The Impact of Different Etiologies of Acute Respiratory Distress Syndrome on the Prognostic Value of Driving Pressure: A Postprint of a Prospective Cohort Study

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Abstract

Background: In patients with acute respiratory distress syndrome (ARDS) receiving mechanical ventilation, excessive airway driving pressure (DP) is an independent risk factor for the risk of all-cause mortality. Although it has been well-documented that ARDS of different etiologies (pulmonary and extrapulmonary) exhibits significant differences in pathophysiology, it remains unclear whether different etiologies influence the prognostic value of DP in ARDS. Objective: This study aims to determine whether the association between DP and the 90-day risk of all-cause mortality in ARDS is influenced by different etiologies. Methods: A total of 172 patients with ARDS over 18 years of age who met the Berlin definition criteria and were admitted to the Intensive Care Unit of Nanjing Gaochun People' s Hospital from December 2021 to October 2023 were selected. Based on clinical data, patients were divided into pulmonary ARDS (n=82) or extrapulmonary ARDS (n=90). On the first day of enrollment, age, sex, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, oxygenation index (PaO2/FiO2), and respiratory mechanics parameters including DP, airway plateau pressure (Pplat), and respiratory system compliance (Crs) were recorded. The study endpoint was 90-day all-cause mortality, and patients were divided into a death group and a survival group based on outcomes at the end of follow-up. Cox proportional hazards regression models were used to evaluate the interaction between DP and etiology on the 90-day mortality risk. Sensitivity analyses included the use of the inverse probability of treatment weighting (IPTW) method based on propensity scores to control for the influence of potential confounding factors. Results: A total of 172 ARDS patients were included, with a mean age of (57$±$18) years; 63 patients died by the end of follow-up, resulting in a mortality rate of 36.3%. The SOFA score, APACHE II

score, DP, and Pplat were higher in the death group than in the survival group, while PaO2/FiO2 and Crs were lower than in the survival group (P<0.05). After adjusting for age, SOFA score, and PaO2/FiO2, excessive DP (HR=1.134, 95%CI=1.067~1.206, P<0.001) was independently associated with the 90-day risk of all-cause mortality. Interaction analysis showed that the difference in the association between DP and 90-day all-cause mortality risk across different ARDS etiology populations was statistically significant (P=0.04). In patients with pulmonary ARDS (n=82), both decreased PaO2/FiO2 (P=0.04) and excessive DP (HR=1.253, 95%CI=1.146~1.370, P<0.01) were independent risk factors for 90-day all-cause mortality risk. In contrast, in patients with extrapulmonary ARDS (n=90), a high SOFA score (P<0.01) was the only independent risk factor for all-cause mortality risk, and DP (HR=1.083, 95%CI=0.957~1.227, P=0.21) was no longer a risk factor for 90-day all-cause mortality. The results of the weighted Cox analysis after IPTW were highly consistent with the primary analysis results (there was a significant interaction between different ARDS etiologies and excessive DP on mortality risk, P=0.009). Conclusion: Although DP is a strong predictor of all-cause mortality risk in ARDS, it is influenced by different etiologies; in extrapulmonary ARDS, it is not significantly associated with poor prognosis. This suggests that the formulation of mechanical ventilation strategies should incorporate the etiological characteristics of ARDS to implement individualized ventilation management.

Full Text

Preamble

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Abstract

In the context of the ongoing transformation of the global healthcare landscape, the discipline of general practice (family medicine) has emerged as a cornerstone of sustainable healthcare systems. This paper examines the current state, challenges, and future trajectories of general practice in China. By analyzing the integration of machine learning and deep learning technologies within primary care settings, we explore how digital health interventions can enhance diagnostic accuracy and patient management. Our findings suggest that while significant progress has been made in policy support and workforce development, further efforts are required to standardize clinical protocols and improve the quality of community-based medical services.

Introduction

General practice serves as the first point of contact within the healthcare system, providing comprehensive, continuous, and personalized care to individuals and families. In China, the rapid aging of the population and the increasing prevalence of chronic diseases have placed unprecedented pressure on tertiary

hospitals. Consequently, the development of a robust general practice framework is essential for achieving the goals of "Healthy China 2030." This transition necessitates not only a shift in clinical focus but also the adoption of advanced computational tools to assist general practitioners (GPs) in complex decision-making processes.

The Role of Artificial Intelligence in General Practice

The integration of artificial intelligence (AI) into primary care offers transformative potential for disease screening and chronic disease management. Machine learning algorithms can analyze vast amounts of electronic health record (EHR) data to identify high-risk patients before the onset of severe symptoms.

1.1 Diagnostic Support Systems Deep learning models, particularly convolutional neural networks (CNNs), have demonstrated remarkable efficacy in interpreting medical imaging and dermatological signs within community clinics. By providing GPs with real-time diagnostic suggestions, these tools help bridge the expertise gap between primary care providers and specialists. For instance, the application of $\mathcal{F}$ as a predictive function for patient outcomes can be modeled as:

$$\hat{y} = \sigma(\mathbf{W}x + b)$$

where x represents the patient' s clinical features and $\hat{y}$ denotes the probability of a specific diagnosis.

[Figure 1: see original paper]

1.2 Chronic Disease Management Effective management of hypertension and diabetes requires continuous monitoring and personalized intervention strategies. Machine learning frameworks allow for the clustering of patient phenotypes, enabling more tailored treatment plans. As shown in , the implementation of AI-driven management protocols has led to a measurable improvement in blood glucose control across several pilot community

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The Impact of Different Etiologies on the Prognostic Value of Driving Pressure in Acute Respiratory Distress Syndrome: A Prospective Cohort Study

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Abstract

Objective: To investigate the impact of different primary etiologies on the prognostic value of driving pressure (ΔP) in patients with acute respiratory distress syndrome (ARDS).

Methods: A prospective cohort study was conducted on ARDS patients admitted to the Intensive Care Unit (ICU). Patients were categorized into pulmonary ARDS (ARDSp) and extrapulmonary ARDS (ARDSexp) groups based on the primary cause of lung injury. Respiratory mechanics parameters, including ΔP, respiratory system compliance (C_{rs}), and plateau pressure (P_{plat}), were recorded within 24 hours of ARDS diagnosis. The primary endpoint was 28-day mortality. Receiver operating characteristic (ROC) curves and Cox proportional hazards models were used to evaluate the prognostic value of ΔP across different etiologies.

Results: A total of [Number] patients were included in the final analysis. In the overall cohort, ΔP was significantly higher in non-survivors than in survivors. Subgroup analysis revealed that while ΔP remained a strong predictor of mortality in the ARDSp group, its prognostic accuracy was significantly altered in the ARDSexp group. In ARDSexp patients, the influence of chest wall compliance and intra-abdominal pressure frequently confounded the relationship between ΔP and lung strain. After adjusting for potential confounders, ΔP was independently associated with 28-day mortality in ARDSp patients (Hazard Ratio [HR] = [Value], 95% CI [Value]), but showed a weaker correlation in the ARDSexp cohort.

Conclusion: The prognostic value of driving pressure in ARDS is influenced by the underlying etiology. While ΔP is a reliable predictor of outcomes in pulmonary ARDS, clinicians should exercise caution when interpreting ΔP in extrapulmonary ARDS, where extrapulmonary factors may influence respiratory mechanics.

Introduction

Acute Respiratory Distress Syndrome (ARDS) remains a significant cause of morbidity and mortality in intensive care units worldwide. Despite advances in lung-protective ventilation strategies, such as low tidal volume (V_t) and optimized positive end-expiratory pressure (PEEP), mortality

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背景

In patients with acute respiratory distress syndrome (ARDS) receiving mechanical ventilation, excessively high airway driving pressure (DP) is an independent

risk factor for all-cause mortality.

Although it is well-established that pulmonary (pARDS) and extrapulmonary (expARDS) ARDS exhibit significant pathophysiological differences, it remains unclear whether these distinct etiologies influence the prognostic value of DP. Objective: This study aims to determine whether the association between DP and the risk of 90-day all-cause mortality is modified by the underlying etiology of ARDS. Methods:

This study aimed to determine the association between DP and 90-day mortality in ARDS.

A total of 172 patients over 18 years of age who met the Berlin definition for ARDS and were admitted to the Intensive Care Unit of Nanjing Gaochun People' s Hospital between December 2021 and October 2023 were selected.

Based on clinical data, patients were categorized into either pulmonary ARDS (n=82) or extrapulmonary ARDS (n=90). On the first day of enrollment, data were recorded for age, sex, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, oxygenation index (PaO_2/FiO_2), and respiratory mechanics parameters, including DP, plateau pressure (P_{plat}), and respiratory system compliance (C_{rs}). The primary endpoint was 90-day all-cause mortality. At the end of the follow-up period, patients were divided into survival and non-survival groups based on their outcomes. Cox proportional hazards regression models were used to evaluate the interaction between DP and etiology regarding the 90-day mortality risk. Sensitivity analyses, including inverse probability of treatment weighting (IPTW) based on propensity scores, were performed to control for potential confounding factors. Results:

Among the 172 included ARDS patients, the mean age was (57 ± 18) years. By the end of the follow-up, 63 patients had died, resulting in a mortality rate of 36.3%.

The non-survival group exhibited significantly higher SOFA scores, APACHE II scores, DP, and P_{plat}, as well as lower PaO_2/FiO_2 and C_{rs} compared to the survival group ($P < 0.05$). After adjusting for age, SOFA score, and PaO_2/FiO_2, high DP ($HR = 1.134$, $95\%CI = 1.067$–1.206, $P < 0.001$) remained independently associated with the risk of 90-day all-cause mortality.

Interaction analysis revealed that the association between DP and 90-day all-cause mortality risk differed significantly across different ARDS etiologies ($P = 0.04$). In patients with pulmonary ARDS (n=82), both decreased PaO_2/FiO_2 ($P = 0.04$) and high DP ($HR = 1.253$, $95\%CI = 1.146$–1.370, $P < 0.01$) were independent risk factors for 90-day mortality. Conversely, in patients with extrapulmonary ARDS (n=90), a high SOFA score ($P < 0.01$) was the only independent risk factor for all-cause mortality, while DP ($HR = 1.083$, $95\%CI = 0.957$–1.227, $P = 0.21$) was no longer a significant risk factor. The results of the weighted Cox analysis after IPTW were highly consistent with the

primary analysis (a significant interaction existed between ARDS etiology and high DP regarding mortality risk, $P = 0.009$). Conclusion:

While DP is a strong predictor of all-cause mortality in ARDS, its prognostic value is influenced by the underlying etiology; specifically, it is not significantly associated with poor outcomes in extrapulmonary ARDS.

These findings suggest that the formulation of mechanical ventilation strategies should incorporate the etiological characteristics of ARDS to implement individualized ventilatory management. [Keywords]

Respiratory Distress Syndrome; Airway Driving Pressure; Precision Medicine; Prognosis; Prospective Study

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【Abstract】

Background

Airway driving pressure (DP)is a recognized independent predictor of mortality in

Impact of Acute Respiratory Distress Syndrome Etiology on the Prognostic Value of Driving Pressure: A Prospective Cohort Study

Abstract

Background Acute respiratory distress syndrome (ARDS) is a common clinical syndrome characterized by acute respiratory failure, carrying a high mortality rate. Driving pressure (ΔP) has been identified as a critical predictor of mortality in ARDS patients. However, ARDS is a heterogeneous condition with diverse etiologies, and it remains unclear whether the prognostic value of ΔP varies across different primary causes.

Objective This study aims to investigate the impact of ARDS etiology—specifically pulmonary ARDS (ARDSp) versus extrapulmonary ARDS (ARDSexp)—on the prognostic value of driving pressure for predicting clinical outcomes.

Methods A prospective cohort study was conducted involving patients diagnosed with ARDS according to the Berlin definition. Patients were categorized into ARDSp and ARDSexp groups based on the primary insult. Respiratory mechanics, including ΔP, tidal volume (V_T), and positive end-expiratory pressure (PEEP), were recorded within the first 24 hours of mechanical ventilation. The primary endpoint was 28-day mortality. Multivariate Cox regression and Receiver Operating Characteristic (ROC) curves were utilized to evaluate the association between ΔP and mortality across different etiologies.

Results A total of [N] patients were enrolled in the study. Preliminary analysis indicates that while ΔP serves as a robust predictor of mortality in the overall cohort, its predictive accuracy and optimal threshold may differ significantly between ARDSp and ARDSexp groups. In ARDSp, ΔP was more closely associated with lung morphology and recruitment potential compared to the ARDSexp group.

Conclusion The etiology of ARDS significantly influences the prognostic utility of driving pressure. Clinicians should consider the underlying cause of ARDS when utilizing ΔP to guide ventilator settings and assess patient prognosis. Further research is needed to refine lung-protective ventilation strategies based on these etiological differences.

Keywords: Acute respiratory distress syndrome; Driving pressure; Etiology; Prognosis; Mechanical ventilation; Prospective cohort study

Introduction

Acute respiratory distress syndrome (ARDS) remains a major challenge in intensive care medicine, characterized by non-cardiogenic pulmonary edema, decreased lung compliance, and severe hypoxemia. Despite advances in supportive care, the mortality rate for ARDS remains high, ranging from 35% to

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mechanically ventilated patients with acute respiratory distress syndrome (ARDS). Although pathophysiological differences between pulmonary and extrapulmonary ARDS are well-established, it remains unclear whether the prognostic value of DP varies by ARDS etiology. Objective This prospective cohort study evaluated whether ARDS etiology modifies the association between DP and 90day all-cause mortality. Methods

We enrolled 172 mechanically ventilated ARDS patients aged>18 years who met the Berlin

definition at Nanjing Gaochun People's hospital from December 2021 to October 2023. Patients were classified as having pulmonary ARDS (n=82) or extrapul-

monary ARDS (n=90)based on clinical features. We collected data on Day 1, including Sequential Organ Failure Assessment (SOFA)score, Acute Physiology and Chronic Health Evaluation II (APACHE II) Score, the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2), and respiratory mechanics including DP, plateau pressures (Pplat), and respiratory system compliance (Crs). The primary outcome was 90-day all-cause mortality. Cox proportional hazards regression models were employed to assess the interaction between DP and ARDS etiology (pulmonary versus extrapulmonary) on 90-day mortality. Sensitivity analyses using inverse probability of treatment weighting (IPTW) based on propensity scores were conducted to account for potential confounders. Results

Among the 172 ARDS patients mean age (57$±$18) years, 63(36.3%)

died during follow-up. Non-survivors had higher SOFA scores, APACHE II scores, DP, Pplat, and lower PaO2/FiO2 ratios and

Crs than survivors(all P<0.05). The association between DP and 90-day mortality (HR=1.134, 95%CI =1.067-1.206, P<0.001) varied by ARDS etiology (P=0.04 for interaction) after adjustment for age, PaO2/FiO2 ratio, and SOFA score. In pulmonary ARDS (n=82), both PaO2/FiO2(P=0.04) and DP (HR=1.253, 95%CI =1.146-1.370, P<0.01) were associated with 90-day mortality.

Conversely, in extrapulmonary ARDS (n=90), DP (HR=1.083, 95%CI=0.957-1.227, P=0.21) was not associated with mortality, while only the SOFA score remained an independent risk factor(P<0.01). These findings were consistent in the IPTW analysis (P=0.009 for interaction between ARDS etiology and DP on mortality). Conclusion While DP is a strong predictor of mortality in ARDS overall, its prognostic significance differs by etiology. Specifically, in extrapulmonary ARDS, elevated DP is not significantly associated with poor prognosis, suggesting that ventilation strategies should be aligned with the underlying ARDS etiology. 【Key words】 Respiratory distress syndrome; Airway driving pressure; Precision therapy; Prognosis; Prospective studies

Acute Respiratory Distress Syndrome (ARDS) is a syndrome of acute respiratory failure caused by various non-cardiogenic intra- and extra-pulmonary factors, with mortality rates as high as 30% to 40%. Mechanical ventilation guided by lung-protective strategies is the primary treatment for ARDS, aiming to reduce ventilator-induced lung injury (VILI) and thereby improve patient prognosis [**?**]. Recent studies have indicated that the fundamental reason for the improved outcomes associated with lung-protective strategies—centered on low tidal volume (V_t)—may be lower airway driving pressure (DP) rather than V_t itself [**?**]. Subsequent research has confirmed this finding [**?**], suggesting that DP can serve as a basis for predicting VILI risk and adjusting mechanical ventilation parameters [**?**].

This result can be explained physiologically: transpulmonary driving pressure (DP_{tp}) is the primary factor determining lung stress, strain, and ultimately VILI.

Under most clinical conditions, DP is significantly and positively correlated with DP_{tp}.

Recent studies have demonstrated that ARDS exhibits high heterogeneity, making the identification of different phenotypes for individualized treatment both necessary and urgent [**?**]. Clinical research focusing on the etiology of ARDS suggests that pulmonary ARDS (pARDS) and extrapulmonary ARDS (expARDS) differ significantly in terms of pathophysiology [**?**]. First, compared to pARDS, expARDS is often characterized by higher chest wall elastance (E_{cw}). Since E_{cw} can significantly influence DP levels without being directly related to VILI risk, DP may not accurately reflect VILI risk or patient prognosis in cases of extrapulmonary ARDS.

Furthermore, patients with extrapulmonary ARDS often present with severe extrapulmonary organ damage in addition to lung injury. Consequently, the primary factor determining prognosis in these patients is the severity of extrapulmonary organ dysfunction, while the correlation between the degree of lung injury and patient outcome may become secondary [**?**]. Based on these two points, our research group

hypothesized that the association between excessively high DP and the risk of all-cause mortality may be weaker or even non-existent in patients with extrapulmonary ARDS compared to those with pulmonary ARDS.

Currently, there is a lack of research regarding the relationship between ARDS etiology, DP, and clinical prognosis. The primary objective of this study is to further determine the association between DP and the risk of all-cause mortality, and to investigate whether this association is influenced by different ARDS etiologies (pulmonary versus extrapulmonary ARDS).

Materials and Methods

Patients over 18 years of age who met the Berlin Definition criteria for ARDS [**?**] and were admitted to the ICU of Nanjing Gaochun People' s Hospital between December 2021 and October 2023 were selected. This study was formally approved by the Ethics Committee of Nanjing Gaochun People' s Hospital (Ethics Approval No.: 2021-171-01). Three ICU physicians not involved in the study categorized the patients into pulmonary ARDS or extrapulmonary ARDS based on clinical data. ARDS was classified as pulmonary if the primary cause was pneumonia or aspiration of gastric contents; it was classified as extrapulmonary if the cause was extrapulmonary sepsis, trauma, pancreatitis, or other similar factors [**?**].

1.1.1 纳入标准

(1) Met the Berlin Definition diagnostic criteria [**?**]. (2) Expected duration of mechanical ventilation via endotracheal intubation exceeded 48 hours. (3) Age was greater than 18 years. (4) Received assist/control mechanical ventilation. (5) Provided signed informed consent.

1.1.2 排除标准

(1) The duration of invasive mechanical ventilation via endotracheal intubation was less than 48 hours. (2)

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pregnancy, bullous lung disease, pneumothorax, and mediastinal emphysema. (3) Patients undergoing extracorporeal membrane oxygenation (ECMO) therapy. (4) Severe hemodynamic instability (defined as a >30% increase in the dose of vasopressors within 6 hours prior to enrollment).

1.2.1 治疗

Upon enrollment, patients received routine sedation and, when necessary, neuromuscular blockade. Mechanical ventilation was administered using volume-assist/control mode. All patients were ventilated according to the lung-protective ventilation strategy recommended by the ARDS Network (ARDSnet) [**?**]. The tidal volume (V_t) was set at 6–8 mL/kg of predicted body weight. Positive end-expiratory pressure (PEEP) was determined by the attending physician based on the PEEP-fraction of inspired oxygen (FiO_2) table, with the goal of maintaining an airway plateau pressure (P_{plat}) of less than 30 cmH_2O. If P_{plat} exceeded 35 cmH_2O or if the attending physician deemed it clinically necessary, an esophageal balloon was placed [**?**] to measure esophageal pressure (P_{es}), thereby ensuring that the patient' s transpulmonary driving pressure (ΔP_{tp}) remained below 15 cmH_2O.

1.2.2 参数测量

Patient age, sex, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were recorded. Respiratory parameters were monitored every 6 hours. During measurements, it was ensured that patients had no spontaneous breathing. A constant flow rate of 50–60 L/min was employed with a 0.3 s end-inspiratory pause, while other mechanical ventilation parameters remained unchanged.

The primary parameters included arterial partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), total PEEP ($PEEP_{tot}$), respiratory rate (RR), tidal volume (V_t), plateau pressure (P_{plat}), driving pressure (DP), and respiratory system compliance (C_{rs}). P_{plat} was obtained via end-inspiratory occlusion, while $PEEP_{tot}$ was measured via end-expiratory occlusion. DP was calculated as the difference between P_{plat} and $PEEP_{tot}$. C_{rs} was derived using the ratio V_t/DP. All respiratory parameters represent the mean values recorded within the first 24 hours of enrollment. Based on previous research [**?**], patients were divided into a low

DP group (< 15 cmH_2O) and a high DP group (≥ 15 cmH_2O) using a threshold of 15 cmH_2O.

1.2.3 随访及结局事件

Follow-up was conducted starting from the time of enrollment using various methods, including telephone interviews, home visits, outpatient follow-ups, medical record reviews, and readmission monitoring. The follow-up period was set at 90 days, with the primary study endpoint defined as all-cause mortality or the completion of the 90-day follow-up period. Based on clinical outcomes at the end of the follow-up, patients were categorized into either a mortality group or a survival group.

The frequency of follow-up was structured as follows: during the ICU stay, patients were monitored once daily; after being transferred to a general ward, follow-up occurred once every three days. Following hospital discharge, follow-ups were conducted on the 7th, 14th, and 28th days post-discharge. Subsequently, follow-ups were performed every 30 days until the 90-day endpoint was reached. If a scheduled follow-up node calculated from the discharge date exceeded the 90th day post-enrollment, the 90th day was strictly used as the final study endpoint.

1.3 样本量计算

The primary objective of this study is to investigate the impact of driving pressure (DP) on the prognosis of patients with Acute Respiratory Distress Syndrome (ARDS) using a Cox proportional hazards regression model. In this model, DP serves as the independent variable, while the 90-day mortality outcome and survival time are defined as the dependent variables. Other covariates included in the analysis are age, Sequential Organ Failure Assessment (SOFA) score, PaO_2/FiO_2 ratio, and the etiology of ARDS (pulmonary vs. extrapulmonary). This study utilizes an internal pilot design [**?**], with the first 30 enrolled patients selected as the pilot sample.

Based on previous research [**?**, **?**] and data from the pilot study, the regression coefficient for DP was set at 0.12 with a standard deviation of 3.5. Furthermore, the coefficient of determination (R^2) for the regression of DP on the other covariates

was determined to be 0.06, with an estimated 90-day mortality rate of 40%. Assuming a significance level (α) of 0.05 and a statistical power ($1-\beta$) of 0.90, a minimum of 159 subjects is required for the study.

Accounting for a potential 5% dropout rate, the minimum required sample size is 167 subjects. Since the inclusion and exclusion criteria, as well as the diagnostic and treatment protocols for the pilot study patients, were identical to those of the subsequent participants, they were all included in the final analysis cohort [**?**].

1.4 统计学分析

Statistical analyses were performed using R software (version 4.3.2). The Shapiro-Wilk test was employed to assess the normality of continuous data. Normally distributed continuous variables are expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between two groups were conducted using the independent samples t-test. Non-normally distributed continuous variables are presented as median and interquartile range ($M(P_{25}, P_{75})$), with group comparisons performed using the rank-sum test. Categorical data are expressed as relative numbers, and intergroup comparisons were conducted using the χ^2 test. Univariate and multivariate Cox proportional hazards regression models were used to explore the association between the exposure factor (high driving pressure, DP) and the outcome variable (90-day all-cause mortality risk); results are reported as hazard ratios (HR) and 95% confidence intervals (95% CI). Multicollinearity among included variables was assessed using the variance inflation factor (VIF) method, and highly correlated variables were removed to adjust for confounding factors and further analyze the independent correlation between DP and mortality. The proportional hazards assumption was verified using Schoenfeld residuals.

In this study, interaction terms between different ARDS etiologies (1 = pulmonary ARDS, 2 = extrapulmonary ARDS) and other variables were introduced into the model to verify interaction effects. Subsequently, Cox proportional hazards regression analyses were repeated within stratified subgroups.

Survival curves were plotted using the Kaplan-Meier method, and differences in cumulative survival rates between groups were compared using the log-rank test.

To verify the robustness of the primary analysis results and further control for confounding bias arising from differences in baseline characteristics between the high and low DP groups, several sensitivity analyses were performed. First, the Inverse Probability of Treatment Weighting (IPTW) method based on propensity scores was used to balance the distribution of other covariates between the two groups, with a standardized mean difference (SMD) < 0.1 set as the criterion for covariate balance. After obtaining the weights, a weighted Cox proportional hazards model was used to re-evaluate the association between high DP and 90-day all-cause mortality risk. This was supplemented by IPTW-weighted Kaplan-Meier curves and weighted log-rank tests for visualization and intergroup comparison. Finally, three independent subgroup analyses were conducted by sequentially excluding elderly patients (age > 75 years), patients with severe ARDS ($PaO_2/FiO_2 < 100$ mmHg), and ARDS patients whose etiology was classified as "other." Multivariate Cox proportional hazards regression models were refitted within each subgroup population. A P-value < 0.05 was considered statistically significant.

结果

Baseline Characteristics and 90-day Prognosis of the Study Population

A total of 172 patients with ARDS were included in this study, with a mean age of 57 ± 18 years. At the end of the follow-up period, 63 patients had died, resulting in a mortality rate of 36.6%. Among the 172 patients, 82 cases were classified as pulmonary ARDS (ARDSp), with etiologies including pneumonia (n=61) and aspiration pneumonia (n=21). The remaining 90 cases were classified as extrapulmonary ARDS (ARDSexp), with etiologies consisting of extrapulmonary sepsis (n=52), trauma (n=14), acute pancreatitis (n=4), and other causes (n=20).

The comparison of baseline characteristics between the non-survivor and survivor groups revealed that the non-survivor group

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The SOFA score, driving pressure (DP), and plateau pressure (P_{plat}) were significantly higher in the non-survivor group compared to the survivor group, while the oxygenation index (PaO_2/FiO_2) and static respiratory system compliance (C_{rs}) were significantly lower ($P < 0.05$). There were no statistically significant differences between the two groups regarding gender, etiology of ARDS, age, partial pressure of carbon dioxide ($PaCO_2$), tidal volume (V_t), or total positive end-expiratory pressure ($PEEP_{tot}$) ($P > 0.05$), as shown in .

2.2 ARDS 患者 90 d 全因死亡风险的的单因素 Cox 比

Cox Proportional Hazards Regression Analysis

A univariate Cox proportional hazards regression model was employed to analyze the risk factors for 90-day all-cause mortality in patients with ARDS. In this model, 90-day all-cause mortality (assigned as: No = 0, Yes = 1) served as the dependent variable. The independent variables consisted of parameters from Table 1 that demonstrated statistically significant differences, including the etiology of ARDS (assigned as: pulmonary ARDS = 1, extrapulmonary ARDS = 2), while all other independent variables were entered using their actual measured values.

The results, detailed in , indicate that increased age, higher SOFA scores, decreased PaO_2/FiO_2 ratios, elevated driving pressure (DP), and elevated plateau pressure (P_{plat}) are all significant risk factors for 90-day all-cause mortality in ARDS patients ($P < 0.05$). Furthermore, both DP and P_{plat} exhibited significant interactions with the etiology of ARDS (pulmonary vs. extrapulmonary) ($P < 0.05$).

2.3 ARDS 患者 90 d 全因死亡风险的多因素 Cox 比例

Risk Regression Model Analysis

Multicollinearity was assessed using the Variance Inflation Factor (VIF) to determine the severity of collinearity among the included variables. The results indicated that static compliance (Crs) exhibited significant multicollinearity (VIF = 7.62); consequently, Crs was excluded from the multivariable Cox proportional hazards regression models.

Plateau pressure (Pplat) demonstrated moderate collinearity (VIF = 4.6), with a correlation coefficient between Pplat and driving pressure (DP) of $r = 0.71$ ($P < 0.001$). Accordingly, this study constructed separate multivariable Cox proportional hazards regression models using DP and Pplat as independent variables. In all models, the dependent variable was 90-day all-cause mortality in ARDS patients (coded as: No = 0, Yes = 1). Model 1 utilized DP as a continuous independent variable (measured value); Model 2 utilized DP as a dichotomous variable (Low DP = 0, High DP = 1); and Model 3 utilized Pplat as a continuous independent variable (measured value). Other covariates included in all models were those identified as statistically significant in the univariate analysis, as shown in . The optimal model was selected based on the lowest Akaike Information Criterion (AIC). [Figure 1: see original paper] presents the Schoenfeld residual plots for each variable in Model 1. The global Schoenfeld test yielded $P = 0.277$, and the residuals for each variable showed no correlation with time, confirming that the covariates in this model satisfied the proportional hazards assumption.

The results indicated that in Model 1, after adjusting for age, SOFA score, and PaO_2/FiO_2, a higher DP (HR = 1.134, 95% CI = 1.067-1.206, $P < 0.001$) served as an independent risk factor for 90-day all-cause mortality. Interaction analysis further demonstrated that the association between DP and the risk of 90-day all-cause mortality remained consistent across different ARDS etiologies (coded as: pulmonary ARDS = 1, extrapulmonary ARDS = 2).

Gender [n (%)]

Crs (x ml/cmH2O)

(mean ± SD, years)

SOFA score (mean ± SD, points); PaO_2/FiO_2 (mean ± SD, mmHg); $PaCO_2$ (mean ± SD, mmHg)

83 (76.15)

26 (23.85)

54$±$16

11.28$±$2.32

144$±$48

51 (80.95)

12 (19.05)

60$±$20

12.32$±$2.25

128$±$34

t (χ^2) value

0.29a

<0.01

<0.01

cmH2O)

Pplat (x cmH2O)

APACHE II score ($\bar{x} \pm s$, points)

Etiology of ARDS [n (%)]

Ideal body weight ($\bar{x} \pm s$, mL/kg); Total PEEP ($PEEP_{tot}$) (cmH_2O)

46 (42.20)

63 (57.80)

6.54$±$0.97

36 (57.14)

27 (42.86)

6.67$±$0.70

The $\chi^2(t)$ value

2.99a

<0.01

<0.01

<0.01

Note: C_{rs} = respiratory system compliance; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2/FiO_2 = oxygenation index; SOFA score = Sequential Organ Failure Assessment score; V_t = tidal volume; $PEEP_{tot}$ = total positive end-expiratory pressure; DP = airway driving pressure; P_{plat} = airway plateau pressure; a denotes the χ^2 value.

HR (95%CI)

P-value for the interaction with ARDS etiology

1.016 (1.001~1.031)

The Sequential Organ Failure Assessment (SOFA) score is a clinical tool used to track a patient' s status during their stay in an intensive care unit (ICU) to determine the extent of a person' s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Scoring System Overview

The SOFA score is calculated by evaluating the following physiological parameters:

1. **Respiratory System**: Measured by the PaO_2/FiO_2 ratio (mmHg).
2. **Nervous System**: Measured by the Glasgow Coma Scale (GCS).
3. **Cardiovascular System**: Measured by mean arterial pressure or the administration of vasopressors (e.g., dopamine, epinephrine, norepinephrine).
4. **Liver Function**: Measured by the concentration of bilirubin (mg/dL or $\mu mol/L$).
5. **Coagulation**: Measured by the platelet count ($\times 10^3/mm^3$).
6. **Renal Function**: Measured by the concentration of creatinine (mg/dL or $\mu mol/L$) or urine output.

Clinical Significance

The SOFA score allows for both individual and serial evaluations of organ dysfunction. A higher SOFA score is associated with an increased probability of mortality. In the context of Sepsis-3 definitions, an acute change in total SOFA score ≥ 2 points secondary to infection is used to identify patients with sepsis.

Advantages and Limitations

The primary advantage of the SOFA score is its simplicity and its ability to provide a dynamic assessment of a patient' s condition over time, rather than a single static prediction at admission. However, it requires laboratory data that may not be immediately available in all clinical settings. In such cases, the "quick SOFA" (qSOFA) may be used as a rapid bedside screening tool, though it is less comprehensive than the full SOFA score.

<0.01

1.178 (1.055~1.315)

PaO2/FiO2

0.993 (0.987~0.999)

0.945 (0.905~0.988)

<0.01

1.127 (1.055~1.205)

Pplat

<0.01

1.134 (1.051~1.226)

<0.01

Note: B = regression coefficient, CI = confidence interval, Crs = respiratory system compliance, HR = hazard ratio, PaO2/FiO2 = oxygenation index, Pplat = plateau pressure, SE = standard error, SOFA score = Sequential Organ Failure Assessment score, Vt = tidal volume, DP = driving pressure.

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Standardized Schoenfeld residuals

P=0.11

Time (days after enrollment)

Scaled Schoenfeld residuals

Scaled Schoenfeld residuals

P=0.72

P=0.69

P=0.08

Time (days after enrollment)

Time (days after enrollment)

Scaled Schoenfeld residuals

P=0.74

Scaled Schoenfeld Residuals

Scaled Schoenfeld Residuals

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Time (days after enrollment)

P=0.07

Time (days after enrollment)

Note: A is the Schoenfeld residual plot for airway driving pressure; B is for ARDS etiology; C is for age; D is for the SOFA score; E is for the oxygenation index (PaO_2/FiO_2); and F is for the interaction term between airway driving pressure and ARDS etiology. The red scatter points represent the standardized Schoenfeld residuals at each event time point, while the solid black

line represents the locally weighted scatterplot smoothing (LOESS) curve. The dashed lines represent the ±2 standard error range around the fit. As shown, the smoothing curves fluctuate steadily around the zero line throughout the follow-up period. The proportional hazards assumption tests for all variables were not statistically significant ($P > 0.05$), indicating that all variables satisfy the proportional hazards assumption.

The difference between populations (assigned as: pulmonary ARDS = 1, extrapulmonary ARDS = 2) was statistically significant ($P = 0.04$). The results of Model 2 showed that after adjusting for age, SOFA score, and PaO_2/FiO_2, patients with a driving pressure (DP) $\geq$ 15 cmH_2O had an increased risk of 90-day all-cause mortality compared to those with DP $<$ 15 cmH_2O, with a Hazard Ratio (HR) and 95% Confidence Interval (CI) of 1.724 (1.007–2.950). Further interaction analysis revealed that the association between DP $\geq$ 15 cmH_2O and the risk of 90-day all-cause mortality differed significantly across different ARDS etiologies ($P < 0.01$). Model 3 results indicated that after adjusting for age, SOFA score, and PaO_2/FiO_2, high plateau pressure (P_{plat}) was an independent risk factor for 90-day all-cause mortality (HR = 1.123, 95% CI = 1.043–1.210, $P < 0.01$). Interaction analysis showed that the association between P_{plat} and 90-day all-cause mortality

differed significantly across different ARDS etiologies (assigned as: pulmonary ARDS = 1, extrapulmonary ARDS = 2) ($P < 0.01$); see . Because Model 1 yielded a lower Akaike Information Criterion (AIC) value, it was ultimately selected as the preferred final model.

2.4 不同 ARDS 病因与 DP 对 90 d 全因死亡风险影响

Subgroup Analysis: Interaction Effects

The impact of Driving Pressure (DP) on the risk of 90-day all-cause mortality varied across different ARDS etiologies (pulmonary vs. extrapulmonary ARDS). To further investigate this, a subgroup analysis based on ARDS etiology was performed using the fully adjusted Model 1. In patients with pulmonary ARDS ($n = 82$), a lower PaO_2/FiO_2 ratio was observed···

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Model 1 (Including DP)

In this section, we present the formulation of Model 1, which incorporates Differential Privacy (DP) mechanisms to ensure data confidentiality during the learning process. By integrating DP, we aim to provide rigorous privacy guarantees while maintaining the utility of the statistical model.

The core objective of this model is to minimize the objective function under the constraint of a predefined privacy budget ϵ. We consider a dataset D and a ran-

domized algorithm $\mathcal{M}$ that satisfies (ϵ, δ)-differential privacy if for all adjacent datasets D and D', and all measurable sets $S \subseteq \text{Range}(\mathcal{M})$:

$$P[\mathcal{M}(D) \in S] \leq e^{\epsilon} P[\mathcal{M}(D') \in S] + \delta$$

To achieve this in the context of our optimization problem, we apply the Gaussian mechanism to the gradients during the training phase. Specifically, for a given loss function $\mathcal{L}(\theta; D)$, the updated parameter θ_{t+1} is computed as:

$$\theta_{t+1} = \theta_t - \eta \left(\nabla \mathcal{L}(\theta_t; D) + \mathcal{N}(0, \sigma^2 I) \right)$$

where η represents the learning rate and σ is determined by the sensitivity of the gradient and the desired privacy parameters (ϵ, δ). This approach ensures that the contribution of any single data point to the final model parameters remains bounded, thereby protecting individual privacy.

[Figure 1: see original paper]

Furthermore, we analyze the trade-off between the privacy budget and the model' s convergence rate. As shown in , increasing the noise level σ to satisfy stricter privacy requirements (smaller ϵ) typically results in a higher steady-state error. Model 1 addresses this by employing an adaptive clipping strategy for the gradients, which limits the influence of outliers and reduces the amount of noise required to achieve a specific privacy level.

In summary, Model 1 provides a robust framework for machine learning tasks where data sensitivity is a primary concern. By mathematically bounding the information leakage, we ensure that the resulting model can be deployed in privacy-sensitive environments without compromising the integrity of the underlying data subjects.

HR (95%CI)

Model 2 (DP as a dichotomous variable) P-interaction value

1.021 (1.004~1.038) 0.014

HR (95%CI)

Model 3 (including P_{plat})

P interaction value

1.020 (1.004~1.037) 0.02

SOFA score 1.202 (1.075–1.343), $p = 0.001$

PaO2/FiO2

0.992 (0.985~0.998) 0.009

.DP/Pplat.

1.134 (1.067~1.206) <0.001

Interaction Value a

In the context of complex system analysis and machine learning interpretability, the interaction value a serves as a critical metric for quantifying the synergistic effects between multiple input variables. Unlike individual feature importance scores, which measure the isolated contribution of a single variable, the interaction value a captures how the presence or state of one variable influences the impact of another on the model' s output. This is particularly vital in high-dimensional datasets where non-linear relationships and dependencies are prevalent.

Mathematically, the interaction value is often derived from game-theoretic frameworks, such as Shapley values, or through second-order partial derivatives in gradient-based models. For a pair of variables x_i and x_j, the interaction value a_{ij} represents the additional predictive power gained by considering both variables simultaneously, beyond what would be expected from their individual contributions alone. If $a_{ij} > 0$, the variables exhibit a positive synergy; conversely, if $a_{ij} < 0$, they exhibit a redundant or competitive relationship.

Understanding these interaction values is essential for ensuring model robustness and scientific validity. In fields such as bioinformatics or structural engineering, the interaction value a can reveal underlying physical or biological mechanisms that are not apparent through univariate analysis. By mapping these interactions, researchers can construct more transparent "white-box" models that reflect the true complexity of the phenomena being studied, moving beyond simple additive approximations.

1.018 (1.001~1.034)

1.205 (1.078~1.346) <0.01

1.232 (1.101，1.378) <0.01

0.992 (0.986~0.998) 0.01

0.997 (0.990~1.003)

HR (95%CI)

1.724 (1.007~2.950) 0.04

1.123 (1.043~1.210) <0.01

<0.01

<0.01

Reduced FiO_2 ($P = 0.04$) and high driving pressure (DP) ($P < 0.01$) were identified as independent risk factors for 90-day all-cause mortality. However, among patients with extrapulmonary ARDS ($n = 90$), a high SOFA score ($P <$

0.01) was the sole independent risk factor for poor prognosis; in this subgroup, DP ($P = 0.21$) was no longer independently associated with 90-day all-cause mortality, as shown in and [Figure 2: see original paper].

As illustrated in [Figure 3: see original paper], for patients with pulmonary ARDS ([Figure 3A: see original paper]), the high DP group exhibited an increased risk of 90-day all-cause mortality compared to the low DP group after adjusting for age, SOFA score, and PaO_2/FiO_2 ($HR = 5.40$, $95\%CI = 2.57 - 11.33$, $P < 0.001$). Conversely, in patients with extrapulmonary ARDS ([Figure 3B: see original paper]), a $DP \geq 15\ cmH_2O$ showed no significant independent correlation with 90-day all-cause mortality ($P = 0.368$).

Etiology of ARDS: (a) Pulmonary ARDS; (b) Extrapulmonary ARDS.

Log AH R (95%CI)

Note: AIC = Akaike Information Criterion; CI = Confidence Interval; DP = Airway Driving Pressure; P_{plat} = Airway Plateau Pressure; High DP = DP $\geq$ 15 cmH_2O; Low DP = DP $<$ 15 cmH_2O; HR = Hazard Ratio; PaO_2/FiO_2 = Oxygenation Index; SOFA Score = Sequential Organ Failure Assessment Score. The symbol a denotes the P-value for the interaction between each variable and the etiology of ARDS (pulmonary ARDS vs. extrapulmonary ARDS).

driving pressure: A subgroup analysis HR (95%CI)

1.014 (0.996~1.033)

Sequential Organ Failure Assessment (SOFA) Score

The Sequential Organ Failure Assessment (SOFA) score is a clinical tool used to track a patient' s status during their stay in an intensive care unit (ICU) to determine the extent of a person' s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Clinical Significance

The SOFA score is widely utilized in critical care medicine to quantify the severity of organ dysfunction. Unlike one-time mortality prediction models, the SOFA score is designed to be calculated serially, allowing clinicians to monitor the progression of a patient' s condition over time. A rising SOFA score during the first 24 to 48 hours of ICU admission is often associated with a higher risk of mortality.

Scoring Components

The total SOFA score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction. The assessment includes the following parameters:

- **Respiratory System**: Evaluated using the PaO_2/FiO_2 ratio (the ratio of arterial oxygen tension to fraction of inspired oxygen).
- **Nervous System**: Assessed via the Glasgow Coma Scale (GCS).
- **Cardiovascular System**: Determined by the mean arterial pressure (MAP) or the requirement for vasopressors (such as dopamine, epinephrine, or norepinephrine) to maintain blood pressure.
- **Liver Function**: Measured by the serum bilirubin level.
- **Coagulation System**: Assessed by the platelet count.
- **Renal Function**: Evaluated based on serum creatinine levels or urine output.

Applications in Research and Practice

In addition to its role in individual patient monitoring, the SOFA score is a critical component in the clinical definition of sepsis. According to the Sepsis-3 guidelines, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, which can be clinically identified by an acute change in total SOFA score of ≥ 2 points consequent to the infection.

In the context of machine learning and deep learning research within the medical field, the SOFA score often serves as a key feature or a target label for predictive modeling. Researchers frequently use the SOFA score to validate the performance of algorithms designed to predict patient deterioration, mortality, or the onset of sepsis in the ICU.

1.115 (0.973~1.278)

PaO2/FiO2

0.990 (0.980~1.000)

1.253 (1.146~1.370)

<0.01

Pulmonary ARDS (n=82)

Extrapulmonary ARDS (n=90)

1.027 (0.996~1.059)

The Sequential Organ Failure Assessment (SOFA) score is a clinical tool used to track a patient' s status during their stay in an intensive care unit (ICU) to determine the extent of a person' s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Scoring System Overview

The SOFA score is calculated by evaluating the following physiological parameters:

1. **Respiratory System**: Measured by the PaO_2/FiO_2 ratio (mmHg).
2. **Nervous System**: Evaluated using the Glasgow Coma Scale (GCS).
3. **Cardiovascular System**: Assessed by the mean arterial pressure (MAP) or the administration of vasopressors (e.g., dopamine, epinephrine, or norepinephrine).
4. **Liver Function**: Determined by the bilirubin level (mg/dL or $\mu mol/L$).
5. **Coagulation**: Measured by the platelet count ($\times 10^3/mm^3$).
6. **Renal Function**: Evaluated by creatinine levels (mg/dL or $\mu mol/L$) or urine output.

Clinical Significance

The SOFA score is widely utilized in clinical research and practice for several reasons:

- **Mortality Prediction**: An initial SOFA score or an increase in the score during the first 24 to 48 hours of ICU admission is highly correlated with increased mortality rates.
- **Sepsis Diagnosis**: According to the Sepsis-3 definitions, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This organ dysfunction can be represented by an acute change in total SOFA score ≥ 2 points consequent to the infection.
- **Dynamic Monitoring**: Unlike static scoring systems, the SOFA score allows for repeated assessments over time, providing a dynamic profile of the patient' s clinical trajectory.

Limitations

While the SOFA score is a robust predictor of clinical outcomes, it is important to note that it was designed to describe a sequence of complications in the critically ill, rather than to predict the outcome of a specific disease. Furthermore, the use of therapeutic interventions (such as vasopressors or mechanical ventilation) can influence the score, potentially confounding the assessment of the underlying organ dysfunction.

1.277 (1.067~1.528)

<0.01

PaO2/FiO2

0.995 (0.986~1.004)

1.083 (0.957~1.227)

Note: ARDS = acute respiratory distress syndrome; CI = confidence interval; DP = driving pressure; HR = hazard ratio; PaO_2/FiO_2 = oxygenation index; SOFA score = Sequential Organ Failure Assessment score.

2.5 Kaplan-Meier Survival Analysis of Patients with Pulmonary and Extrapulmonary ARDS

Kaplan-Meier survival curves were plotted for patients with pulmonary and extrapulmonary ARDS to compare differences in cumulative survival rates across different DP groups during the follow-up period. In the pulmonary ARDS group [Figure 4: see original paper]A, the 90-day cumulative survival probability for patients in the high DP group (DP $\geq$ 15 cmH_2O) was significantly lower than that of the low DP group (DP $<$ 15 cmH_2O) ($P < 0.001$).

[Figure 4: see original paper] Note: ARDS = acute respiratory distress syndrome; DP = driving pressure; Log AHR = adjusted log hazard ratio for 90-day mortality. The hazard ratio was adjusted for age, SOFA score, and oxygenation index. Interaction analysis using multivariate Cox regression revealed that the association between DP and the risk of 90-day all-cause mortality differed significantly between ARDS etiologies (pulmonary vs. extrapulmonary ARDS) ($P = 0.04$). The figure illustrates the association with the log adjusted hazard ratio (Log AHR) for 90-day all-cause mortality, stratified by ARDS etiology.

In contrast, within the extrapulmonary ARDS group [Figure 4: see original paper]B, there was no statistically significant difference in the 90-day survival probability between the high DP group and the low DP group ($P = 0.6$).

2.6 敏感性分析

First, Inverse Probability of Treatment Weighting (IPTW) based on propensity scores was employed to balance the baseline characteristics between the exposure group (DP $\geq$ 15 cmH_2O) and the non-exposure group (DP $<$ 15 cmH_2O). As demonstrated, a satisfactory balance was achieved between the groups. Within this balanced sample, the weighted Cox model confirmed that high DP and the etiology of ARDS were significantly associated with the risk of 90-day all-cause mortality.

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(N=50)

A 1.00

reference <0.001***

(N=32) (2.57~11.33)

The Sequential Organ Failure Assessment (SOFA) score is a clinical tool used to track a patient' s status during their stay in an intensive care unit (ICU) to determine the extent of a person' s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Scoring System Overview

The SOFA scoring system assigns points from 0 (normal) to 4 (high degree of dysfunction) for each of the six organ systems. The total score ranges from 0 to 24. A higher SOFA score is associated with an increased probability of mortality.

Clinical Application and Significance

The SOFA score is widely utilized in clinical research and practice for several key reasons:

1. **Sepsis Diagnosis:** According to the Sepsis-3 definitions, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This organ dysfunction can be represented by an increase in the total SOFA score of ≥ 2 points consequent to the infection.
2. **Dynamic Monitoring:** Unlike static scoring systems, the SOFA score is designed to be calculated daily. This allows clinicians to monitor the progression of organ dysfunction over time. An increase in the SOFA score during the first 24 to 48 hours of ICU admission is a strong predictor of mortality.
3. **Prognostic Value:** The initial SOFA score and the highest SOFA score recorded during an ICU stay are both significantly correlated with patient outcomes. Specifically, a total SOFA score of more than 15 is often associated with a mortality rate exceeding 80%.

Limitations

While the SOFA score is a robust tool, it has certain limitations. It requires laboratory data (such as bilirubin, creatinine, and platelet counts) which may not be immediately available in emergency or resource-limited settings. Furthermore, the neurological component relies on the Glasgow Coma Scale (GCS), which can be difficult to assess accurately in patients who are sedated or intubated.

In summary, the SOFA score remains a cornerstone of critical care medicine, providing a standardized method for quantifying organ dysfunction and assisting in the risk stratification of critically ill patients.

(N=82) (0.98~1.30)

PaO2/FiO2

(N=82) (0.98~1.00)

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Log-rank P<0.000 1

0.023*

Days after enrollment

Days after enrollment

(N=82) (0.99~1.02)

Events: 36; Global p-vale (Log-Rank): 2.056e-06 AIC: 275.2; Concordance Index: 0.77

HR (95%CI)

Strata

reference

(N=20)

(N=70) (0.27~1.61)

The Sequential Organ Failure Assessment (SOFA) score is a clinical tool used to track a patient' s status during their stay in an intensive care unit (ICU) to determine the extent of a person' s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Scoring System Overview

The SOFA score is calculated by evaluating the following physiological parameters:

1. **Respiratory System**: Measured by the PaO_2/FiO_2 ratio (mmHg).
2. **Nervous System**: Measured by the Glasgow Coma Scale (GCS).
3. **Cardiovascular System**: Measured by mean arterial pressure or the administration of vasopressors (e.g., dopamine, epinephrine, norepinephrine).
4. **Liver Function**: Measured by the concentration of bilirubin (mg/dL or $\mu mol/L$).
5. **Coagulation**: Measured by the platelet count ($\times 10^3/mm^3$).
6. **Renal Function**: Measured by the concentration of creatinine (mg/dL or $\mu mol/L$) or urine output.

Clinical Significance

The SOFA score allows for both individual and serial evaluations of organ dysfunction. A higher SOFA score is associated with an increased probability of mortality. In the context of Sepsis-3 definitions, an acute change in total SOFA score ≥ 2 points consequent to infection is used to identify patients with sepsis.

(Commonly used to display the SOFA score calculation criteria)

Applications in Research

In machine learning and clinical informatics research, the SOFA score often serves as a gold-standard label or a critical feature for predicting patient outcomes. Researchers frequently utilize the SOFA score to: - Benchmarking the performance of predictive models for sepsis. - Stratify patient risk levels in retrospective cohort studies. - Monitor the progression of multi-organ dysfunction syndrome (MODS) in real-time using electronic health record (EHR) data.

(N=90) (1.08~1.56)

0.006**

Log-rank P=0.6

Days after enrollment

Days after enrollment

PaO2/FiO2

(N=90)

(N=90)

(0.99~1.00)

(1.00~1.05)

Events: 27; Global p-vale (Log-Rank): 0.03144 AIC: 231.69; Concordance Index: 0.69

Note: ARDS = acute respiratory distress syndrome; DP = airway driving pressure; CI = confidence interval; HR = hazard ratio; PaO_2/FiO_2 = oxygenation index; SOFA score = Sequential Organ Failure Assessment score. High DP is defined as DP $\geq$ 15 cmH_2O, and low DP is defined as DP $<$ 15 cmH_2O.

Forest plot illustrating the association between high driving pressure (DP $\geq$ 15 cmH_2O) and the risk of 90-day all-cause mortality in (A) Pulmonary and (B) Extrapulmonary Acute Respiratory Distress Syndrome.

A significant interaction was observed between the ARDS phenotype and the impact of driving pressure on mortality risk ($P = 0.009$). High DP was identified as an independent risk factor for 90-day all-cause mortality in patients with pulmonary ARDS (HR = 1.27, 95%CI = 1.15–1.40, $P < 0.001$), whereas no significant association was found in patients with extrapulmonary ARDS, as shown in [Figure 6: see original paper]. This finding is consistent with the results of the primary analysis. The corresponding IPTW-weighted Kaplan-Meier survival curves ([Figure 7: see original paper]) visually demonstrate these associations: in pulmonary ARDS···

Strata

Strata

Note: ARDS = Acute Respiratory Distress Syndrome; DP = Airway Driving Pressure. Kaplan–Meier survival curves comparing the high DP group (DP $\geq$ 15 cmH_2O) and the low DP group (DP $<$ 15 cmH_2O), stratified by etiology: (A) Pulmonary ARDS, (B) Extrapulmonary ARDS.

In pulmonary ARDS, the 90-day cumulative survival rate was significantly lower in the high DP group compared to the low DP group ($P < 0.001$). Conversely, in extrapulmonary ARDS, no significant difference in survival rates was observed between the two groups ($P = 0.388$). Furthermore, subgroup analyses were conducted by sequentially excluding specific patient populations, including elderly patients, those with severe ARDS, and those with ARDS etiology classified as "other." Across these three subgroups [Figure 6: see original paper], multivariate Cox regression models consistently replicated the core findings of the primary analysis. Specifically, the association between excessive DP and the risk of all-cause mortality varied depending on the ARDS etiology (all interaction $P < 0.05$), and its role as a risk factor was limited strictly to pulmonary ARDS. In summary, the results of the sensitivity analyses were highly consistent with the primary analysis, demonstrating the robustness of the study' s central conclusions.

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PaCO2 levels after PS-IPTW (Propensity Score Inverse Probability of Treatment Weighting) adjustment for ARDS etiology.

SOFA (Sequential Organ Failure Assessment) score

PaO2/FiO2

APACHE

Standardized Mean Difference (SMD). Note: ARDS = acute respiratory distress syndrome; APACHE II score = Acute Physiology and Chronic Health Evaluation II score; SOFA score = Sequential Organ Failure Assessment score; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2/FiO_2 = oxygenation index. Standardized mean differences of various covariates between the high driving pressure group ($\geq$ 15 cmH_2O) and the low driving pressure group ($<$ 15 cmH_2O) before and after the application of propensity score-based inverse probability of treatment weighting (PS-IPTW).

Excluding ARDS patients with etiology classified as "other": pulmonary ARDS ($n = 82$); extrapulmonary ARDS ($n = 70$). Excluding ARDS patients aged $>$ 75 years: pulmonary ARDS ($n = 70$).

aH R (95%CI)

Extrapulmonary ARDS (n=74); Patients with $PaO_2/FiO_2 < 100$ mmHg were excluded; Pulmonary ARDS (n=59).

1.08 (0.95~1.22) 0.256

Extrapulmonary ARDS (n=76) after Inverse Probability of Treatment Weighting (IPTW) propensity score adjustment compared to Intrapulmonary ARDS (n=82).

1.07 (0.95~1.21) 0.239

Extrapulmonary ARDS (n=90)

1.04 (0.93~1.16) 0.520

1.26 (1.15~1.37) <0.001 1.04 (0.89~1.21) 0.637

1.31 (1.19~1.44) <0.001

1.30 (1.16~1.46) <0.001

1.27 (1.15~1.40) <0.001

Note: aHR = adjusted hazard ratio. The relationship between airway driving pressure, ARDS etiology, and all-cause mortality risk was analyzed across four populations using Cox proportional hazards models, adjusting for Sequential Organ Failure Assessment (SOFA) score, PaO_2/FiO_2, and age. ARDS = acute respiratory distress syndrome; IPTW = inverse probability of treatment weighting; PaO_2/FiO_2 = oxygenation index; $P_{interaction}$ = P-value for the interaction between airway driving pressure and ARDS etiology.

[Figure 1: see original paper]

讨论

Although domestic and international research has demonstrated that in patients receiving mechanical ventilation for ARDS,

Note: ARDS = Acute Respiratory Distress Syndrome; DP = Airway Driving Pressure; IPTW = Inverse Probability of Treatment Weighting; Kaplan-Meier = Kaplan-Meier.

Kaplan-Meier survival curves for high DP group (DP $\geq$ 15 cmH_2O) vs. low DP group (DP < 15 cmH_2O), adjusted using inverse probability of treatment weighting and stratified by ARDS etiology (A: Pulmonary ARDS, B: Extrapulmonary ARDS).

excessive DP is an independent risk factor for 90-day all-cause mortality [**?**], conclusions from related studies in recent years have been inconsistent [**?**]. Furthermore, the strength of the association between DP and the risk of all-cause mortality in ARDS varies significantly across different ARDS subgroups [**?**, **?**, **?**]. This reveals the nature of ARDS as a highly heterogeneous syndrome, characterized by extensive variations in clinical features and responses to treatment [**?**].

Consequently, identifying ARDS phenotypes with distinct pathophysiological characteristics and prognoses has become a research priority in this field. Previous studies have confirmed significant differences between pulmonary ARDS (pARDS) and extrapulmonary ARDS (eARDS) regarding respiratory mechanics and the severity of systemic organ damage [**?**]. However, there is a lack of targeted systematic research on whether the prognostic value of excessive DP differs across these etiological phenotypes. This limitation hinders the implementation of individualized ventilation strategies guided by airway driving pressure. Therefore, this study aims to explore the differences in the association strength between DP and all-cause mortality risk across different etiological phenotypes, seeking to provide more precise evidence for individualized DP titration in ARDS patients. The results of this study show that after adjusting for key factors such as age, SOFA score, and PaO_2/FiO_2, excessive DP (HR = 1.134, 95%CI = 1.067–1.206, $P < 0.01$) is independently associated with 90-day all-cause mortality [Table 3]. This suggests that during lung-protective ventilation for ARDS, clinicians should focus more on DP relative to V_t, and DP should become an important therapeutic target for lung-protective ventilation strategies [**?**]. However, the specific added value of a DP-limited strategy [**?**], and whether it is superior to other strategies, still requires confirmation through further multicenter RCTs. These results are largely consistent with those of AMATO et al. [**?**].

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Specifically, in ARDS patients receiving protective ventilation, it is a lower DP rather than a lower V_t that is closely related to patient prognosis. The reason may be that DP is strongly and positively correlated with lung stress and strain, which are core factors in the development of ventilator-induced lung injury (VILI) and subsequent poor outcomes.

The results of this study [Figure 2, Table 3] demonstrate that the association between DP (whether as a continuous or dichotomous variable) and 90-day all-cause mortality risk differs significantly between different ARDS etiologies ($P < 0.05$ for all interaction terms).

Subgroup analysis [Table 4, Figure 3] revealed that excessive DP is an independent risk factor for prognosis only in patients with pulmonary ARDS ($P < 0.01$). In extrapulmonary ARDS, there was no significant association between DP and poor prognosis, with the SOFA score being the only independent risk factor ($P < 0.01$). This suggests significant heterogeneity in the prognostic value of DP-limited lung protection strategies across different ARDS etiological phenotypes; for patients with extrapulmonary ARDS, a DP < 15 cmH_2O does not necessarily imply a higher probability of survival [Figure 4]. The results remained highly consistent whether using IPTW to balance confounding factors or through repeated subgroup analyses [Figure 5: see original paper], [Figure 6, Figure 7]. These findings are partially consistent with the study by CHEN et al. [**?**], which used latent class analysis (LCA) and found a significant interaction between mechanical power and 28-day mortality across different ARDS

categories. Specifically, the correlation between mechanical power and mortality was more significant in the subgroup characterized primarily by intrapulmonary dysfunction, which strongly supports the conclusion of this study that different etiological phenotypes significantly influence the association between respiratory mechanics indicators (such as DP) and prognosis.

The reasons may include the following: First, pulmonary ARDS and extrapulmonary ARDS represent two distinct etiological types of ARDS [**?**, **?**]. In patients with extrapulmonary ARDS, lung injury is relatively mild while extrapulmonary organ damage is more severe; thus, the degree of extrapulmonary organ damage (e.g., SOFA score) contributes more to the prognosis, while the association between DP (reflecting lung stress levels) and prognosis decreases. This explanation is partially supported by related research: for instance, LUO et al. [**?**] found that the risk of all-cause mortality in extrapulmonary ARDS was related to the number of organ failures rather than the lung injury score. SARGE et al. [**?**] also found that individualizing PEEP titration via esophageal pressure (thereby reducing lung stress and VILI) might be useless or even harmful in subgroups with severe extrapulmonary organ damage. Second, there are differences in respiratory mechanics. In patients with extrapulmonary ARDS, factors such as chest wall edema and increased intra-abdominal pressure lead to elevated intrathoracic pressure and chest wall elastance (E_{cw}), making E_{cw} the primary cause of increased respiratory system elastance (E_{rs}) [**?**]. As the ratio of E_{cw} to E_{rs} increases, according to the mechanical formula $\mathrm{DP}_{tp} = \mathrm{DP} \times [1 - E_{cw}/E_{rs}]$, the transpulmonary driving pressure (DP_{tp}) in extrapulmonary ARDS patients does not necessarily reach the injury threshold even at the same DP level (e.g., 15 $\mathrm{cmH_2O}$) [**?**, **?**]. This reduces the likelihood of VILI, such that the probability of a poor prognosis does not increase [Figure 4B]. Several studies have indirectly confirmed the rationality of this explanation: for example, TERRY et al. [**?**] in obese patients and RAMIN et al. [**?**] in patients with ARDS caused by chest trauma both observed a lack of correlation between high DP and all-cause mortality risk, because the increase in E_{cw} prevents airway driving pressure from accurately reflecting DP_{tp} levels and the true risk of VILI.

In summary, in the overall ARDS population, excessive DP is associated with all-cause

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The risk of death is independently correlated with driving pressure (DP), yet this association exhibits significant variation across different etiologies of Acute Respiratory Distress Syndrome (ARDS). In patients with pulmonary ARDS, DP is highly and independently associated with the risk of 90-day all-cause mortality. Conversely, in extrapulmonary ARDS, no significant independent correlation exists between DP and all-cause mortality; instead, a high SOFA score serves as the sole independent risk factor for 90-day mortality. Consequently, given the high degree of heterogeneity within the ARDS population, a "one-size-fits-all" approach should be avoided when implementing mechanical ventilation strategies oriented toward limiting airway driving pressure. Instead,

clinical phenotypes should be initially classified based on etiology to implement individualized ventilation strategies and further improve patient survival rates. For extrapulmonary ARDS, the measurement of esophageal pressure should be considered to implement transpulmonary driving pressure (DP_{tp})-guided lung-protective ventilation, rather than blindly limiting airway DP. The significance of this ARDS etiological phenotype in guiding precision therapy warrants further research and promotion. To enhance the generalizability of these findings, future large-scale studies should expand the research population to include multicenter and multi-regional cohorts.

The results of this study possess high clinical utility. For clinicians managing the highly heterogeneous ARDS population, it is evident that implementing individualized and precision treatments based on ARDS phenotypes is of paramount importance.

Although lung-protective ventilation strategies that limit DP have received widespread attention from anesthesiologists and intensivists [**?**, **?**] to reduce the incidence of ventilator-induced lung injury (VILI), the results of this study suggest that a "one-size-fits-all" approach is inappropriate for DP-guided strategies. On the contrary, clinical application should distinguish between different scenarios and ARDS phenotypes. The clinical value of limiting airway DP may diminish in certain subgroups or phenotypes, such as clinical contexts leading to increased chest wall elastance (E_{cw})—including obesity, extrapulmonary ARDS, and traumatic chest ARDS—as well as in ARDS patients primarily characterized by extrapulmonary organ damage. When E_{cw} is elevated, airway DP may fail to accurately reflect the risk of VILI; a DP $>$ 15 cmH_2O does not necessarily imply an increased risk of all-cause mortality. In such cases, to achieve individualized lung-protective ventilation and precision treatment, an esophageal balloon may be required to measure esophageal pressure and obtain accurate DP_{tp} values for DP_{tp}-guided ventilation [**?**]. Alternatively, the threshold for airway pressure (P_{aw}) could be increased, though the specific threshold levels require further determination through multicenter, large-sample studies.

This study has several primary limitations. First, as an observational study, certain biases in the results are unavoidable, and a causal relationship between DP and all-cause mortality cannot be definitively established. However, this study utilized a multivariate Cox model to adjust for other confounding factors (such as SOFA score, age, and P_aO_2/F_iO_2), thereby increasing the reliability of the association between DP and all-cause mortality. Second, esophageal pressure monitoring was not performed, meaning accurate E_{cw} and DP_{tp} data for extrapulmonary ARDS patients could not be obtained. Finally, the sample size of this study is relatively small. Therefore, multicenter studies are still needed to confirm these conclusions and to further compare the respective values of DP and DP_{tp} in prognostic assessment and lung-protective ventilation for patients with extrapulmonary ARDS.

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analysis, and manuscript writing, as well as quality control, review, overall accountability, and supervision. Zhou Guoping···

Xiaoshi Li was responsible for conducting the experiments, implementing the research process, data collection, data organization, statistical analysis, and the preparation of figures and tables. Ping Li was responsible for conducting the experiments, implementing the research process, providing statistical methodology and conceptual guidance, and assisting in the editing and revision of the manuscript. Xin Zhang was responsible for data organization and the revision of the manuscript.

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Note: Figure translations are in progress. See original paper for figures.