Journal of Clinical Anesthesia 110 (2026) 112120

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Potentially modifiable ventilatory factors contributing to outcome in patients with pulmonary and extrapulmonary ARDS — An individual patient data analysis

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https://doi.org/10.1016/j.jclinane.2025.112120
Received 23 September 2025; Received in revised form 24 November 2025; Accepted 27 December 2025
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HIGHLIGHTS

- ΔP was associated with 60-day mortality in pulmonary and extrapulmonary ARDS.
- The association between ΔP and 60-day mortality differed by ARDS subphenotypes.
- RR was associated with 60-day mortality, with no difference between ARDS subphenotypes.
- Tidal volume was not associated with 60-day mortality.

ARTICLE INFO

Keywords:
Acute respiratory distress syndrome
ARDS
Mechanical ventilation
Tidal volume
Respiratory rate
Positive end–expiratory pressure
Driving pressure
Mortality

ABSTRACT

Background: Previous studies have identified potentially modifiable factors associated with mortality from acute respiratory stress syndrome (ARDS), however these studies did not differentiate between underlying causes of ARDS. As the etiology of ARDS may influence patient outcomes, we aimed to identify potentially modifiable factors associated with 60-day mortality from pulmonary and extrapulmonary ARDS.
Methods: Secondary pooled analysis of six observational studies studies on mechanical ventilation in patients with pulmonary and extrapulmonary ARDS. The primary endpoint was mortality at day 60 after inclusion. Exploratory outcomes included length of stay in hospital and ICU, duration of ventilation and ventilator-free days at day 28.
Results: Out of 7934 patients with pulmonary or extrapulmonary ARDS, 3402 (43%) did not survive. Potentially modifiable factors associated with 60-day mortality included high driving pressure (ΔP) and high respiratory rate (RR). There was an interaction between etiology of ARDS and ΔP on 60-day mortality, with ΔP showing a stronger association in pulmonary ARDS compared with extrapulmonary ARDS ($p < 0.001$). In a sensitivity analysis excluding COVID-19 patients, RR was no longer associated with 60-day mortality, whereas ΔP remained associated. Tidal volume was not associated with 60-day mortality in either pulmonary or extrapulmonary ARDS. No interaction was found between ARDS etiology and RR or tidal volume on 60-day mortality.

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Conclusion: High ΔP and high RR were associated with 60-day mortality in patients with pulmonary and extrapulmonary ARDS receiving mechanical ventilation, with ΔP showing a stronger association in pulmonary ARDS compared with extrapulmonary ARDS.
Registration: The pooled database was registered at ClinicalTrials.gov (identifier NCT05650957).

1. Introduction

While ventilatory variables are associated with acute respiratory distress syndrome (ARDS) outcomes, including mortality and duration of ventilation [1–4], the role of the underlying cause of ARDS in these associations has been less well studied [5]. ARDS represents a major clinical challenge among critically ill patients. Despite advances in critical care, ARDS remains associated with high morbidity and mortality rates worldwide [6,7]. ARDS is recognized as a clinically and biologically heterogenous syndrome and can be triggered by various pulmonary and extrapulmonary conditions. Pulmonary ARDS results from direct lung injury, typically caused by conditions such as pneumonia, aspiration or lung contusion, where the lungs are directly affected leading to more localized damage. In contrast, extrapulmonary ARDS typically involves more diffuse lung injury secondary to systemic conditions such as sepsis, pancreatitis, trauma or blood transfusion [8]. It has been suggested that different subtypes of ARDS may respond differently to management strategies [9].

Recent perspectives in critical care research have highlighted the importance of identifying modifiable factors as a strategy to improve patient outcomes [10]. While certain factors that affect ARDS outcomes, such as age and comorbidities are non-modifiable [11], there are also potentially modifiable factors. In particular, ventilatory variables play an important role in influencing outcomes. High airway pressures and high respiratory rate (RR) have been associated with worse outcomes in patients with ARDS, as these factors can exacerbate lung injury [2,4,12–15].

Therefore, the aim of this analysis was to assess whether the association between ventilatory variables and outcomes differs between pulmonary and extrapulmonary ARDS. We hypothesized that the association between ventilatory variables and mortality may be modified by the underlying etiology of ARDS, using pooled individual data of ARDS patients in six observational invasive ventilation studies.

2. Methods

2.1. Study design

For this analysis, we used pooled individual data of patients with ARDS included in six observational studies on invasive ventilation. This database included 'ERICC – Epidemiology of Respiratory Insufficiency in Critical Care' [16], 'LUNG -SAFE - Large Observational Study to UNderstand the Global Impact of Severe Acute Respiratory FailurE' study [7], 'Practice of VENTilation in COVID-19 patients' (PRoVENT-COVID) [17], 'Epidemiology of COVID-19 patients in the ICU' (EPICCoV) [18], 'SATI-COVID-19 - Clinical Characteristics and Outcomes of Patients With COVID-19 on Mechanical Ventilation in Argentina: a Prospective, Multicenter Cohort Study' [19] and CIBERESUCICOVID - Personalized Risk and Prognosis Factors and Follow-up at One Year of the Patients Hospitalized in the Spanish Intensive Care Units Infected with COVID-19′ [20]. The studies included in the pooled database adhered to local legislation. The study protocols of the original studies were approved by Institutional Review Boards when applicable, and the need for individual patient informed consent was waived for all studies due to their observational designs. Details of all studies can be found in the original publications. The creation of the pooled database did not require additional ethical approval. This study was conducted and reported in accordance with the STROBE statement for observational studies [21].

2.2. Patients

The inclusion and exclusion criteria from the original studies are detailed in the original publications. For the current analysis, patients were eligible if they: (1) were >18 years old; (2) received invasive mechanical ventilation; and (3) met the Berlin definition of ARDS at the start of ventilation [6]. We limited the analysis to patients with evidence of absence of spontaneous ventilation.

2.3. Data collected

The pooled database included baseline characteristics such as sex, age, weight and height, Sequential Organ Failure Assessment (SOFA) score; comorbidities including heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, liver failure and active neoplasm, ARDS risk factor including COVID–19, pneumonia from another infection, aspiration, inhalation injury, contusion, vasculitis, sepsis, trauma, pancreatitis, burns, non-cardiac shock, drug overdose, transfusion-related acute lung injury (TRALI) or unknown; ventilation variables were collected shortly after study inclusion and included tidal volume (V_T), maximum airway pressure in pressure-controlled ventilation, plateau pressure (Plat) in volume-controlled ventilation, positive end–expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), RR and arterial blood gas analyses results; rescue strategies and therapy including prone positioning, neuromuscular blockade, recruitment maneuvers, extracorporeal membrane oxygenation (ECMO), continuous sedation, vasopressor use, tracheostomy, renal replacement therapy; and mortality at day 60.

2.4. Endpoint

The primary endpoint was 60-day mortality, defined as mortality at 60 days after study inclusion. Exploratory endpoints were length of stay in hospital and ICU, duration of ventilation and ventilator-free days at day 28 (VFD-28).

2.5. Definitions

ARDS severity was defined according to the Berlin definition of ARDS: mild (PaO_2/FiO_2 ratio 201–300 mmHg), moderate (PaO_2/FiO_2 ratio 101–200 mmHg), and severe (PaO_2/FiO_2 ratio ≤100 mmHg). Patients were categorized as having either pulmonary or extrapulmonary ARDS. Pulmonary ARDS was defined by the presence of one or more lung-related risk factors (e.g., COVID-19, pneumonia from another infection, aspiration, lung contusion) and extrapulmonary was defined by the presence of one or more extrapulmonary risk factors (e.g., sepsis, trauma, TRALI) [8]. Patients with both types of risk factors were considered as pulmonary. We stratified the study sample according to V_T (≤8 vs. >8 mL/kg PBW), PEEP (≤12 vs. >12 cmH_2O), ΔP (≤14 vs. >14 cmH_2O) and RR (≤20 vs. >20 breaths/min) as measured on the first day of ventilation at study inclusion. The V_T cut-off of 8 mL/kg PBW was selected based on its common use as a threshold for lung-protective ventilation [22]. The thresholds for PEEP, RR and ΔP were chosen based on previous studies [12,23]. Pmax was defined as maximum airway in pressure-controlled assist modes and Pplat in volume-controlled assist modes, when available [24]. Ventilator-free days at day 28 (VFD-28) were defined as the number of calendar days alive and free from invasive mechanical ventilation between intubation and day 28 after study inclusion.

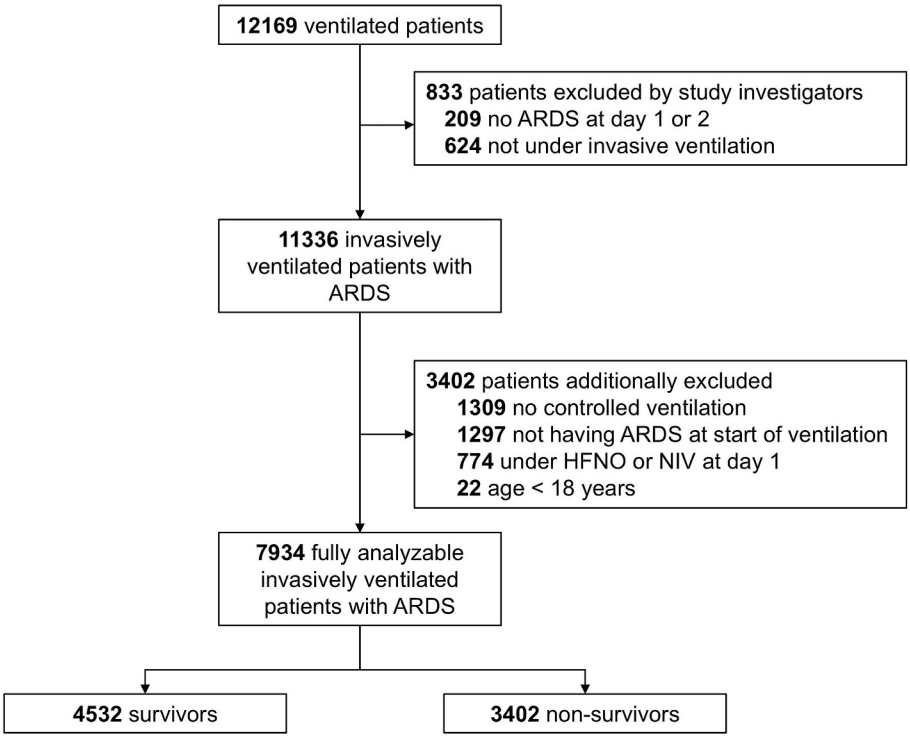

Fig. 1. CONSORT flow chart.

2.6. Calculations

V_T was expressed per predicted body weight (PBW). The PBW of male patients was calculated using the following formula: 50 + 0.91 (centimeters of height—152.4); in females: 45.5 + 0.91(centimeters of height—152.4). Driving pressure (ΔP) was calculated by subtracting PEEP from Pmax. Mechanical power (MP) was calculated using the following formula: 0.098 * V_T * RR * (Pmax−0.5 * ΔP). Minute ventilation was calculated as the product of V_T and RR. The ventilatory ratio was calculated using the formula [minute ventilation (mL/min) × $PaCO_2$ (mmHg)]/(predicted body weight × 100 × 37.5).

2.7. Sample analysis

No sample size calculation was performed for this analysis, the number of available patients served as the sample size.

2.8. Statistical analysis

Baseline demographics were compared using the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Continuous variables were expressed as medians and interquartile ranges and categorical variables were expressed as frequencies and proportions.

In all descriptive analyses, patients were stratified into survivors and non-survivors according to mortality at day 60. In univariate analyses, the impact of single ventilatory variables was assessed by estimating the relative risk of mortality at day 60 in pulmonary and extrapulmonary ARDS patients. Additionally, we used locally estimated scatterplot smoothing (LOESS) to visualize the relationship between the proportion of in-hospital deaths and respiratory variables including V_T per PBW, RR, PEEP and ΔP.

To identify whether V_T per PBW, PEEP, RR and ΔP were associated with mortality at day 60, a multivariable model was built with study treated as random effect. These ventilatory variables were included as continuous variables in the model. We adjusted for the following variables, based on clinical relevance: SOFA score, comorbidities including heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, liver failure, active neoplasm, PaO_2/FiO_2 and ARDS risk factor. To assess whether ARDS subphenotype modified the association between ventilatory variables and 60-day mortality, each model was repeated with an interaction term between ARDS subphenotype (pulmonary vs. extrapulmonary) and the ventilatory variable of interest (V_T per PBW; PEEP; RR and ΔP) on the outcome. Missing data in covariates were imputed by multiple imputation. Results are shown as odds ratios (ORs) with 95% confidence interval (CI). One sensitivity analysis was performed in which patients with COVID-19 were excluded.

We performed post hoc Kaplan-Meier survival analyses for 60-day survival, stratified by main causes of ARDS (COVID-19, pneumonia from other infections, pancreatitis, aspiration pneumonia, inhalation injury, lung contusion, sepsis, and trauma), and compared the curves using the log-rank test. Survival in pulmonary versus extrapulmonary ARDS was also analyzed. Additionally, a post hoc mediation analysis was conducted to explore whether the association between ΔP and mortality was driven by PEEP, Pmax, or the direct effect of ΔP itself. For each mediator, we fitted a linear mixed-effects model with Pmax or PEEP as the dependent variable, ΔP as the fixed effect, and a random intercept for study. We then fitted logistic regression models for 60-day mortality including ΔP and the mediator, adjusting for SOFA score, P/F ratio, age, sex, ARDS cause, RR, V_T per PBW, and including a random intercept for study. Mediation effects were estimated, with the average causal mediation effect (ACME) representing the part of the ΔP effect transmitted through PEEP or Pmax, the average direct effect (ADE) representing the remaining effect not explained by the mediator, and the total effect defined as the sum of these components.

All analyses were conducted in R v.4.2.1 (Vienna, Austria). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patients

A total of 12,169 patients were included in the database (Fig. 1). Main reasons for exclusion were not fulfilling the Berlin definition of ARDS at start of ventilation and lacking evidence of absence of spontaneous ventilation. For the current analysis, we included 7934 fully analyzable pulmonary or extrapulmonary ARDS patients. Among these, 3402 (43%) did not survive. Survivors were older and more often female (Table 1). The severity of illness, as indicated by the SOFA score, was lower in survivors. Comorbidities were less prevalent among survivors. Specifically, survivors had lower rates of heart failure, COPD, diabetes mellitus, chronic kidney disease, liver failure and active neoplasm. ARDS was more often classified as 'mild' or 'moderate' in survivors than in non-survivors. Regarding ARDS causes, COVID-19 was the most common cause of ARDS in both survivors and non-survivors. Trauma and drug overdose were more common in survivors, whereas vasculitis and non-cardiac shock were more prevalent in non-survivors.

3.2. Ventilation characteristics, adjunctive therapies and arterial blood gas results

The median V_T per PBW was slightly higher in survivors (Table 2). Survivors were ventilated with a higher PEEP and lower median RR, FiO_2 and ΔP compared to non-survivors. Prone positioning, neuromuscular blockade and recruitment maneuvers were used less often in survivors. In survivors, vasopressor use and renal replacement therapy were lower, while tracheostomy rates were higher. PaO_2/FiO_2, PaO_2 and pH were higher in patients who survived, while $PaCO_2$ levels were lower.

3.3. Factors associated with outcome from pulmonary and extrapulmonary ARDS

The unadjusted association of single ventilatory variables on 60-day mortality in pulmonary and extrapulmonary ARDS are shown in Fig. 2. Mortality was similar between patients receiving a low V_T (≤8 mL/kg PBW) and those receiving a high V_T (>8 mL/kg PBW) in both pulmonary and extrapulmonary ARDS. For both pulmonary and extrapulmonary ARDS, a high RR (>20 breaths/min) was associated with an increased risk of hospital mortality. In pulmonary ARDS patients, a high PEEP (>12 cmH_2O) was associated with decreased mortality. However, this was not seen in extrapulmonary ARDS patients. Regarding high ΔP (>14 cmH_2O), the 60 day-mortality risk was increased in pulmonary ARDS patients but not in extrapulmonary ARDS patients. In the LOESS plots, both an increase in driving pressure and RR show an association with 60-day mortality (eFigure 1). After multivariable adjustment, RR and ΔP were the only ventilatory variables associated with mortality at day 60 in the entire cohort (eTable 2). There was an interaction between ARDS subphenotype (pulmonary vs. extrapulmonary) and ΔP on 60-day mortality, with ΔP demonstrating a stronger association with mortality in pulmonary ARDS compared with extrapulmonary ARDS ($p < 0.001$).

Table 1
Baseline characteristics of patients with pulmonary and extrapulmonary ARDS.

	Survivors	Non-survivors	*p*-value
	N = 4532	*N* = 3402	
Age, years, median [IQR]	61 [51–69]	67 [58–74]	<0.001
Male sex n (%)	2948 (66.4)	2408 (68.9)	0.02
BMI, kg/m^2, median [IQR]	28.3 [25.1–32.4]	28.0 [25.0–31.9]	0.03
<18.5, n (%)	38 (0.9)	44 (1.4)	
18.5–24.9, n (%)	928 (22.6)	721 (22.7)	
25.0–29.9, n (%)	1481 (36.1)	1242 (39.1)	0.01
30.0–39.9, n (%)	1366 (33.3)	962 (30.3)	
≥40.0, n (%)	294 (7.2)	205 (6.5)	
SOFA score, median [IQR]	7 [4–9]	8 [5–10]	<0.001
Comorbidities, n (%)			
Heart failure	333 (7.5)	427 (12.2)	<0.001
COPD	487 (11.0)	498 (14.2)	<0.001
Diabetes mellitus	1046 (23.6)	1117 (32.0)	<0.001
Chronic kidney disease	235 (5.3)	323 (9.2)	<0.001
Liver failure	72 (1.6)	124 (3.5)	<0.001
Active neoplasm	170 (3.8)	254 (7.3)	<0.001
ARDS cause*, n (%)			
COVID-19	3310 (74.5)	2782 (79.6)	<0.001
Pneumonia from another infection	627 (14.1)	387 (11.1)	0.66
Sepsis	167 (3.8)	140 (4.0)	0.008
Aspiration	163 (3.6)	117 (3.3)	0.27
Non-cardiac shock	74 (1.7)	66 (1.9)	0.01
TRALI	39 (0.9)	31 (0.9)	0.39
Trauma	67 (1.5)	25 (0.7)	0.03
Inhalation injury	34 (0.8)	17 (0.5)	0.66
Pulmonary contusion	38 (0.9)	17 (0.5)	0.29
Pulmonary vasculitis	11 (0.2)	16 (0.5)	0.03
Pancreatitis	16 (0.4)	13 (0.4)	0.62
Drug overdose	29 (0.7)	7 (0.2)	0.03
Burns	5 (0.1)	1 (0.0)	0.49
Unknown	80 (1.8)	45 (1.3)	0.59
ARDS severity category, n (%)			<0.001
Mild	1023 (23.0)	647 (18.5)	
Moderate	2250 (50.7)	1732 (49.6)	
Severe	1168 (26.3)	1116 (31.9)	

Abbreviations: IQR: Interquartile Range; BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; COPD; Chronic Obstructive Pulmonary Disease: ARDS: Acute Respiratory Distress Syndrome; COVID-19: Coronavirus Disease 2019; TRALI: Transfusion-Related Acute Lung Injury.
* An individual patient may have multiple causes.

Table 2
Ventilation characteristics, adjunctive therapies, arterial blood gas results and outcomes.

	Survivors	Non-survivors	*p*-value
	N = 4532	N = 3402	
Ventilation characteristics			
Tidal volume, mL/kg/PBW, median [IQR]	6.8 [6.1–7.7]	6.6 [6.0–7.5]	<0.001
<6, n (%)	815 (21.0)	736 (24.4)	
6–8, n (%)	2333 (60.2)	1799 (59.6)	0.001
8–10, n (%)	601 (15.5)	404 (13.4)	
>10, n (%)	128 (3.3)	80 (2.6)	
PEEP, cm H_2O, median [IQR]	12 [10–14]	10 [8–14]	<0.001
≤5, n (%)	312 (7.0)	239 (6.8)	
6–8, n (%)	696 (15.7)	696 (19.9)	<0.001
8–10, n (%)	1036 (23.3)	866 (24.8)	
>10, n (%)	2397 (54.0)	1694 (48.5)	
Maximum airway pressure*, median [IQR]	25 [21–28]	25 [22–28]	0.05
Driving pressure, cm H_2O, median [IQR]	13 [10–16]	14 [11–17]	<0.001
Mechanical power, J/min, median [IQR]	16 [13−20]	16 [13–20]	0.13
FiO_2, median [IQR]	0.6 [0.5–0.9]	0.7 [0.5–1.0]	<0.001
Respiratory rate, breaths/min, median [IQR]	22 [18–25]	22 [19–26]	<0.001
Minute ventilation, L/min, median [IQR]	9.4 [8.0–10.9]	9.5 [8.0–11.1]	0.12
Ventilatory ratio, median [IQR]	1.7 [1.4–2.1]	1.8 [1.5–2.3]	<0.001
Adjunctive therapies			
Prone positioning, n/N (%)	2338/4426 (52.8)	2126/3478 (61.1)	<0.001
Use of neuromuscular blockade, n/N (%)	2348/3856 (60.9)	1680/2589 (64.9)	0.001
Recruitment maneuvers, n/N (%)	1264/3683 (34.3)	961/2516 (38.2)	0.002
ECMO, n/N (%)	112/4042 (2.8)	84/2798 (3.0)	0.62
Continuous sedation, n/N (%)	1661/1826 (91.0)	1208/1336 (90.4)	0.65
Vasopressor use, n/N (%)	3054/3850 (79.3)	2317/2590 (89.5)	<0.001
Tracheostomy, n/N (%)	1434/4423 (32.4)	764/3481 (21.9)	<0.001
Renal replacement therapy, n/N (%)	500/4431 (11.3)	1049/3492 (30.0)	<0.001
Arterial blood gas results			
pH, median [IQR]	7.36 [7.30–7.42]	7.32 [7.24–7.38]	<0.001
PaO_2, mm Hg, median [IQR]	83 [69–103]	82 [68–100]	0.02
$PaCO_2$, mm Hg, median [IQR]	43 [37–51]	45 [38–54]	<0.001
PaO_2/FiO_2, median [IQR]	142 [99–196]	130 [90–181]	<0.001
Outcomes			
Hospital length of stay, days, median [IQR]	33 [21–53]	17 [10–26]	<0.001
ICU length of stay, days, median [IQR]	18 [10−33]	13 [7–22]	<0.001
Duration of ventilation, days, median [IQR]	13 [7–25]	12 [6–21]	<0.001
Ventilator-free days at day 28, days, median [IQR]	12 [0−20]	0 [0–0]	<0.001

Abbreviations: PBW: Predicted Body Weight; PEEP: Positive End-Expiratory Pressure; FiO_2: Fraction of Inspired Oxygen; ECMO: Extracorporeal Membrane Oxygenation; PaO_2: Partial Arterial Oxygen Pressure; $PaCO_2$: Partial Arterial Carbon Dioxide Pressure; ICU: Intensive Care Unit.
* Pmax was defined as maximum airway pressure in pressure-controlled assist modes and plateau pressure in volume-controlled assist modes.

3.4. Other outcomes

Survivors had a longer stay in hospital and ICU, longer duration of ventilation and more ventilator-free days at day 28 compared to non-survivors (Table 2).

3.5. Pulmonary versus extrapulmonary ARDS

60-day survival differed across ARDS causes, with the highest fatality rates in COVID-19, pancreatitis and sepsis. There was no difference in survival between pulmonary and extrapulmonary ARDS (Fig. 3). There was an interaction between ARDS etiology (pulmonary vs. extrapulmonary) and ΔP on 60-day mortality, with ΔP showing a stronger association with 60-day mortality in pulmonary ARDS compared with extrapulmonary ARDS ($p < 0.001$).

3.6. Sensitivity analysis

In a sensitivity analysis excluding COVID-19 patients, ΔP remained significantly associated with 60-day mortality ($p < 0.001$) whereas the association with RR was no longer statistically significant ($p = 0.49$). An interaction between ARDS etiology and ΔP on 60-day mortality persisted ($p < 0.001$).

3.7. Post hoc mediation analysis of ΔP

For Pmax, the ACME was −0.070 (95% CI −0.091 to −0.049), and the ADE was 0.109 (95% CI 0.083–0.133), resulting in a total effect of 0.038 (95% CI 0.024–0.052). For PEEP, the ACME was 0.008 (95% CI 0.006–0.011), with an ADE of 0.030 (95% CI 0.015–0.044), resulting in a total effect of 0.038 (95% CI 0.023–0.052). When expressed as normalised proportions of the total effect, 37.5% was mediated through Pmax, 4.7% through PEEP, and 57.9% reflected the direct effect of ΔP (Fig. 4).

4. Discussion

The findings of this secondary pooled analysis of six observational studies of ventilation in ARDS patients can be summarized as follows. (1) ΔP was associated with 60-day mortality in pulmonary and extrapulmonary ARDS. (2) The association between ΔP and 60-day mortality differed by ARDS subphenotype, with a stronger effect observed in pulmonary ARDS compared with extrapulmonary ARDS. (3) RR was associated with 60-day mortality in the overall cohort, and this

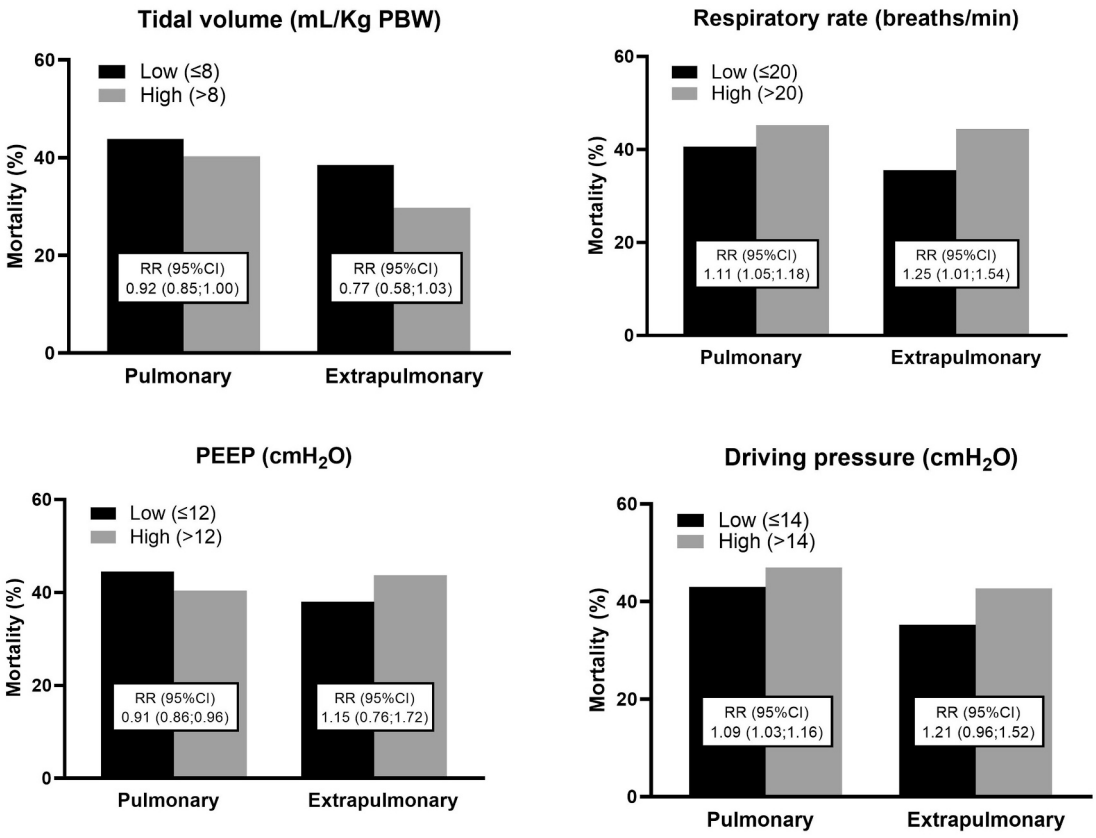

Fig. 2. Unadjusted relative risks of 60-day mortality in pulmonary and extrapulmonary ARDS patients.

association did not differ between ARDS subphenotypes. (4) V_T was not associated with 60-day mortality in either pulmonary or extrapulmonary ARDS.

Our study has several strengths. First, we used data from six large observational studies on ventilation management and outcomes of invasively ventilated ARDS patients from pulmonary and extrapulmonary causes. The included studies were conducted in different hospitals across various countries, which increases the generalizability of our findings. Second, the datasets were comprehensive, capturing baseline and demographic data, detailed ventilator settings and variables, as well as key clinical outcomes. Third, we had an analysis plan before opening of the database that was strictly followed.

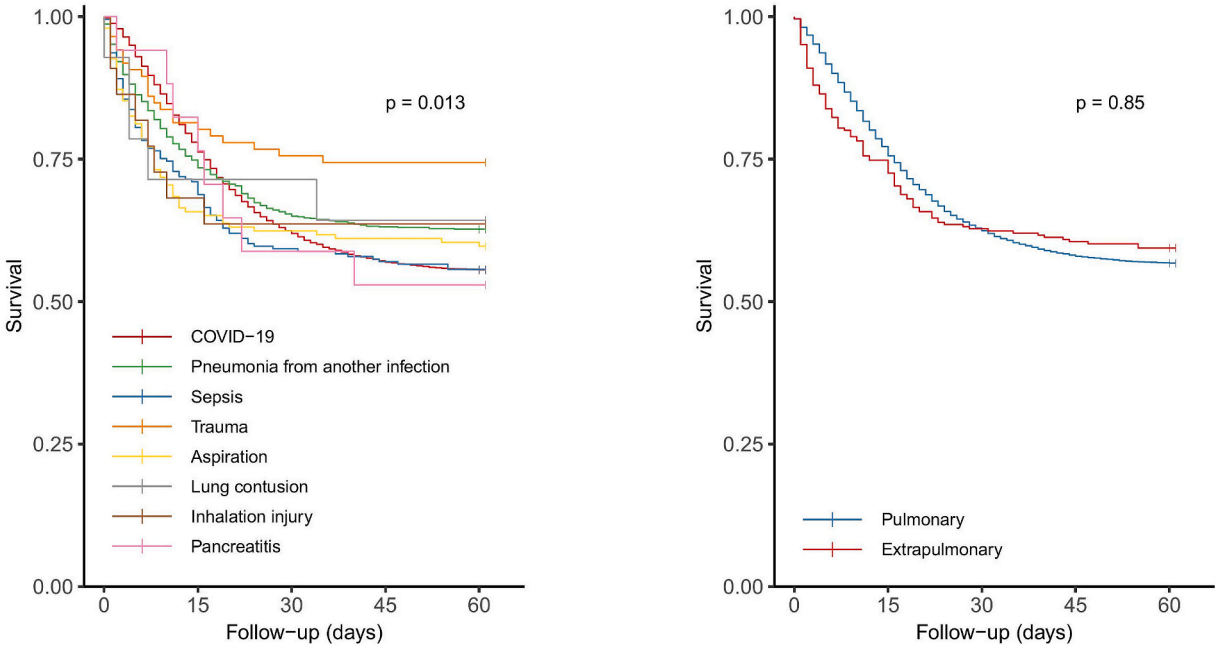

Fig. 3. Kaplan-Meier survival curves for 60-day mortality in ARDS patients.

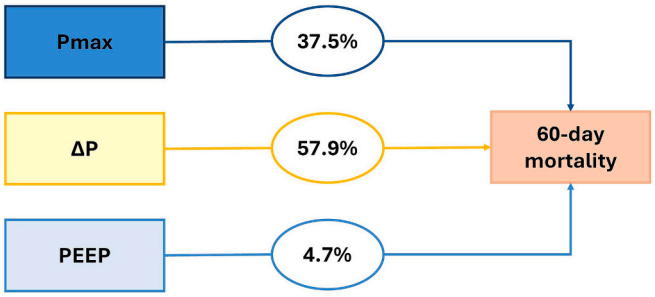

Fig. 4. Mediation analysis of the relationship between driving pressure ΔP and 60-day mortality.

Consistent with previous studies, we found that high RR and ΔP were associated with worse outcomes in ARDS patients [2,4,12–15]. Costa et al. demonstrated that both ΔP and RR were associated with mortality in ARDS patients and the effect of ΔP was not modified by the RR. Indicating that both the stress during each breath, reflected by ΔP, and how frequently this stress occurs, reflected by the RR, are important variables factors in ARDS outcome [4]. While lung-protective ventilation traditionally involves limiting V_T [22], increasing the RR is often necessary to maintain adequate gas exchange. However, several studies have shown that a high RR increases the MP delivered to the lungs, making them more susceptible to ventilator-induced lung injury [25–27]. In a recent post-hoc analysis of three randomized clinical trials in critically ill patients without ARDS, an increase in MP was mainly driven by a rise in peak inspiratory pressure (Ppeak) and RR. Additionally, both RR and Ppeak were associated with mortality [28]. Prior studies have also demonstrated that MP itself is associated with mortality in ARDS patients [4,29–31]. Since both high ΔP and RR contribute to MP [29], this could explain the observed associations between these ventilatory variables and 60-day mortality in our cohort. Although we did not directly assess MP in this study, the relationship between ΔP, RR, and mortality suggests that optimizing these ventilatory variables aimed at reducing MP may represent a modifiable target in future ARDS ventilation studies. However, in our sensitivity analysis excluding COVID-19 patients, the association between RR and 60-day mortality disappeared. Since patients were not spontaneously breathing in our cohort, this suggests that the RR more likely reflected clinician-set ventilator settings, which were determined according to institutional protocols, V_T targets, and the patient's condition, rather than representing a truly modifiable factor.

To examine whether the association between ΔP and 60-day mortality was driven by PEEP, Pmax, or by the direct effect of ΔP itself, we conducted a post hoc mediation analysis. The results indicated that the mortality associated with ΔP was explained predominantly by its direct effect (57.9%), with Pmax accounting for 37.5% of the total effect and PEEP contributing for 4.7%. This aligns with previous studies demonstrating that ΔP is a stronger predictor of outcome than its individual components [2,31]. Taken together, these findings underscore the importance of ΔP in relation to clinical outcomes.

Our analysis did not find an association between V_T and 60-day mortality. V_T was within the lung-protective range in the majority of both survivors and non-survivors and only a small proportion received higher V_T. This may explain why V_T was not associated with 60-day mortality in our analysis, as most patients were ventilated within the recommended lung-protective ventilation range [22]. However, recent studies indicate that a uniform low V_T strategy may not always be beneficial, particularly in patients with preserved lung compliance [32].

We found that survivors were ventilated with higher PEEP levels than non-survivors, with median values of 12 cmH_2O in survivors and 10 cmH_2O in non-survivors. This is in line with a previous study where high PEEP was associated with better outcomes in COVID-ARDS patients [33]. While the difference in PEEP in our cohort is modest, survivors were generally healthier and therefore possibly more hemodynamically stable, and might have better able to tolerate higher PEEP levels. Studies have suggested that ARDS subphenotypes may respond differently to PEEP, highlighting the need for an individualized approach in PEEP settings to improve outcomes [34,35].

With regard to differences between pulmonary and extrapulmonary ARDS, there was an interaction between ΔP and ARDS subphenotype on 60-day mortality, with ΔP showing a stronger association in pulmonary ARDS compared with extrapulmonary ARDS. This finding may be explained by the differing pathophysiology of ARDS subphenotypes. Pulmonary ARDS is typically characterized by more focal, consolidated, and less recruitable lung injury with predominant alveolar epithelial injury and inflammation, making the lungs potentially more susceptible to additional damage from higher airway pressures. In contrast, in extrapulmonary ARDS there is an increase in endothelial dysfunction and systemic inflammation, resulting in a more diffuse injury pattern, potentially making the lung tissue less sensitive to ventilatory pressures and recruitment strategies [8,34,36]. No interaction was found between ARDS subphenotype and RR or V_T. Our findings regarding differences in survival across individual ARDS causes are consistent with previous studies. In particular, causes such as sepsis, and pancreatitis have been associated with higher mortality rates, whereas trauma-related ARDS is associated with more favorable outcomes [5,37]. However, when these risk factors were grouped into pulmonary versus extrapulmonary categories, overall survival did not differ between these two subphenotypes in our cohort. Prior work has also reported no mortality differences between pulmonary and extrapulmonary ARDS [38]. These findings suggest that such a classification may not adequately reflect the underlying prognostic differences among ARDS risk factors and could overlook clinically relevant heterogeneity [8,39].

Our analysis has several limitations. First, since the database was derived from observational studies, our findings can only imply associations rather than causation. Second, the willingness of certain hospitals in the original studies to share data may have led to selection bias, resulting in the inclusion of ICUs with a specific interest in invasive ventilation and ARDS management. Third, while we classified ventilator-related variables as potentially modifiable, it is important to acknowledge that non-modifiable factors, such as disease severity, also partly influence ventilator settings. Fourth, there is a temporal gap between the cohorts, with the majority of included patients from the COVID-19 pandemic, which may have influenced clinical decisions. Nevertheless, previous studies have shown mortality not to be different between ARDS patients from COVID-19 and non-COVID-19 ARDS [40,41]. Fifth, we used maximum airway pressure in pressure-controlled assist mode to calculate ΔP as a surrogate for the plateau pressure, although this was only done when there was no proof of spontaneous breathing efforts to minimize erroneous measurements. However, we cannot rule out the possibility that some patients with spontaneous breathing were included, which may have led to an underestimation of driving pressure and could affect the ΔP-PEEP interplay. Last, the thresholds used for ventilatory variables were based on previously published studies and may not represent true physiological cut-offs. The relationship between ventilatory variables and outcomes likely follows a continuous scale rather than discrete cut-off values. Consequently, ventilatory variables were included as continuous variables in our multivariate analysis and showed similar results.

In conclusion, the present secondary pooled analysis from six large prospective observational studies on mechanical ventilation, underscores that ΔP is a potentially modifiable factor associated with 60-day mortality in patients with pulmonary and extrapulmonary ARDS. The interaction between ARDS subphenotype ΔP and highlights the importance of a personalized approach in mechanical ventilation. While RR was also associated with mortality in the overall cohort, it should be noted that RR may primarily reflect disease severity and ventilatory demand rather than representing a truly modifiable factor. By optimizing ventilatory variables, ventilation management can be better

tailored to individual patient needs, ultimately improving outcomes in ARDS patients.

Accountability and author declaration

The authors confirm that the manuscript represents valid work, that all authors have contributed to the research and writing, and that they agree to be held accountable for the accuracy and integrity of the entire work.

Author contribution

All authors have approved the final manuscript and are responsible for the integrity and accuracy of the work.

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Funding

This analysis was performed without additional funding.

Declaration of competing interest

The authors declare that they have no conflicts of interest related to this work. The manuscript has not been published previously and is not under consideration elsewhere.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.112120.

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