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Effect of Respiratory Phenotype on Extrapulmonary Organ Dysfunction in Patients with ARDS: A Multicenter Study

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Abstract

Background: The heterogeneity of acute respiratory distress syndrome (ARDS) extends beyond the lungs, with mortality driven primarily by extrapulmonary organ dysfunction rather than refractory hypoxemia. While individual respiratory parameters have been linked to extrapulmonary injury, their combined influence remains underexplored. This study aimed to identify respiratory phenotypes based on multiple parameters and examine their associations with extrapulmonary organ dysfunction.

Methods: We conducted a multidatabase study based on the Chinese Database in Intensive Care (CDIC) and the ALVEOLI trial, focusing on patients with ARDS who underwent invasive mechanical ventilation. Latent profile analysis (LPA) and Consensus *k*-means clustering were applied to derive ARDS respiratory phenotypes on the basis of eight respiratory parameters. Extrapulmonary organ dysfunction during the first seven days was assessed, and linear mixed-effects models were used to compare the severity and temporal evolution of SOFA scores across respiratory phenotypes.

Findings: A total of 769 patients with ARDS included in the CDIC were enrolled, and a three-class LPA model with optimal fit was identified: Class 1 (n=137, 17.9%) exhibited the highest PaO_2/FiO_2, lowest ventilatory ratio, and lowest 28-day mortality rate. Class 2 (n=67, 8.7%) presented the highest driving pressure, mechanical power, minute ventilation, ventilatory ratio, and $PaCO_2$, along with the lowest PaO_2/FiO_2 and respiratory system compliance and exhibited the highest 28-day mortality. Class 3 (n=565, 73.3%), the largest group, was characterized by intermediate values across all the variables. These phenotypes were externally validated in the ALVEOLI cohort. Extrapulmonary organ dysfunction varied across respiratory phenotypes. Class 2 had the highest burden, with 41.8% developing four organ dysfunctions and the most severe circulatory, kidney, and liver impairment (P<0.001). Hematologic dysfunction was more common in Class 2 and 3 than Class 1 (P=0.001). Within seven days, new-onset kidney dysfunction occurred more frequently in Class 2 (36.5% vs. 19.4% and 19.8%, P=0.012), and new-onset hematologic dysfunction was higher in Class 2 and Class 3 (31.5% and 33.7% vs. 19.3%, P=0.004). Mixed-effects modeling showed a significant phenotype × time interaction (P<0.001), indicating distinct trajectories of extrapulmonary SOFA scores across phenotypes, consistent with findings in the ALVEOLI cohort.

Interpretation: We identified and validated three distinct ARDS respiratory phenotypes with differing severity, ventilatory mechanics, and outcomes. Class 2, characterized by severe lung injury and high mechanical load, had the highest mortality and burden of extrapulmonary organ dysfunction. These findings emphasize the need for phenotype-guided management strategies.

Introduction

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by progressive respiratory distress and refractory hypoxemia and is associated with a high mortality rate[1, 2].

Mechanical ventilation (MV) remains a cornerstone of ARDS management, yet it can paradoxically contribute to ventilator-induced lung injury (VILI) and diaphragmatic dysfunction. These injuries promote the release of inflammatory mediators that extend beyond the lungs, triggering systemic inflammation and driving progression to multiple organ dysfunction syndrome (MODS), the leading cause of death in patients with ARDS [3–5]. This pathophysiological cascade is facilitated by organ cross-talk: injury to the pulmonary capillary endothelium leads to the release of proinflammatory, procoagulant, and chemoattractant mediators into the circulation, thereby initiating inflammatory responses in distant organs[6]. Highly vascularized exchange organs such as the kidneys, intestines, and liver are particularly susceptible, often becoming early targets in a self-perpetuating cycle of injury and dysfunction [7]. Among the manifestations, pulmonary–renal syndrome is frequently observed as an early manifestation of MODS in ARDS, with secondary acute kidney injury (AKI) increasing mortality rates to 60–80%[8]. Given the central role of extrapulmonary organ dysfunction in ARDS outcomes, understanding the broader impact of MV beyond the lungs is critically important.

Individual respiratory parameters—such as the PaO_2/FiO_2 ratio, driving pressure, respiratory system compliance, the ventilatory ratio, positive end-expiratory pressure (PEEP), and tidal volume—have been associated not only with the severity and clinical outcomes of ARDS but also with extrapulmonary organ dysfunction in some studies[9–15]. While PEEP improves oxygenation and lung compliance, excessive levels can lead to hemodynamic instability and renal congestion, impairing kidney function by reducing venous return and increasing intra-abdominal pressure. This lung-kidney cross-talk exacerbates renal injury and increases the risk of AKI, a major mortality factor in ARDS patients[16]. However, relying on single variables may oversimplify the complex and dynamic effects of MV on extrapulmonary organs[17]. This reductionist approach risks misclassification and may obscure important pathophysiological insights.

To address these limitations, a multivariate subphenotyping approach that integrates multiple respiratory parameters may better capture the complex interplay among key pathophysiological features, offering a more comprehensive understanding of ventilatory burden and ARDS heterogeneity[18]. This data-driven strategy holds promise for improving the characterization of patient subgroups and guiding more targeted management of extrapulmonary organ dysfunction.

To date, research on ARDS subphenotypes has largely focused on disease severity and systemic inflammation, while the contribution of respiratory mechanics remains underexplored. In patients with coronavirus disease 2019 (COVID-19)-related ARDS, recent studies have demonstrated a link between respiratory phenotypes and extrapulmonary organ injury. Bos et al. identified two phenotypes on the basis of respiratory mechanics using latent class analysis; patients with phenotype 2—characterized by a higher minute ventilation, mechanical power, and ventilatory ratio—were more likely to develop AKI and deep vein thrombosis[19]. These findings underscore the potential impact of respiratory heterogeneity on extrapulmonary organ dysfunction. However, such evidence is limited in non-COVID-19-related ARDS populations, where etiological and physiological diversity may yield different phenotypic patterns.

Therefore, this study aimed to use respiratory variables such as mechanical power, driving pressure, and the ventilatory ratio to identify ARDS respiratory phenotypes and explore their clinical characteristics, prognosis, and effect on extrapulmonary organ dysfunction.

Method

Study design and participants

This multidatabase study was conducted on the basis of data from the Chinese Database in Intensive Care (CDIC) and the ALVEOLI trial[20]. The CDIC comprises data from 14,500 patients admitted to the Department of Critical Care Medicine, Zhongda Hospital, Southeast University, China, from January 2014 to October 2022. We included patients in the CDIC who met the Berlin ARDS criteria[21] and required mechanical ventilation (detail in Additional file: Additional methods). Exclusion criteria included: 1) patients younger than 18 years old; 2) patients ventilated for less than 24 h. Only the first intensive care unit (ICU) admission was considered for patients with multiple stays. The ALVEOLI trial served as the validation cohort, with all patients intubated and on MV. The details of the CDIC and ALVEOLI trial are presented in Table S1.

The present study was approved by the Research Ethics Commission of Zhongda Hospital Southeast University (2022ZDSYLL177-P01). For the ALVEOLI trial, the use of all data was approved by the Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were followed.

Data collection and outcomes

Clinical data, including demographic, comorbidity, and key respiratory and hemodynamic data, were collected from Days 1 to 7. If a variable was recorded more than once in 24 h, we used the value related to the greatest severity of illness. The details of the data collection process are presented in the supplementary material. The outcomes included 28-day mortality, ICU mortality, hospital mortality, and extrapulmonary organ dysfunction assessed through the sequential organ failure assessment (SOFA) score and the vasoactive-inotropic score (VIS).

Derivation and validation of phenotypes

Latent profile analysis (LPA)[22] was used to identify ARDS phenotypes. Clinical variables were selected based on Bos's COVID-19 respiratory phenotypes framework[19]., in conjunction with the completeness and characteristics of our dataset[23]., and their established association with the severity of ARDS-related lung injury. The following readily available clinical variables were used as inputs for the identification of latent classes: pH, $PaCO_2$, the PaO_2/FiO_2 ratio, driving pressure, respiratory system compliance, minute

volume ventilation, the ventilatory ratio, and the mechanical power of ventilation. Certain clinically relevant parameters, such as PEEP and tidal volume, were excluded due to their mathematical coupling or direct functional dependence with other variables, which could result in multicollinearity and redundancy within the model. By focusing on variables that independently reflect key physiological dimensions of respiratory failure, the final set was designed to capture the essential aspects of gas exchange, respiratory mechanics, and ventilatory load, minimizing redundancy while ensuring robustness in phenotype identification. (Table S2).

Before LPA, we first assessed the distributions and missingness of candidate variables. Multiple imputations with chained equations (MICE) were used to account for missing data (detail in Additional file: Additional methods). The best number of phenotypes was determined by the combination of model fit statistics and clinical relevance[24, 25]. A bootstrap likelihood ratio test was performed to compare whether the k-class model was better than the (k-1)-class model. Lower Akaike information criterion (AIC) and sample-size-adjusted Bayesian information criterion (SABIC) values and higher entropy values were considered to indicate better model fit. The minimum percentage of patients in a class should be greater than 5%. To ensure the stability of the class membership, the minimum probability of assignment to one class should be greater than 0.85. LPA was performed via the tidyLPA package in R.

To further assess the robustness and stability of the phenotype classification identified by LPA, we performed consensus k-means clustering as a complementary distance-based approach.

Clustering stability was assessed by examining the consensus matrix heatmaps, the cumulative distribution function (CDF) curves, the elbow point of the area under the CDF curve, and cluster consensus values[26, 27]. After determining the optimal number of clusters, phenotypic differences were visualized using a heatmap based on the mean standardized differences and hierarchical clustering of variables. Consensus k-means clustering was implemented using the ConsensusClusterPlus package in R.

Statistical analyses

Values are expressed as proportions for categorical variables and as the means (standard deviations) or medians [interquartile ranges (IQRs)] for continuous variables. Comparisons were made via analysis of variance and the Kruskal–Wallis test for continuous data, whereas the chi–square test was employed for categorical data.

After deriving the ARDS phenotypes, we compared key variables across phenotypes and visualized these comparisons via rank plots. Class transitions between Days 1 and 3 were analyzed via alluvial plots.

Kaplan–Meier curves and Cox regression were used to evaluate 28-day mortality by phenotype, adjusting for baseline Sequential Organ Failure Assessment (SOFA) scores, age, sex, and BMI[23]. Additionally, in the ALVEOLI trial, heterogeneity of treatment effect (HTE) was evaluated via interaction tests to

determine whether treatment effects differed across phenotypes. HTE was assessed through the interaction term (class × treatment strategy) in the Cox regression model for mortality.

Organ dysfunction within the first seven days after enrollment was assessed to explore differences across respiratory phenotypes. Linear mixed-effects models were constructed to evaluate differences in the severity and temporal evolution of extrapulmonary SOFA scores across respiratory phenotypes. The models included fixed effects for phenotype, time (days 1–7), and their interaction (phenotype × time), with random intercepts for individual patients to account for repeated measurements.

The p value was calculated to evaluate the differences between phenotypes, and $P < 0.05$ was considered to indicate statistical significance. All the statistical analyses were performed via R studio (version 4.3.1).

Results

Study population

In the CDIC derivation cohort, 769 patients met the inclusion and exclusion criteria and were included in the final analysis (Figure S1). The median age was 65 years, with a median PaO_2/FiO_2 ratio of 154.0 mmHg and an Acute Physiology And Chronic Health Evaluation II (APACHE II) score of 23.0 ± 8.4. The 28-day mortality rate was 33.3% (Table S3). In the ALVEOLI validation cohort (n = 549), the 60-day mortality rate was 22.7%.

Phenotype derivation and validation

A three-class model based on first-day respiratory variables was determined to have an optimal fit in the CDIC cohort (entropy: 87.9%, class membership probability: 85.6–96.9%, Table 1). The consensus clustering results supported the three-class solution identified by LPA. Visual inspection of consensus matrices demonstrated clear cluster boundaries at k = 3, while the relative increase in the area under the CDF curve plateaued beyond three clusters, suggesting limited additional stability gain with higher k values (Figure S2). The phenotypes varied significantly in terms of clinical traits (Table 2, Fig. 1): Class 1 (17.9%) had the highest PaO_2/FiO_2 ratio and lowest ventilatory ratio. Class 2 (8.7%) had severe lung injury, with the highest driving pressure, mechanical power, minute ventilation, ventilatory ratio, and $PaCO_2$, along with the lowest PaO_2/FiO_2 ratio and respiratory system compliance. Class 3 (73.3%) had the largest sample size and was characterized by average values for all the variables. Sensitivity analysis including only the patients who required invasive mechanical ventilation without chronic lung disease in CDIC (n = 725, 94.2% of the cohort) and yielded a similar result, with only 2.48% of patients changing class membership. (Figure S3).

Table 1

Metrics for choosing the best number of classes for LPA in CIDC. * For patients who required invasive mechanical ventilation without chronic lung disease in CDIC

Classes	AIC	SABIC	Entropy	prob_min	prob_max	n_min	n_max	BLRT_p
CDIC (Full analysis)								
2	16295	16331	0.966	0.947	0.996	0.094	0.906	0.01
3	16081	16131	0.879	0.856	0.969	0.087	0.739	0.01
4	15737	15801	0.89	0.878	0.983	0.022	0.681	0.01
5	15434	15511	0.882	0.849	0.996	0.022	0.609	0.01
6	14940	15030	0.898	0.856	1	0.004	0.603	0.01
CDIC (Sensitivity analysis*)								
2	15343	15378	0.964	0.949	0.995	0.095	0.905	0.01
3	15141	15189	0.875	0.862	0.971	0.084	0.743	0.01
4	14802	14863	0.889	0.867	0.986	0.022	0.681	0.01
5	14562	14635	0.903	0.777	0.996	0.022	0.702	0.01
6	14381	14467	0.87	0.835	0.998	0.022	0.57	0.01

Table 2
Clinical characteristics of respiratory phenotypes in CDIC

Age (years)	**Class1**	**Class 2**	**Class 3**	***P*-value**
	(n = 138)	**(n = 67)**	**(n = 564)**	
	5.0 (51.25–76.75)	**60.0 (51.5–72.5)**	**66.0 (52–76)**	**0.595**
BMI, kg/m²	23.9 (20.8–26.1)	23.5 (21.3–25.6)	23.7 (21.3–26.1)	0.954
Male (gender), *n* (%)	97 (70.3)	50 (74.6)	402 (71.3)	0.813
ARDS Primary risk factor, n (%)				0.258
Pneumonia	77 (55.8)	46 (68.7)	353 (62.6)	
Sepsis (non-pulmonary)	22 (15.9)	9 (13.4)	94 (16.7)	
Aspiration	13 (9.4)	7 (10.4)	59 (10.5)	
Trauma	17 (12.3)	3 (4.5)	36 (6.4)	
Other	9 (6.5)	2 (3.0)	22 (3.9)	
Vital signs				
Temperature (°C)	38.0 (37.3–38.5)	38.0 (37.4–38.5)	38.0 (37.3–38.6)	1
Respiratory rate (breaths min − 1)	27.0 (24–31)	30.0 (26–35)	28.0 (24–32)	0.004
Heart rate (beats min − 1)	112 (98–126)	130 (119–142)	122 (109–137)	< 0.001
MAP (mm Hg)	70.5 (65–79)	71.0 (63–75)	71.0 (64–78)	0.916
Laboratory data				
White blood cell count (10^9/L)	11.3 (7.7–14.0)	11.1 (7.5–18.9)	11.5 (7.7–16.0)	0.745
Hemoglobin (g/L)	99.5 (82–115)	92.0 (80-107.75)	103 (87.5-117.5)	0.008
Platelet count (10^9/L)	160 (93-202.5)	108 (57.54–218.1)	129 (80-197.5)	0.146

ARDS= acute respiratory distress syndrome; BMI= Body mass index; MAP=mean arterial blood pressure; PBW=Predicted body weight; SOFA= Sequential organ failure assessment; APACHE= Acute Physiology and Chronic Health Evaluation II;

Age (years)	**Class1**	**Class 2**	**Class 3**	***P*-value**
	(n = 138)	**(n = 67)**	**(n = 564)**	
	5.0 (51.25–76.75)	**60.0 (51.5–72.5)**	**66.0 (52–76)**	**0.595**
Blood urea nitrogen (mg/dl)	13.3 (9.1–21.9)	15.0 (9.1–29.8)	16.0 (10.2–26.5)	0.213
Creatinine (umol/L)	90.0 (71-165.5)	116 (81–188)	108 (76-184.3)	0.087
Total Bilirubin (umol/L)	13.3 (9.05–21.9)	15.0 (9.1–29.8)	16.0 (10.2–26.5)	0.213
pH	7.42 (7.39–7.44)	7.30 (7.27–7.34)	7.38 (7.33–7.41)	< 0.001
PaO_2(mm Hg)	99.8 (87.8-121.2)	83.7 (73.1–97.7)	87.7 (77.7-100.9)	< 0.001
$PaCO_2$ (mm Hg)	33.5 (30.1–37.7)	50.9 (44.2–57.0)	36.4 (32.5–40.6)	< 0.001
Bicarbonate (mmol/L)	22.0 (19.7–24.3)	24.3 (20.8–28.3)	21.2 (19.0-23.6)	< 0.001
PaO_2/FiO_2 ratio (mm Hg)	209 (176.3–235)	105 (79.4–157)	144 (108.9-190.6)	0.002
Lactate (mmol/L)	1.57 (1.21–2.2)	2.20 (1.42–3.67)	1.82 (1.32–2.65)	0.002
Parameters of mechanical ventilation in the first 24 h				
Tidal volume (ml/kg PBW)	6.64 (6.30–7.31)	6.46 (5.61–7.48)	6.67 (6.01–7.37)	0.745
Minute ventilation (L/min)	7.64 (6.70–8.61)	9.63 (8.706–10.57)	7.700 (6.670–8.76)	< 0.001
Driving pressure (cmH2O)	11.7 (10.1–13.3)	16.6 (13.9–19.4)	11.1 (9.7–13.0)	< 0.001
Compliance (ml/cmH2O)	36.8 (31.0-45.1)	25.5 (18.9–37.4)	39.1 (30.3–48.2)	< 0.001
Mechanical power (J/min)	10.2 (8.6–12.7)	18.8 (16.4–23.9)	11.3 (9.3–13.5)	< 0.001
Ventilatory ratio	1.28 (1.05–1.44)	2.90 (2.57–3.61)	1.42 (1.19–1.71)	< 0.001

ARDS= acute respiratory distress syndrome; BMI= Body mass index; MAP=mean arterial blood pressure; PBW=Predicted body weight; SOFA= Sequential organ failure assessment; APACHE= Acute Physiology and Chronic Health Evaluation II;

Age (years)	**Class1**	**Class 2**	**Class 3**	***P*-value**
	(n = 138)	**(n = 67)**	**(n = 564)**	
	5.0 (51.25–76.75)	**60.0 (51.5–72.5)**	**66.0 (52–76)**	**0.595**
APACHE II score	17.9 ± 9.67	27.1 ± 7.47	23.7 ± 7.76	0.002
SOFA score	6.00 (4–8)	10.0 (8–12)	9.00 (7–11)	< 0.001
Outcomes				
Mortality at day 28, n (%)	26 (18.8)	38 (56.7)	192 (34.0)	< 0.001
Ventilator-free days	17.2 (15. 1-19.1)	11.8 (9.2–16.2)	17.3 (15.4–18.9)	< 0.001
Mortality in ICU, n (%)	22 (15.9)	36 (53.7)	194 (34.4)	< 0.001
Mortality in hospital, n (%)	25 (18.1)	36 (53.7)	200 (35.5)	< 0.001

ARDS= acute respiratory distress syndrome; BMI= Body mass index; MAP=mean arterial blood pressure; PBW=Predicted body weight; SOFA= Sequential organ failure assessment; APACHE= Acute Physiology and Chronic Health Evaluation II;

In the CDIC training cohort, a total of 271 patients (35.3%) completed interleukin-6 testing on D1, while 668 patients (86.9%) completed high-sensitivity C-reactive protein testing on D1. It was found that patients with phenotype 2 exhibited the highest interleukin-6 levels [pg/ml, 265.0 (IQR: 114.15-816.75)] (P = 0.505) and the highest high-sensitivity C-reactive protein levels [mg/L, 161.0 (IQR: 75.29-252.49)] (P = 0.003), suggesting that phenotype 2 resembles a hyperinflammatory phenotype (Figure S4). Class 2 consistently presented the highest driving pressure, mechanical power, and ventilatory ratio during the first three days (Figure S5). The ALVEOLI cohort presented similar phenotype distributions and characteristics (Figure S6, Table S4).

Effect of respiratory phenotypes on outcomes

For the CDIC cohort, 28-day mortality was highest in Class 2 (56.7%), followed by Class 3 (34.0%) and Class 1 (18.8%). Adjusted Cox regression confirmed higher mortality risk for Class 2, with a hazard ratio (HR) of 3.11 and 95% confidence interval (CI) 1.75–5.55, while Class 3 also showed an elevated but nonsignificant risk (HR 1.39, CI 0.86–2.25) (Table S5). The results for the ALVEOLI cohort were consistent, with Class 2 showing the worst outcomes (Fig. 2). Additionally, the derived phenotypes showed significant differences in ventilator-free days (VFDs) across both cohorts, with Class 2 having the fewest VFDs (Table 2).

A total of 59.5% of patients in the CDIC group exhibited phenotypic changes within the first three days (Figure S7). Class 3 was the most common phenotype across days, with the number of patients in Class 1 gradually increasing. In the ALVEOLI, Class 2 had the fewest patients, but the number of patients increased steadily from Day 1 to Day 3 (Figure S8). Transition status was related to clinical outcomes. Patients who were initially in Class 1 had lower mortality regardless of transition, whereas those who remained in Class 2 had the worst outcomes (58.3% mortality in the CDIC cohort and 37.8% in the ALVEOLI cohort, $p < 0.05$).

We also assessed HTE in the ALVEOLI cohort on the basis of respiratory phenotypes. Significant HTE of different PEEP strategies was observed across phenotypes (p for interaction = 0.041), with the high-PEEP strategy demonstrating a protective effect specifically in Class 3 (HR = 0.43, 95% CI 0.19–0.97; Table S6).

Effect of respiratory phenotypes on extrapulmonary organ dysfunction

Distinct patterns of extrapulmonary organ dysfunction were observed across respiratory phenotypes. Patients in Class 2 exhibited the highest burden of multiple organ dysfunction, with a markedly greater proportion of patients (41.8%) developing four extrapulmonary organ dysfunction (P < 0.001). This phenotype was characterized by the most severe circulatory dysfunction, as reflected by higher rates of circulatory dysfunction, severe circulatory SOFA scores, and vasopressor requirements. In addition, kidney and liver dysfunction were also more prevalent in Class 2. In addition, kidney and liver dysfunction were more prevalent in Class 2, with kidney dysfunction occurring in 73.1% of patients compared with 44.9% in Class 1 and 58.7% in Class 3 (P < 0.001), and liver dysfunction in 56.7% vs. 37.0% and 49.5%, respectively (P = 0.01). Hematologic dysfunction was also more common in Class 2 and Class 3 than in Class 1 (P = 0.001).

Regarding new-onset organ dysfunction within 7 days, the incidence of circulatory dysfunction was comparable across phenotypes. However, new-onset kidney dysfunction occurred more frequently in Class2 (36.5% vs. 19.4% and 19.8%, P = 0.012), while new-onset hematologic dysfunction was more common in Class2 and Class3 (31.5% and 33.7% vs. 19.3%, P = 0.004). (Table 3).

Table 3
Overall and new-onset extrapulmonary organ dysfunction within 7 days across respiratory phenotypes in ARDS

Multiple extrapulmonary organ failures	**Class1 (n = 138)**	**Class 2 (n = 67)**	**Class 3 (n = 564)**	***P*-value**
				< 0.001
N = 0	14 (10.1%)	-	13 (2.3%)	
N = 1	26 (18.8%)	9 (13.4%)	58 (10.3%)	
N = 2	41 (29.7%)	8 (11.9%)	125 (22.2%)	
N = 3	36 (26.1%)	22 (32.8%)	218 (38.7%)	
N = 4	21 (15.2%)	28 (41.8%)	150 (26.6%)	
Overall extrapulmonary organ failure				
Circulatory failure	105 (76.1%)	65 (97.0%)	529 (93.8%)	< 0.001
$SOFA_{Circulatory}$ =4	35 (25.4%)	51 (76.1%)	352 (62.4%)	< 0.001
VIS max	11.7 (7.4–33.3)	43.0 (18.6–96.9)	23.9 (11.8–53.5)	< 0.001
Kidney failure	62 (44.9%)	49 (73.1%)	331 (58.7%)	< 0.001
Liver failure	51 (37.0%)	38 (56.7%)	279 (49.5%)	0.01
Hematologic dysfunction	82 (59.4%)	51 (76.1%)	423 (75.0%)	0.001
New-onset organ failure*				
Circulatory failure	46/103 (44.7%)	7/16 (43.8%)	104/212 (49.1%)	0.764
Kidney failure	25/129 (19.4%)	23/63 (36.5%)	105/529 (19.8%)	0.012
Liver failure	30/138 (21.7%)	16/66 (24.2%)	174/561 (31.0%)	0.072
Hematologic failure	26/135 (19.3%)	17/54 (31.5%)	181/537 (33.7%)	0.004

*New onset is defined as organ failure not being present for the 24 hours before randomization, and organ failure included circulatory failure, kidney failure, liver failure and hematologic failure, and which was defined as a delta score > = 1.

The severity of extrapulmonary organ dysfunction varied significantly among different respiratory phenotypes. In the mixed-effects model, a significant phenotype × time interaction was observed (P <

0.001), indicating that the trajectory of extrapulmonary SOFA scores over the first seven days differed significantly across respiratory phenotypes. Similar dynamic changes in extrapulmonary SOFA scores were observed in the ALVEOLI cohort (Fig. 3).

Discussion

We identified and validated three distinct respiratory phenotypes of ARDS with varying clinical characteristics and outcomes. Class 1 (17.9%) presented the highest PaO_2/FiO_2 ratio, lowest ventilatory ratio, and lowest 28-day mortality. Class 2 (8.7%) presented the highest driving pressure, mechanical power, minute ventilation, ventilatory ratio, and $PaCO_2$, along with the lowest PaO_2/FiO_2 and respiratory system compliance, had the highest 28-day mortality. Class 3 (73.3%) had the largest sample size and was characterized by average values for all the variables. Class 2 had the highest burden of extrapulmonary organ dysfunction. Patients in Class 2 had significantly higher risks of circulatory dysfunction and renal dysfunction than other phenotypes.

The phenotypes in our study differ from those in previous ARDS phenotype studies in several key aspects. First, the ARDS respiratory phenotypes identified in our study differ from earlier classifications on the basis of inflammatory markers or clinical data[28, 29], focusing instead on gas exchange and respiratory mechanics that directly reflect pulmonary pathophysiology. While some overlap may exist—patients with severe hypoxemia and poor compliance may correspond to the hyperinflammatory subgroup—our phenotypes are primarily data-driven representations of respiratory function rather than systemic inflammatory states. Therefore, our findings complement, rather than replace, existing biological subphenotype frameworks and provide a pragmatic approach for bedside phenotyping based on routinely available respiratory variables. Second, unlike the study by Bos et al., which identified two COVID-19-related ARDS phenotypes[19], our research encompassed ARDS with diverse causes and identified an additional mild phenotype (Class 1) characterized by better oxygenation, ventilatory function, and prognosis. This highlights ARDS heterogeneity and suggests that classification on the basis of gas exchange and respiratory mechanics offers a more comprehensive assessment. Additionally, unlike prior studies reporting stable ARDS phenotypes[30], we found respiratory phenotypes to be dynamic, reflecting significant physiological variability over time.

In this study, we observed distinct patterns of extrapulmonary organ dysfunction across respiratory phenotypes in patients with ARDS. The association between respiratory phenotypes and circulatory dysfunction was particularly pronounced in patients classified as Class 2, accompanied by impaired microcirculatory perfusion (elevated lactate levels) and greater vasopressor requirements, as reflected by higher maximum VIS scores. This phenotype may represent a subgroup characterized by more pronounced hemodynamic instability and systemic hypoperfusion, which could contribute to downstream organ injury.

Several mechanisms may explain this association. Factors such as high driving pressure, increased mechanical power, and hypercapnia can exacerbate hemodynamic instability through multiple pathways,

including reduced systemic vascular resistance, impaired myocardial contractility, and increased pulmonary vascular resistance leading to pulmonary hypertension. These pathophysiologic alterations may further compromise tissue perfusion and organ function, highlighting the importance of comprehensive management strategies and enhanced circulatory support for these patients[31].

We also observed a significant association between respiratory phenotypes and the risk of acute kidney injury, with new-onset kidney dysfunction occurring more frequently in Class 2. This finding is consistent with previous studies showing that high mechanical power is particularly detrimental in patients with severe ARDS[32]. Increasing evidence suggests a complex bidirectional interaction between the lungs and kidneys in critical illness. Lung–kidney cross-talk plays an important role in the development of both ARDS and AKI. In patients with ARDS, increased intrathoracic pressure, neurohormonal activation, and systemic inflammatory responses associated with mechanical ventilation may contribute to renal dysfunction[33, 34]. Moreover, mechanical ventilation itself—especially when delivered with injurious settings such as high tidal volumes—may induce ventilator-induced kidney injury (VIKI) by altering renal perfusion and amplifying systemic inflammatory responses[35]. These mechanisms highlight the importance of integrated management strategies that simultaneously address pulmonary and renal dysfunction to improve patient outcomes.

The significant phenotype × time interaction suggests that respiratory mechanical phenotypes are associated not only with the initial severity of extrapulmonary organ dysfunction but also with its subsequent evolution and recovery pattern. These findings highlight the importance of prioritizing strategies to mitigate extrapulmonary organ complications, which may have a greater impact on improving ARDS survival rates than focusing solely on severe hypoxemia[36, 37].

Our study also found that high PEEP improved survival only in Class 3 ARDS patients, who had moderate hypoxemia and preserved lung recruitability, allowing alveolar recruitment, better mechanics, and lower driving pressure. Class 2 patients had severely reduced compliance and poor recruitability, so higher PEEP mainly raised intrathoracic pressure and risked worsening injury. These results suggest phenotype-based stratification may guide PEEP selection and optimize outcomes in ARDS ventilation trials.

This study has several limitations: (1) As a retrospective study, it faces risks of missing data, outliers, and inconsistencies in ventilation strategies and treatment, which may affect phenotype stability. Multicenter, prospective studies are needed for more accurate validation of ARDS respiratory phenotypes. (2) Inflammatory biomarker data were incomplete, with only a subset of patients having IL-6 or hs-CRP measurements, potentially limiting characterization of inflammatory features. (3) Although we had validated phenotypes in the ALVEOLI cohort, external generalizability to other ARDS populations or non-ventilated patients remains uncertain. (4) Phenotypes were derived from first-day respiratory variables, and frequent transitions suggest dynamic physiology that may not be fully captured by a single-day classification. (5) Observational design precludes causal inference regarding ventilatory strategies or organ dysfunction outcomes, highlighting the need for mechanistic or interventional studies.

Conclusion

We identified and validated three distinct ARDS respiratory phenotypes with differing severity, ventilatory mechanics, and outcomes. Patients with severe lung injury and high mechanical load, had the highest mortality and burden of extrapulmonary organ dysfunction. These findings support phenotype-based stratification, individualized ventilation, and monitoring of dynamic physiology and organ function in ARDS.

Abbreviations

ARDS
Acute Respiratory Distress Syndrome
CDIC
Chinese Database in Intensive Care
ICU
Intensive Care Unit
MP
Mechanical Power
DP
Driving Pressure
VR
Ventilatory Ratio
VFDs
Ventilator-free Days
LPA
Latent Profile Analysis
LCA
Latent class analysis
SOFA
Sequential Organ Failure Assessment
VIS
Vasoactive-Inotropic Scores
BMI
Body Mass Index
AKI
Acute Kidney Injury
APACHE II
Acute Physiology and Chronic Health Evaluation II
PEEP
Positive End-Expiratory Pressure
MICE

Multiple Imputations with Chained Equations

Declarations

Human Ethics and Consent to Participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Zhongda Hospital Southeast University (2022ZDSYLL177-P01). Given the retrospective nature of this study, the requirement for informed consent was waived by the IRB of Zhongda Hospital Southeast University. For the ALVEOLI trial, all data were approved by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC, https://biolincc.nhlbi.nih.gov).

Consent for publication

Not applicable.

Availability of data and materials

CDIC cohort data are available upon reasonable request and with approval from the Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University. The ARDSNets datasets are available on the BioLINCC website (https://biolincc.nhlbi.nih.gov).

Clinical trial number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

H.C., J.X., S.Li., L.L., Y.Y. and Q.H. had the idea of the study and conceptualized the research aims; H.C., Q.H. and S.Li. design the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S.Li., H.C., J.X. and S. Liu contributed to the acquisition of data; S.Li. did the statistical analysis, H.T. contributed to the optimization of the figures. S.Li. wrote the first draft of the paper; N.S.,

X.L., C.S., R.Y. and other authors provided comments and approved the final manuscript. All the authors reviewed the manuscript.

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References

1. Bellani G, Laffey J G, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries [J]. JAMA, 2016, 315(8): 788-800.
2. Liu L, Yang Y, Gao Z, et al. Practice of diagnosis and management of acute respiratory distress syndrome in mainland China: a cross-sectional study [J]. J Thorac Dis, 2018, 10(9): 5394-5404.
3. Montgomery A B, Stager M A, Carrico C J, et al. Causes of mortality in patients with the adult respiratory distress syndrome [J]. Am Rev Respir Dis, 1985, 132(3): 485-489.
4. Doyle R L, Szaflarski N, Modin G W, et al. Identification of patients with acute lung injury. Predictors of mortality [J]. Am J Respir Crit Care Med, 1995, 152(6 Pt 1): 1818-1824.
5. RD S, BM W, LD H, et al. Causes and timing of death in patients with ARDS [J]. Chest, 2005, 128(2): 525-532.
6. Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome [J]. JAMA, 2003, 289(16): 2104-2112.
7. Seeley E, McAuley D F, Eisner M, et al. Predictors of mortality in acute lung injury during the era of lung protective ventilation [J]. Thorax, 2008, 63(11): 994-998.
8. Quilez M E, Lopez-Aguilar J, Blanch L. Organ crosstalk during acute lung injury, acute respiratory distress syndrome, and mechanical ventilation [J]. Curr Opin Crit Care, 2012, 18(1): 23-28.
9. Acute Respiratory Distress Syndrome N, Brower R G, Matthay M A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome [J]. N Engl J Med, 2000, 342(18): 1301-1308.

10. Panitchote A, Mehkri O, Hastings A, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome [J]. Ann Intensive Care, 2019, 9(1): 74.
11. Vemuri S V, Rolfsen M L, Sykes A V, et al. Association Between Acute Kidney Injury During Invasive Mechanical Ventilation and ICU Outcomes and Respiratory System Mechanics [J]. Crit Care Explor, 2022, 4(7): e0720.
12. Leite T T, Gomes C A M, Valdivia J M C, et al. Respiratory parameters and acute kidney injury in acute respiratory distress syndrome: a causal inference study [J]. Ann Transl Med, 2019, 7(23): 742.
13. Serpa Neto A, Deliberato R O, Johnson A E W, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts [J]. Intensive Care Med, 2018, 44(11): 1914-1922.
14. Amato M B, Meade M O, Slutsky A S, et al. Driving pressure and survival in the acute respiratory distress syndrome [J]. N Engl J Med, 2015, 372(8): 747-755.
15. Sinha P, Calfee C S, Beitler J R, et al. Physiologic Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome [J]. Am J Respir Crit Care Med, 2019, 199(3): 333-341.
16. Benites M H, Suarez-Sipmann F, Kattan E, et al. Ventilation-induced acute kidney injury in acute respiratory failure: Do PEEP levels matter? [J]. Crit Care, 2025, 29(1): 130.
17. Silva P L, Ball L, Rocco P R M, et al. Physiological and Pathophysiological Consequences of Mechanical Ventilation [J]. Semin Respir Crit Care Med, 2022, 43(3): 321-334.
18. Bos L D J, Ware L B. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes [J]. Lancet, 2022, 400(10358): 1145-1156.
19. Bos L D J, Sjoding M, Sinha P, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts [J]. Lancet Respir Med, 2021, 9(12): 1377-1386.
20. Brower R G, Lanken P N, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome [J]. N Engl J Med, 2004, 351(4): 327-336.
21. Force A D T, Ranieri V M, Rubenfeld G D, et al. Acute respiratory distress syndrome: the Berlin Definition [J]. JAMA, 2012, 307(23): 2526-2533.
22. Hong Y, Chen L, Pan Q, et al. Individualized Mechanical power-based ventilation strategy for acute respiratory failure formalized by finite mixture modeling and dynamic treatment regimen [J]. EClinicalMedicine, 2021, 36: 100898.
23. Chen H, Yu Q, Xie J, et al. Longitudinal phenotypes in patients with acute respiratory distress syndrome: a multi-database study [J]. Crit Care, 2022, 26(1): 340.
24. Nylund K L, Asparouhov T, Muthén B O. Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study [J]. Structural Equation Modeling: A Multidisciplinary Journal, 2007, 14(4): 535-569.

25. Nasserinejad K, van Rosmalen J, de Kort W, et al. Comparison of Criteria for Choosing the Number of Classes in Bayesian Finite Mixture Models [J]. PLoS One, 2017, 12(1): e0168838.
26. Seymour C W, Kennedy J N, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis [J]. JAMA, 2019, 321(20): 2003-2017.
27. Monti S, Tamayo P, Mesirov J, et al. Consensus Clustering: A Resampling-Based Method for Class Discovery and Visualization of Gene Expression Microarray Data [J]. Machine Learning, 2003, 52(1): 91-118.
28. Liu X, Jiang Y, Jia X, et al. Identification of distinct clinical phenotypes of acute respiratory distress syndrome with differential responses to treatment [J]. Crit Care, 2021, 25(1): 320.
29. Calfee C S, Delucchi K, Parsons P E, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials [J]. Lancet Respir Med, 2014, 2(8): 611-620.
30. Delucchi K, Famous K R, Ware L B, et al. Stability of ARDS subphenotypes over time in two randomised controlled trials [J]. Thorax, 2018, 73(5): 439-445.
31. Lai C, Monnet X, Teboul J L. Hemodynamic Implications of Prone Positioning in Patients with ARDS [J]. Crit Care, 2023, 27(1): 98.
32. Zhang Z, Zheng B, Liu N, et al. Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome [J]. Intensive Care Med, 2019, 45(6): 856-864.
33. Kallet R H. Mechanical Ventilation in ARDS: Quo Vadis? [J]. Respir Care, 2022, 67(6): 730-749.
34. Mendes R S, Silva P L, Robba C, et al. Advancements in understanding the mechanisms of lung-kidney crosstalk [J]. Intensive Care Med Exp, 2024, 12(1): 81.
35. Hepokoski M L, Malhotra A, Singh P, et al. Ventilator-Induced Kidney Injury: Are Novel Biomarkers the Key to Prevention? [J]. Nephron, 2018, 140(2): 90-93.
36. Pelosi P, Ball L, Barbas C S V, et al. Personalized mechanical ventilation in acute respiratory distress syndrome [J]. Crit Care, 2021, 25(1): 250.
37. Del Sorbo L, Slutsky A S. Acute respiratory distress syndrome and multiple organ failure [J]. Curr Opin Crit Care, 2011, 17(1): 1-6.

Figures

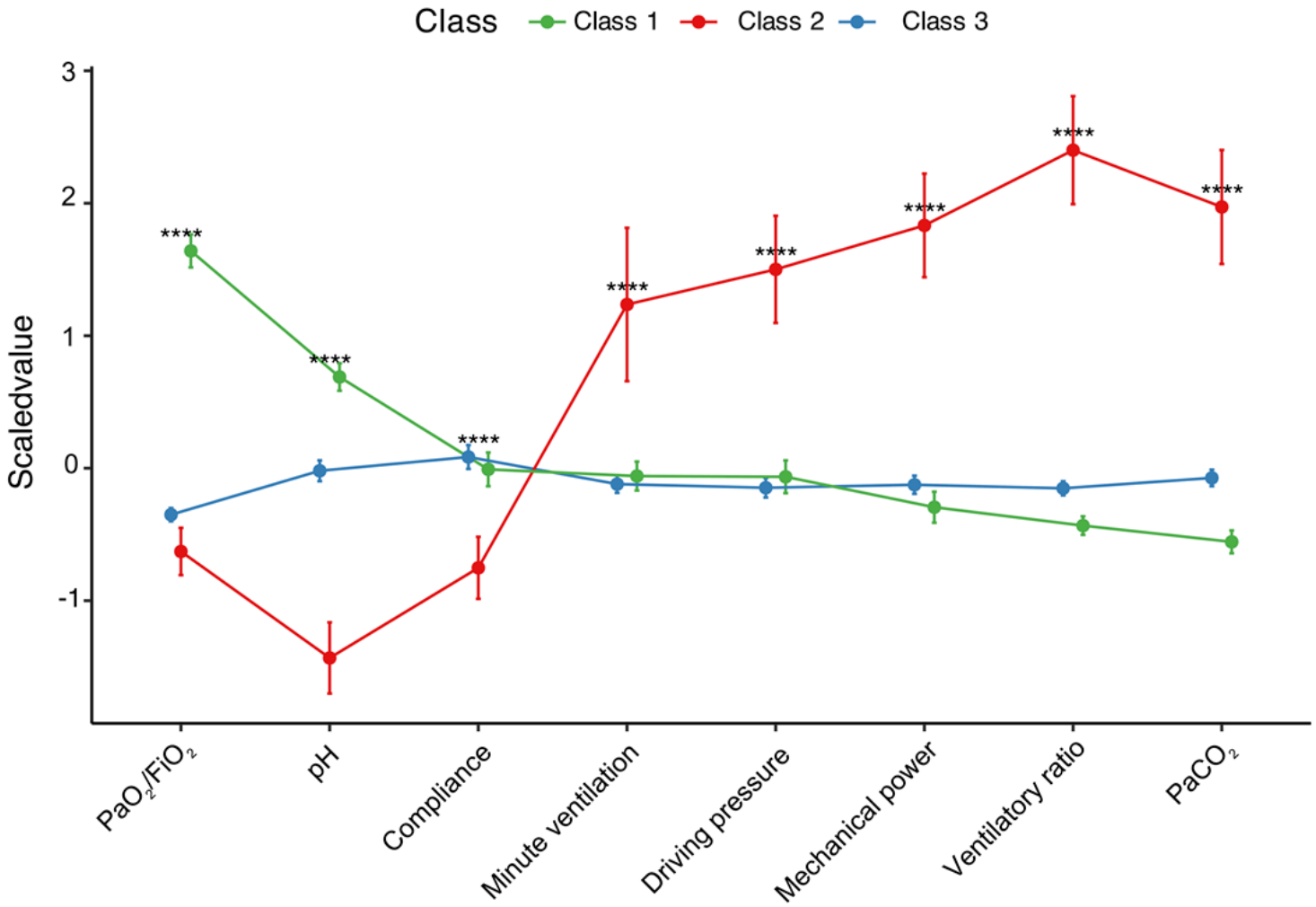


Figure 1

Standardized mean differences between respiratory phenotypes in CDIC derivation cohort.
PaO_2=partial pressure of oxygen; FiO_2=fraction of inspired oxygen; $PaCO_2$=partial pressure of Carbon Dioxide.

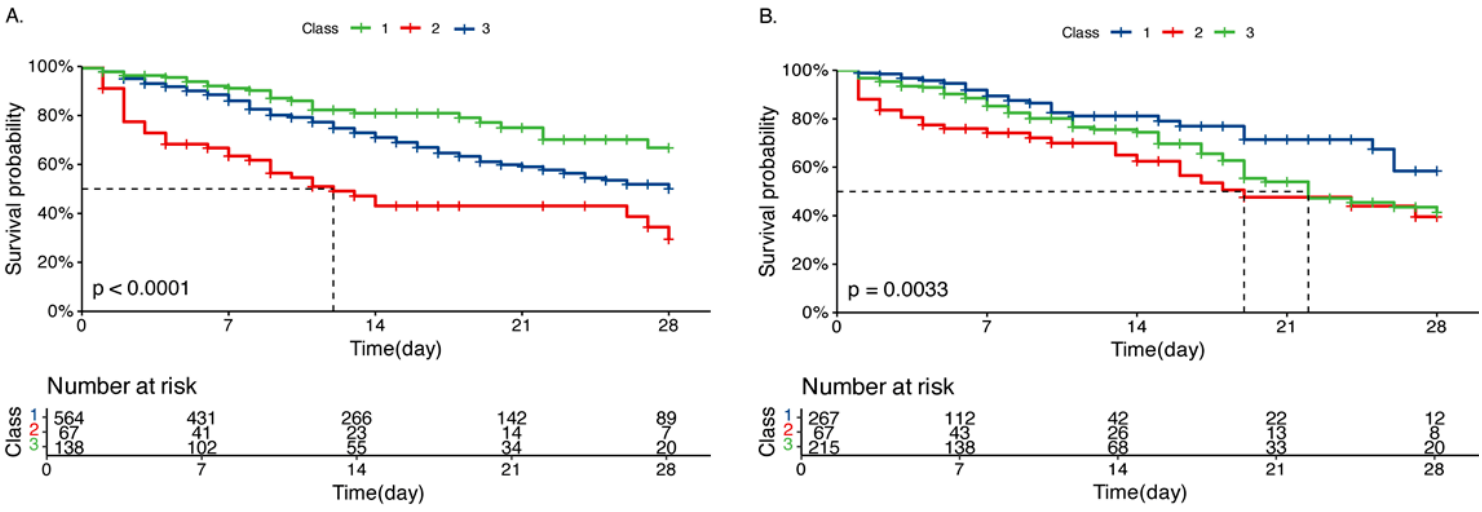


Figure 2

28-day mortality stratified by phenotypes in CDIC derivation cohort and ALVEOLI validation cohort.

A 28-day mortality stratified by phenotype assignment in CDIC. After adjusting for age, gender, BMI and baseline SOFA score, compared with Class 1, the adjusted hazard ratio of 28-day mortality for Class 2 and Class 3 were 3.11 (95% CI 1.75-5.55), 1.39 (95% CI 0.86–2.25), respectively.

B 28-day mortality stratifed by phenotype assignment in ALVEOLI trial, compared with Class 1, the adjusted hazard ratio of 28-day mortality for Class 2 and Class 3 were 2.59 (95% CI (1.56-4.29)), 1.42 (95% CI 0.94-2.15), respectively.

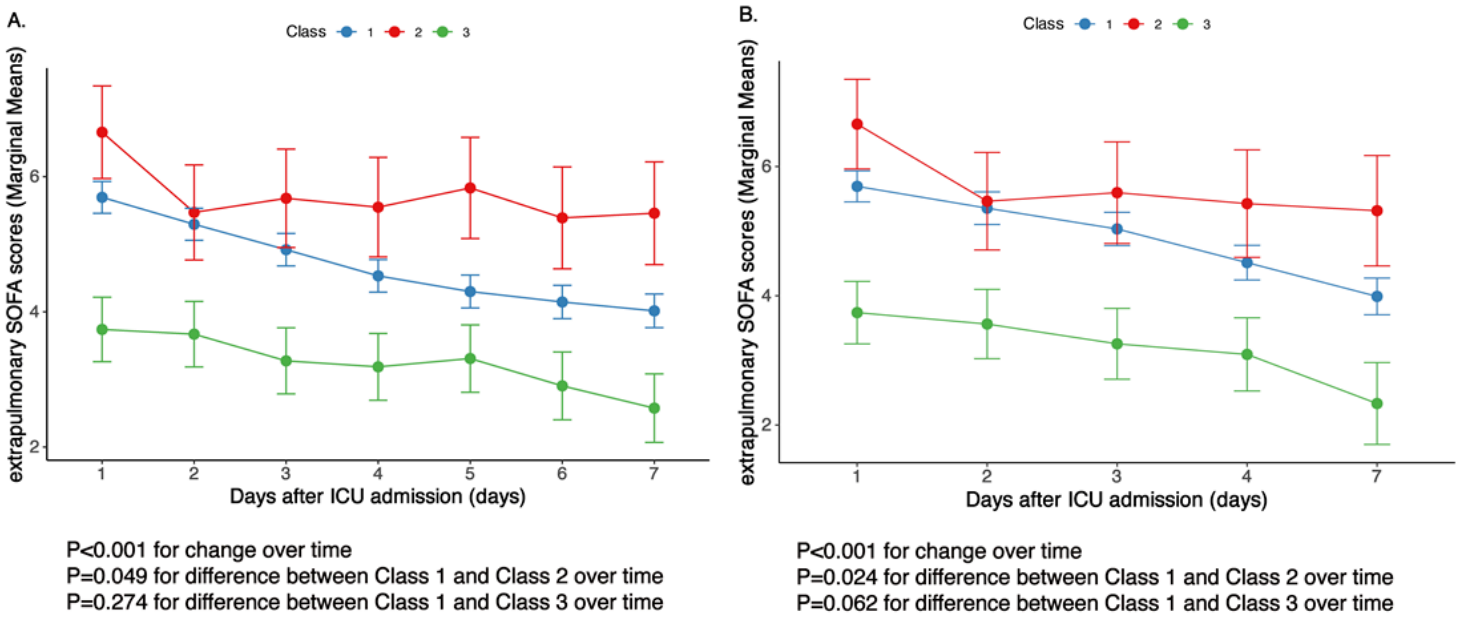


Figure 3

Temporal changes of extrapulmonary organ dysfunction severity among different respiratory phenotypes within the first seven days of mechanical ventilation in CDIC derivation cohort (A) and ALVEOLI validation cohort (B).

Extrapulmonary SOFA scores declined steadily in all phenotypes; however, Class 2 remained consistently higher throughout the 7-day period, with a visibly flatter slope.

Supplementary Files

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- Supplementaryappendix.docx