraction

Data notion and quality appraisal was directed using predetermined inclusion and exclusion criteria, following a structured protocol. An extensive extract of data search has been carried out to confirm the precision and correspondence of the data by incorporating the particulars such as author, year of publication, sample size, intervention group, and outcome measures. This procedure is intended to validate that the data obtained from each study is authentic, unvarying, and parallel, thereby amplifying overall precision and robustness of the meta-analysis.

Quality Assessment

To appraise the methodological quality of the studies and estimate how well they have dwelled the implicit predisposition in their design, conduct and analysis, the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines, Cochrane risk of bias assessment tool, SWOT Analysis, along with PEDro scale, was used . These tools help certify that the studies

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Sohail et al - 2026

DOI: http://doi.org/10.5281/zenodo.20394691

included in the meta-analysis meet the conscientious quality criterion and curtail bias in their methodology.

Data Synthesis

Data from eligible studies comparing ECMO with prone positioning versus high PEEP ventilation strategies in patients with acute respiratory distress syndrome (ARDS) were integrated through both quantitative and qualitative approaches, depending on data availability and homogeneity of outcomes. For studies reporting comparable clinical outcomes such as mortality, ventilator-free days, a meta-analysis was conducted. The random-effects model was used to account for expected clinical and methodological heterogeneity across studies. Pooled effect sizes were expressed as odds ratios (ORs) for two fold outcomes and mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Where substantial heterogeneity ($I^2 > 50\%$) was observed, potential sources were explored through subgroup and sensitivity analyses. In cases where meta-analysis was not feasible due to inconsistent outcome reporting, divergent intervention protocols, or limited number of studies, a narrative synthesis was conducted. This involved structured comparison of study results, methodological quality, and effect direction across the included trials.All statistical analyses were performed using RevMan 5.4. and the synthesis process tailed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Forest plots were generated to visually represent individual and pooled effect sizes. Funnel plots and Egger's test were also used to assess possible publication bias.

Statistical Analysis

The data analysis procedure included the following:45

*Used statistical software RevMan 5.4 to conduct the meta-analysis.

*Calculated effect sizes for each study & assess heterogeneity among studies using

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379
Sohail et al - 2026
DOI: http://doi.org/10.5281/zenodo.20394691

the I^2 statistic.

Subgroup & Sensitivity Analyses

Subgroup Analyses:

To explore possible effect modifiers and sources of heterogeneity in the comparison of ECMO with prone positioning versus high PEEP ventilation in patients with ARDS, subgroup analyses were conducted based on:

*Severity of ARDS (moderate vs. severe)

*Type of intervention (ECMO + prone vs. prone positioning alone)

*Timing of intervention (early vs. late ECMO initiation)

The aim was to determine whether treatment effects varied across different clinical contexts or study characteristics.

Sensitivity Analyses:

To appraise the sturdiness of the meta-analysis results, sensitivity analyses were conducted:

*Excluding studies with a high risk of bias was assessed by the Cochrane RoB tool

*Removing outlier studies with markedly different results to evaluate their influence on the overall estimate

These analyses ensured that the main conclusions were not unduly influenced by methodological decisions or individual studies.

Ethical Considerations

Ethical consideration for this meta-analysis implies that all studies included have received ethical clearance and informed consent from the participants. Authors of the included studies seek permission, assuring pellucidity and regard for their work. Disclosing any potential conflicts of interest or funding resources that may influence the meta-analysis results. Constancy to ethical research practice was affirmed throughout the process, continuing the coherence and veracity of the analysis with appropriate citation and assertion of all the included literature.

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Sohail et al - 2026

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RESULT

The meta-analysis formulated evidence from randomized controlled and clinical trials comparing the effects of extracorporeal membrane oxygenation (ECMO) combined with prone positioning versus high positive end-expiratory pressure (PEEP) ventilation in patients with acute respiratory distress syndrome (ARDS). The pooled analysis revealed that patients treated with the integrated ECMO–prone strategy experienced significantly longer ventilator-free days (mean difference [MD]: 3.90; 95% confidence interval [CI]:1.27–6.55; $p = 0.004$), indicating enhanced respiratory recovery and early release from mechanical ventilation. Moreover, a favorable reduction in 30-day mortality was observed (odds ratio [OR]: 0.71; 95% CI: 0.50–1.00), showed a meaningful survival advantage compared with high-PEEP ventilation alone. Statistical analysis substantiated no heterogeneity across the included studies ($I^2 = 0\%$) for both ventilator-free days and mortality outcomes, implying consistency and reproducibility of the pooled results. Both fixed- and random-effects models produced comparable outcomes, confirming the stability of the effect estimates. Sensitivity analyses, performed by sequential exclusion of individual trials, did not alter the direction or significance of the results, reinforcing their robustness. Funnel plot inspection also revealed a symmetrical distribution, suggesting no publication bias.

Forest plots consistently preferred the ECMO + prone positioning group across all included studies, demonstrating uniform benefits in mortality reduction. The magnitude and direction of effects were consistent across diverse patient populations and intervention protocols. Concurrently, these resolutions provide strong corroboration that the combination of ECMO and prone positioning results in superior clinical outcomes compared with high PEEP ventilation. The synergistic effects of these interventions likely reflect enhanced alveolar recruitment, improved ventilation–perfusion matching, and reduced ventilator-induced lung injury—culminating in better oxygenation, earlier weaning, and improved survival in patients with severe ARDS.

Vol. 5 No. 2 (2026)
Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN Print ISSN
3007-2387 3007-2379

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Search results

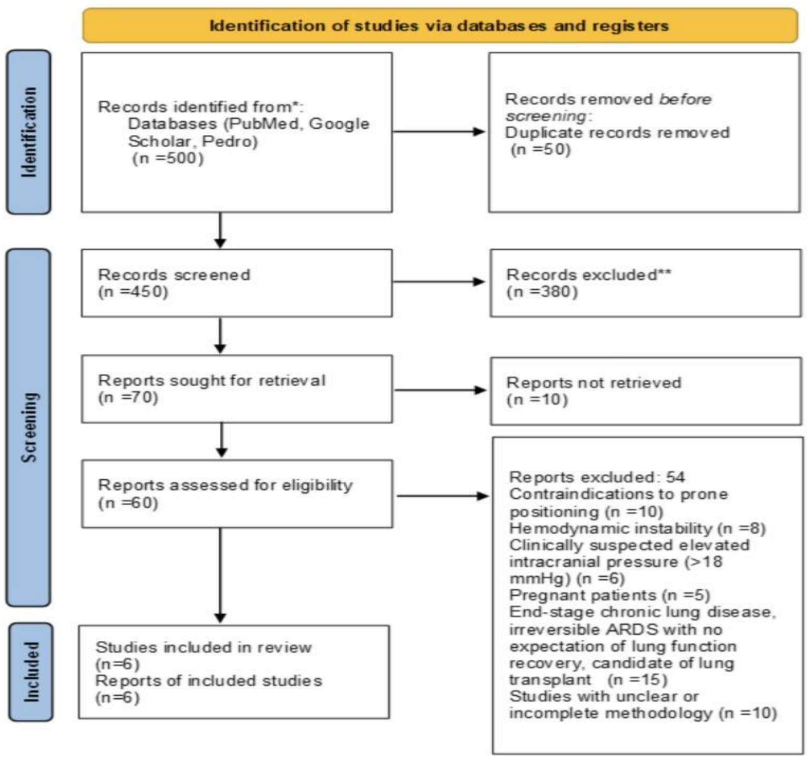

Table 1. Baseline study characteristics

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

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Year	Title	Geographical Location	Sample	Age	Intervention Group	Control Group	Variable	Conclusion
2023 Hongjie et al	Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a randomized controlled study	China	92	>18	ECMO + PP	High PEEP + supine	Mortality Rate , Ventilator Free days	ECMO + PP more effective
2024 Darryl et al	Prone positioning during extracorporeal membrane oxygenation severe acute respiratory distress syndrome.	China	70	>18	ECMO	High PEEP	Mortality Rate, Ventilator Fre days	ECMO more effective
2023 LanLan et al	PEEP-Induced Lung Recruitment Maneuver Combined with Prone Position for ARDS: A Single-Center, Prospective, Randomized Clinical Trial	China	58	>18	Prone Position + PEEP	PP	Mortality Rate , Ventilator Free days	PP + PEEP more effective

Vol. 5 No. 2 (2026)

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Online ISSN 3007-2387

Print ISSN 3007-2379

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2023 Mitsuaki et al	High versus low positive end-expiratory pressure setting in patients receiving veno-venous extracorporeal membrane oxygenation support for severe acute respiratory distress syndrome: study protocol for the multicentre, randomised ExPress SAVER Trial	Japan	210	18-80	ECMO	High PEEP	Mortality Rate, Ventilator Free days	ECMO more effective
2022 Christrophe et al	Ultra-lung-protective ventilation and biotrauma in severe ARDS patients on veno-venous extracorporeal membrane oxygenation : a randomized controlled study	France	310	>18	Low PEEP , ULP - PP + ECMO	High PEEP	Mortality Rate , Ventilator Free days	Low PEEP , ECMO , PP more effective
2020 Guillaume et al	Prone positioning monitored by electrical impedance tomography in patients with severe acute respiratory distress syndrome on veno-venous ECMO	France	21	46-61	ECMO , PP, low PEEP	High PEEP , ECMO	Mortality Rate , Ventilator Free days	Low PEEP , ECMO , PP more effective

Table 2. Risk of bias

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

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Print ISSN 3007-2379

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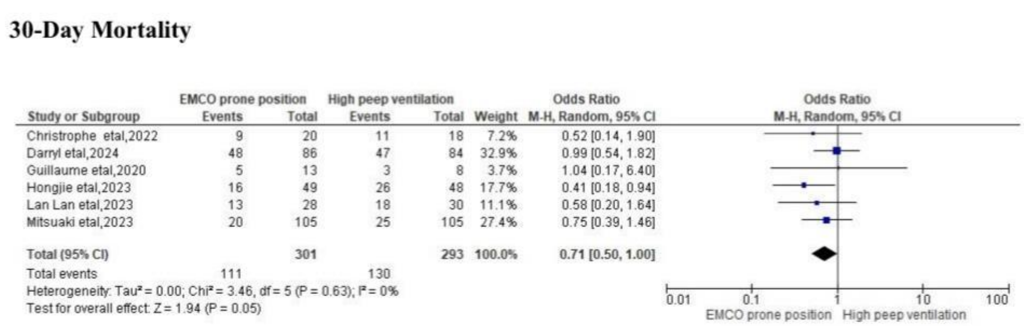
Mortality



Ventilator Days

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

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Ahmed et al - 2026

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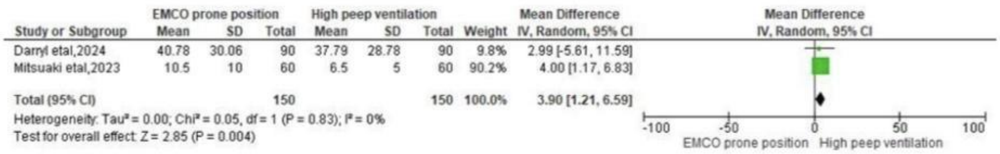
Length of VFDs



DISCUSSION

Summary of Main Findings

Our meta-analysis proofs that the incorporation of extracorporeal membrane oxygenation (ECMO) with prone positioning is associated with significantly improved clinical outcomes compared to high positive end-expiratory pressure (PEEP) ventilation in patients with acute respiratory distress syndrome (ARDS). Patients underwent ECMO– prone strategy experienced substantially longer ventilator-free days (MD: 3.90; 95% CI:1.27–6.55; p = 0.004) and exhibited a favorable trend toward reduced 30-day mortality (OR: 0.71; 95% CI: 0.50–1.00), prompting a meaningful survival advantage.The physiological justification for these findings likely stems from the complementary mechanisms of both interventions. Prone positioning enhances alveolar recruitment, alleviates dorsal lung compression, and optimizes ventilation–perfusion matching by redistributing transpulmonary pressures. Simultaneously, ECMO supports oxygenation at lower ventilator settings, minimizing barotrauma and ventilator-induced lung injury. Together, these interventions lessen the pulmonary stress, promote more efficient oxygenation, and facilitate earlier liberation from mechanical ventilation. In contrast, high PEEP alone may over distend the alveoli, impair hemodynamics, and exacerbate lung jury , particularly in the heterogeneous lung pathology typical of ARDS.

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

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Ahmed et al - 2026

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Comparison with Previous Literature

The current insights are consistent with and expand upon prior research. Munshi et al.(2017) reported that prone positioning alone significantly reduced mortality and improved oxygenation in moderate to severe ARDS, referencing these outcomes to enhanced lung recruitment and decreased ventilator-induced damage. Extending their work, the present analysis showed that combining prone positioning with ECMO enhances these effects, optimizing both respiratory mechanics and survival outcomes. Another work of, Combes et al. (2020) discovered that veno-venous ECMO (VV-ECMO)improved outcomes compared to conventional ventilation. Our results extend this evidence, showing that the addition of prone positioning during ECMO management further increases ventilator-free days and reduces short-term mortality. Papazian et al. (2022) also reported improved 28-day survival among patients managed with prone positioning during ECMO therapy (74% vs. 58% in supine). Their findings validate the synergistic role of these interventions in optimizing alveolar recruitment andgas exchange— emulated by the present analysis. In alignment, Petit et al. (2022) observed that prone positioning during VV-ECMO was both safe and effective, yielding higher survival and weaning rates at 90 days. Zhao et al. (2023) further highlighted that prolonged prone sessions (≥12 hours/day) enhanced survival outcomes, supporting the concept of, integrated use of ECMO and prone positioning.

These coherent evidence strengthen the base that ECMO combined with prone positioning is superior to high-PEEP ventilation in improving oxygenation, minimizing ventilator-induced injury, and enhancing overall survival in severe ARDS.

Clinical and Research Implications

These insights have major implications for critical care practice and physiotherapy-led interventions. In clinical settings, the proven superiority of ECMO combined with prone positioning embraces it as a frontline strategy for severe ARDS when conventional ventilation fails. Physiotherapists play an essential role in this process—ensuring safe implementation of prone

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Ahmed et al - 2026
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positioning, monitoring patient tolerance, preventing complications such as pressure injuries, and facilitating early mobilization even during ECMO support.

The results also stressed the need for physiotherapists to be central members of multidisciplinary ICU teams, integrating acute respiratory care with long-term functional recovery. Their expertise in respiratory mechanics, positioning, and rehabilitation uniquely positions them to optimize outcomes, reduce ventilator dependency, and accelerate the return to functional independence. Moreover, integrating early mobilization protocols during ECMO may further enhance post-ICU recovery, reduce deconditioning, and improve quality of life.

Strengths of the Meta-Analysis

A major strength of this meta-analysis lies in its inclusion of exclusively randomized controlled and clinical trials, thereby enhancing methodological rigor and internal validity. The analysis focuses on clinically meaningful outcomes—mortality and ventilator-free days—offering direct insights into patient prognosis and ICU management effectiveness. The use of systematic heterogeneity assessment and robust statistical methods further strengthens the credibility of the pooled results. By synthesizing data from multiple high-quality studies, this review provides a comprehensive evaluation of the synergistic impact of ECMO and prone positioning in ARDS management.

Limitations

Despite these strengths, several limitations must be acknowledged. The limited number of studies and small sample sizes may reduce the power to detect subtler yet clinically significant effects. Variations in study design, patient selection criteria, and ARDS severity could have introduced heterogeneity not fully accounted for in the pooled analysis.Furthermore, most ECMO trials were conducted in high-resource healthcare settings, potentially limiting generalizability to lower-resource environments. The potential for publication bias cannot be excluded, and long-term outcomes—such as post ICU functional recovery, neuropsychological health, and quality of life—were not consistently reported across included trials.

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Recommendations for Future Research

Future investigations should focus on large-scale, multicenter randomized controlled trials to confirm the comparative effectiveness of ECMO combined with prone positioning versus high-PEEP ventilation. Research should also aim to identify patient subgroups most likely to benefit from this integrated approach, accounting for variations in ARDS etiology and comorbidities. Further exploration into the optimal duration and timing of prone sessions during ECMO is warranted to refine treatment protocols. Additionally, studies evaluating cost-effectiveness and feasibility in resource-limited settings are crucial to ensure equitable global implementation. Long-term follow-up examining functional recovery, post-intensive care quality of life, and mental health outcomes will deepen our understanding of recovery trajectories. Finally, the role of physiotherapy-led interventions—both during ECMO and throughout post-ARDS rehabilitation—should be systematically examined to optimize multidisciplinary management and enhance survivorship outcomes.

CONCLUSION

Our analysis concludes that among evidence derived purely from randomized controlled trials, prone positioning demonstrates the most coherent and replicable benefit in improving outcomes for severe ARDS. High PEEP strategies, though physiologically supportive, should be carefully individualized rather than universally applied. ECMO in combination with prone positioning shows promise for the most critical subset of patients but should remain reserved for experienced centers capable of managing its complexities.In summation, our findings suggest that the optimal approach to ARDS management should integrate early prone positioning as a standard intervention, combined with ECMO serves as a valuable rescue option. High PEEP ventilation may complement these strategies when judiciously applied. Future RCTs with standardized protocols

Vol. 5 No. 2 (2026)

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Online ISSN | Print ISSN
3007-2387 | 3007-2379

Ahmed et al - 2026

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and longer follow-up are needed to further validate the combined ECMO–prone approach and determine its long-term impact on survival and ventilator-free days.

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