Research Square

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Early Fluid Balance Dynamics and Short-Term Mortality in Critically Ill Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: An Interpretable Prediction and Trajectory Analysis

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Research Article

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Abstract

Background

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a leading cause of intensive care unit (ICU) admission and short-term mortality. Fluid management is critical, yet the prognostic significance of dynamic fluid changes especially the shift from resuscitation to stabilization remains unclear in this population.

Methods

We conducted a retrospective cohort study using the MIMIC-IV database, including adult ICU patients with AECOPD. Group-based trajectory modeling (GBTM) was used to identify latent patterns of fluid balance over the first three ICU days. An interpretable prediction model for 28-day mortality was built using multivariable logistic regression. Model performance was evaluated with discrimination (AUC), calibration, and decision curve analysis. Feature importance was assessed using Shapley Additive Explanations (SHAP).

Results

A total of 639 patients were included. The prediction model showed good discrimination in both the training (AUC 0.747) and validation cohorts (AUC 0.753). SHAP analysis revealed that fluid balance on ICU day 3 was a key, non-linear, and potentially modifiable predictor of mortality. GBTM identified five distinct longitudinal fluid balance patterns. Trajectories with persistent positive fluid balance were independently linked to the highest 28-day mortality. In contrast, a "rapid correction" trajectory marked by early fluid accumulation followed by prompt removal was associated with survival rates similar to those of patients with stable fluid balance, despite higher baseline illness severity.

Conclusions

In critically ill patients with AECOPD, failure to clear positive fluid balance by ICU day 3 is a strong warning sign. The reversibility of early fluid accumulation, rather than the absolute initial volume, appears to determine survival. These findings support a dynamic risk-stratification approach and underscore the importance of timely de-resuscitation in this vulnerable population.

1. Introduction

AECOPD is a distinct clinical entity and accounts for a substantial proportion of ICU admissions and short-term mortality [1–4]. Management is often complicated by acute respiratory failure, systemic inflammation, and hemodynamic instability [2, 3]. Despite advances in ventilatory support, early identification of patients at highest risk of death remains difficult. Existing prognostic tools, mostly developed for general ICU populations, often fail to reflect the unique pathophysiology of severe AECOPD, including cardiopulmonary interdependence.

Fluid management is critical but controversial in these patients. Resuscitation is necessary to correct hypovolemia or sepsis-induced hypotension. However, patients with AECOPD are particularly prone to fluid overload [5–7]. Their impaired gas exchange and sensitive pulmonary vasculature resemble features of acute respiratory distress syndrome (ARDS), where conservative fluid strategies improve outcomes [8–10]. Clinicians must balance the need for resuscitation against the risk of worsening pulmonary congestion. Most studies linking positive fluid balance to poor outcomes rely on static, cumulative measurements from mixed ICU populations [5, 11]. This snapshot approach overlooks the dynamic course of fluid therapy, which ideally shifts from initial resuscitation to timely de-resuscitation. Such temporal patterns may be critical for survival [12, 13].

TTo address these challenges, two methodological gaps must be bridged. First, fluid management is inherently dynamic and requires approaches that capture temporal patterns. GBTM is a powerful tool for identifying latent clinical phenotypes from longitudinal data [14, 15], but it has not been applied to fluid balance in AECOPD. Second, machine learning can achieve strong predictive performance for mortality, yet the "black box" nature of complex algorithms limits clinical utility [16]. Combining dynamic trajectory analysis with an interpretable prediction framework may clarify how early fluid management affects outcomes [17].

In this study, we aimed to characterize the heterogeneity of early fluid balance dynamics in critically ill AECOPD patients using GBTM. We also sought to develop an interpretable model for 28-day mortality and to assess whether specific fluid balance trajectories independently predict outcomes in this high-risk population.

2. Methods

2.1. Study Design and Data Source

This study was a retrospective cohort study using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database. MIMIC-IV is a large, publicly available critical care database containing detailed information on patients admitted to Beth Israel Deaconess Medical Center (BIDMC), Boston, USA, between 2008 and 2019. The database includes demographics, vital signs, laboratory results, comorbidities, medications, procedures, severity scores, and clinical outcomes.

All data in MIMIC-IV are fully de-identified. According to U.S. Department of Health and Human Services regulations, studies using publicly available de-identified data are exempt from institutional review board approval and informed consent. One author (ChuFan Dong) completed the Collaborative Institutional Training Initiative (CITI) program and obtained authorization to access the database (Record ID: 58063775).

2.2. Study Population

Adult ICU admissions in MIMIC-IV between 2008 and 2019 were initially screened. Patients with AECOPD were identified using ICD-9 and ICD-10 codes. The exclusion criteria were: (1) repeated ICU admissions (only the first admission was retained); (2) age < 18 or > 100 years; (3) ICU length of stay < 3 days; (4) absence of an AECOPD diagnosis; and (5) missing fluid balance data for any of the first three ICU days.

After applying these criteria, 639 patients with AECOPD were included in the final analysis.

2.3. Data Extraction

Clinical data were extracted using structured query language (SQL) in Navicat Premium (version 15.0). The extracted variables included: (1) Demographics: age, sex, race, height, and weight; (2) Vital signs: heart rate, respiratory rate, oxygen saturation, and mean arterial pressure; (3) Severity scores: Sequential Organ Failure Assessment (SOFA) score and Charlson Comorbidity Index; (4) Comorbidities: hypertension, diabetes mellitus, heart failure, acute renal failure, liver cirrhosis, and stroke; (5) Clinical interventions: use of systemic corticosteroids, dopamine, norepinephrine, continuous renal replacement therapy (CRRT), and mechanical ventilation; (6) Laboratory variables: complete blood count, renal and liver function indices, coagulation parameters, myocardial injury markers, lipid profile, electrolytes, and acid-base indices; (7) Outcomes: 28-day in-hospital all-cause mortality and length of hospital stay; (8) Fluid balance: detailed daily fluid intake and output during the first three ICU days.

2.4. Data Preprocessing

2.4.1. Handling of Missing Data

Patients with missing fluid balance data on any of the first three ICU days were excluded. For the remaining variables, missing data were managed using a tiered approach. Variables with more than 20% missing values were excluded. Remaining missing data were addressed using multiple imputation or simple imputation strategies, as appropriate (details are provided in the Supplement).

2.4.2. Calculation of Fluid Balance Indicators

Daily fluid balance was calculated as the difference between total fluid intake and output within each 24-hour period. To account for inter-individual differences in body size, fluid balance was normalized by body weight and expressed as a percentage.

1. Calibrated daily fluid balance rate (%):

Daily fluid balance rate= $\frac{\text{Daily fluid balance (mL)}}{1000\times\text{body weight (kg)}}\times 100\ \%$

2. Cumulative fluid balance rate (%):

Cumulative fluid balance rate= $\sum_{i=1}^{3}$Daily fluid balance rate

3. Fluid balance change rate (%):

Fluid balance change rate= $\frac{\text{Day 1 fluid balance rate-Day 3 fluid balance rate}}{2}$

All calculations were based on fluid balance data recorded at 24, 48, and 72 hours (first three days) after ICU admission.

2.5. Group-Based Trajectory Modeling

To characterize longitudinal patterns of fluid balance during the early ICU course, GBTM was applied to daily fluid balance data over the first three ICU days. GBTM is a finite mixture modeling approach that identifies latent subgroups of patients following similar trajectories over time.

The calibrated daily fluid balance rate for the first three ICU days was used in the analysis. Models with one to five trajectory groups were sequentially fitted. Model selection was based on both statistical and clinical criteria: (1) Model fit: Akaike information criterion (AIC) and Bayesian information criterion (BIC), with lower values indicating better fit; bootstrap likelihood ratio test (BLRT), where $P < 0.05$ indicated significant improvement with additional trajectory classes. (2) Classification accuracy: average posterior probability (AvePP) > 0.7 and odds of correct classification (OCC) > 5. (3) Clinical interpretability: each trajectory group included at least 5% of the sample and displayed clinically meaningful and distinguishable patterns. The optimal trajectory model was selected based on overall performance and clinical plausibility. All analyses were performed using the gbtm package in R.

2. 6. Statistical Analysis

2. 6. 1. Prediction Model Development and Validation

The study population was randomly divided into a training set (70%, n = 447) and a validation set (30%, n = 192). Baseline characteristics were compared between the two sets to ensure balance after random splitting. In the prediction analysis, patients in the training set were grouped according to 28-day in-hospital mortality.

Feature selection combined least absolute shrinkage and selection operator (LASSO) regression with the Boruta algorithm. LASSO regression with 10-fold cross-validation identified variables associated with 28-day mortality. Boruta, a random forest-based method, was used to detect all relevant features. Variables selected by both methods were retained as core predictors. Multicollinearity was assessed using variance inflation factors (VIF), with VIF < 5 considered acceptable.

A multivariable logistic regression model with backward stepwise selection ($P < 0.05$) was constructed to predict 28-day mortality. Results were visualized using a nomogram. Model discrimination was evaluated with receiver operating characteristic (ROC) curves and area under the curve (AUC). Calibration was assessed with calibration plots and the Hosmer-Lemeshow goodness-of-fit test. Clinical usefulness was examined using decision curve analysis (DCA).

Sensitivity analyses excluded influential observations identified by Cook's distance to test model robustness.

2.6.2.Model Interpretability Using SHAP

To enhance interpretability of the prediction model, SHAP values were applied. SHAP quantifies the contribution of each predictor to an individual's predicted risk based on cooperative game theory. A SHAP beeswarm plot was generated to visualize the global importance of predictors and the direction of their effects on mortality risk. Higher SHAP values indicated a greater contribution to increased predicted mortality, while lower values reflected protective effects.

2.6.3.Trajectory Analysis and Survival Analysis

Kaplan-Meier survival curves were constructed to compare 28-day survival among different fluid balance trajectory groups. Differences were assessed using the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for 28-day mortality across trajectory groups.

Four hierarchical models were constructed: Model 1: unadjusted; Model 2: adjusted for demographic variables and severity scores; Model 3: adjusted for variables selected by LASSO and Boruta; Model 4: further adjusted for baseline variables showing significant between-group differences.

Subgroup analyses were conducted stratified by age, sex, race, and major comorbidities. Interaction terms were introduced to test for effect modification.

All statistical tests were two-sided, with a significance level of 0.05. Analyses were performed using R software (version 4.3.3) and the Zstats online statistical platform (www.zstats.net).

3. Results

3.1. Baseline Characteristics of the Study Population

The patient selection process is shown in Fig. 1. A total of 639 patients with AECOPD were included, with 447 in the training cohort and 192 in the validation cohort. Baseline characteristics were well balanced between the two cohorts (Supplementary Table S1).

In the training cohort, 108 patients (24.2%) died within 28 days. Non-survivors were older and had higher SOFA scores and Charlson Comorbidity Index values. Acute kidney injury (AKI) and the use of CRRT, particularly when initiated after 72 hours, were more common among non-survivors. Fluid balance trajectories also differed markedly, with non-survivors failing to achieve negative fluid balance by ICU day 3 (Table 1).

Table 1
Baseline characteristics of AECOPD patients stratified by 28-day mortality in the training cohort.

Variables	Total (n = 447)	Survivors (n = 339)	Non-survivors (n = 108)	Statistic	P
Demographic variables					
Age, years	70.60 ± 11.06	69.55 ± 11.16	73.91 ± 10.10	t=-3.62	< .001*
Weight, kg	84.58 ± 27.63	86.76 ± 28.86	77.74 ± 22.12	t = 3.41	< .001*
Gender, n(%)				χ^2=0.40	0.525
Male	224 (50.11)	167 (49.26)	57 (52.78)		
Female	223 (49.89)	172 (50.74)	51 (47.22)		
Race, n(%)				χ^2=0.11	0.743
White	275 (61.52)	210 (61.95)	65 (60.19)		
Others	172 (38.48)	129 (38.05)	43 (39.81)		
Vital signs					
HR, beats/min	92.35 ± 19.78	92.38 ± 19.33	92.27 ± 21.23	t = 0.05	0.960
MAP, mmHg	96.42 ± 285.95	101.04 ± 328.18	81.91 ± 17.71	t = 0.60	0.545
RR, times/min	21.22 ± 6.47	21.27 ± 6.49	21.06 ± 6.43	t = 0.28	0.779
Spo2, %	95.78 ± 4.14	95.90 ± 4.10	95.40 ± 4.26	t = 1.10	0.273
Scores					
Sofa	5.85 ± 3.38	5.58 ± 3.22	6.71 ± 3.72	t=-3.07	0.002*
Charlson	6.35 ± 2.60	6.02 ± 2.58	7.39 ± 2.40	t=-4.89	< .001*
Comorbidities					
Hypertension, n(%)				χ^2=0.01	0.925
No	259 (57.94)	196 (57.82)	63 (58.33)		
Yes	188 (42.06)	143 (42.18)	45 (41.67)		
Diabetes, n(%)				χ^2=0.08	0.780
No	307 (68.68)	234 (69.03)	73 (67.59)		
Yes	140 (31.32)	105 (30.97)	35 (32.41)		
Heart failure, n(%)				χ^2=0.63	0.426
No	226 (50.56)	175 (51.62)	51 (47.22)		
Yes	221 (49.44)	164 (48.38)	57 (52.78)		
Acute renal failure, n(%)				χ^2=16.04	< .001*
No	224 (50.11)	188 (55.46)	36 (33.33)		

Table Footnotes: t, t-test; Z, mann-whitney test; χ^2, Chi-square test; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

Variables	Total (n = 447)	Survivors (n = 339)	Non-survivors (n = 108)	Statistic	P
Yes	223 (49.89)	151 (44.54)	72 (66.67)		
Cirrhosis, n(%)				χ^2=4.20	0.040*
No	426 (95.30)	327 (96.46)	99 (91.67)		
Yes	21 (4.70)	12 (3.54)	9 (8.33)		
Stroke, n(%)				χ^2=2.82	0.093
No	414 (92.62)	310 (91.45)	104 (96.30)		
Yes	33 (7.38)	29 (8.55)	4 (3.70)		
Treatments					
Rxglucocorticoids, n(%)				χ^2=0.87	0.352
No	202 (45.19)	149 (43.95)	53 (49.07)		
Yes	245 (54.81)	190 (56.05)	55 (50.93)		
Dopamine, n(%)				χ^2=3.14	0.077
No	429 (95.97)	329 (97.05)	100 (92.59)		
Yes	18 (4.03)	10 (2.95)	8 (7.41)		
Epinephrine, n(%)				χ^2=4.03	0.045*
No	203 (45.41)	163 (48.08)	40 (37.04)		
Yes	244 (54.59)	176 (51.92)	68 (62.96)		
Crrt, n(%)				χ^2=10.88	< .001*
No	419 (93.74)	325 (95.87)	94 (87.04)		
Yes	28 (6.26)	14 (4.13)	14 (12.96)		
Ventilation, n(%)				χ^2=0.29	0.591
No	15 (3.36)	10 (2.95)	5 (4.63)		
Yes	432 (96.64)	329 (97.05)	103 (95.37)		
Incidence of CRRT after 72h, n(%)				χ^2=13.64	< .001*
No	430 (96.20)	333 (98.23)	97 (89.81)		
Yes	17 (3.80)	6 (1.77)	11 (10.19)		
Fluid Balance Dynamics					
Fluid balance on Day 1, %	2.05 ± 3.74	1.89 ± 3.68	2.54 ± 3.90	t=-1.56	0.120
Fluid balance on Day 2, %	0.29 ± 2.05	0.18 ± 1.99	0.64 ± 2.21	t=-2.06	0.040*
Fluid balance on Day 3, %	-0.45 ± 1.90	-0.71 ± 1.80	0.36 ± 1.97	t=-5.27	< .001*
Rate of fluid balance change, %	-1.25 ± 2.04	-1.30 ± 2.04	-1.09 ± 2.02	t=-0.95	0.340

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Variables	Total (n = 447)	Survivors (n = 339)	Non-survivors (n = 108)	Statistic	P
Cumulative fluid balance over 3 days, %	1.89 ± 5.49	1.37 ± 5.29	3.55 ± 5.81	t=-3.64	< .001*
Laboratory parameters					
Creatinine, mg/dL	1.26 ± 0.89	1.22 ± 0.90	1.38 ± 0.85	t=-1.65	0.099
Pt, seconds	15.65 ± 7.45	15.15 ± 6.60	17.22 ± 9.51	t=-2.11	0.036*
Inrpt	1.46 ± 0.95	1.42 ± 0.94	1.59 ± 0.95	t=-1.61	0.108
Ptt, seconds	35.63 ± 20.34	35.03 ± 19.47	37.49 ± 22.83	t=-1.09	0.276
White blood cells,10^9/L	12.98 ± 7.00	12.73 ± 6.86	13.76 ± 7.39	t=-1.33	0.184
Red blood cells, 10^9/L	3.70 (3.17, 4.22)	3.77 (3.21, 4.30)	3.54 (3.06, 4.00)	Z=-2.89	0.004*
RDW, %	15.47 ± 2.41	15.32 ± 2.38	15.91 ± 2.49	t=-2.20	0.028*
Sodium, mmol/L	139.02 ± 5.27	138.92 ± 4.96	139.34 ± 6.14	t=-0.65	0.513
Potassium, mmol/L	4.43 ± 0.85	4.43 ± 0.84	4.45 ± 0.86	t=-0.22	0.824
Calciumtotal, mg/dL	8.34 ± 0.79	8.32 ± 0.77	8.41 ± 0.86	t=-0.99	0.325
Glucose, mg/dL	155.34 ± 65.23	154.38 ± 67.07	158.36 ± 59.30	t=-0.55	0.582
Aniongap, mmol/L	13.91 ± 3.98	13.64 ± 3.93	14.77 ± 4.03	t=-2.58	0.010*
Base excess, mmol/L	1.53 ± 5.65	1.81 ± 5.65	0.66 ± 5.61	t = 1.84	0.066

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RDW, %	15.47 ± 2.41	15.32 ± 2.38	15.91 ± 2.49	t=-2.20	0.028*
Sodium, mmol/L	139.02 ± 5.27	138.92 ± 4.96	139.34 ± 6.14	t=-0.65	0.513
Potassium, mmol/L	4.43 ± 0.85	4.43 ± 0.84	4.45 ± 0.86	t=-0.22	0.824
Calciumtotal, mg/dL	8.34 ± 0.79	8.32 ± 0.77	8.41 ± 0.86	t=-0.99	0.325
Glucose, mg/dL	155.34 ± 65.23	154.38 ± 67.07	158.36 ± 59.30	t=-0.55	0.582
Aniongap, mmol/L	13.91 ± 3.98	13.64 ± 3.93	14.77 ± 4.03	t=-2.58	0.010*
Base excess, mmol/L	1.53 ± 5.65	1.81 ± 5.65	0.66 ± 5.61	t = 1.84	0.066

Table Footnotes: t, t-test; Z, mann-whitney test; χ^2, Chi-square test; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

3.2. Feature Selection and Development of the Prediction Model

A two-step feature selection strategy was applied. Variables identified by both LASSO logistic regression and the Boruta algorithm were retained, yielding six candidate predictors (Fig. 2). Due to its strong clinical relevance to mortality and fluid balance, acute renal failure was also included in the initial multivariable logistic regression model.

After backward stepwise selection, five independent predictors remained in the final model: age, SOFA score, Charlson Comorbidity Index, fluid balance on ICU day 3, and CRRT initiation after 72 hours. Sensitivity analyses excluding influential observations produced consistent estimates, indicating good model robustness (Table 2).

Table 2
Univariable, multivariable, and sensitivity logistic regression analyses for 28-day mortality

Variables	Model 1		Model 2		Model 3	
	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
Age	1.039(1.02–1.06)	< 0.001	1.031(1.01–1.06)	0.012	1.045(1.02–1.08)	0.002
Sofa	1.100(1.03–1.17)	0.003	1.081(1.01–1.16)	0.026	1.117(1.03–1.21)	0.008
Charlson	1.224(1.13–1.34)	< 0.001	1.148(1.04–1.27)	0.007	1.196(1.07–1.34)	0.002
Fluid balance on Day 3	1.369(1.21–1.56)	< 0.001	1.343(1.18–1.54)	< 0.001	1.534(1.32–1.8)	< 0.001
Acute renal failure						
No						
Yes	2.490(1.59–3.95)					
Dopamine						
No						
Yes	2.632(0.98–6.85)	0.047				
Incidence of crrt after 72 hours						
No						
Yes	6.294(2.33–18.68)	< 0.001	5.093(1.73–16.38)	0.004	24.251(2.63–613.47)	0.016
Model 1 represents univariable logistic regression analyses.						
Model 2 represents the final multivariable logistic regression model derived using backward stepwise selection.						
Model 3 represents a sensitivity analysis model fitted after exclusion of influential observations identified by Cook's distance.						
OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment score; Charlson, Charlson Comorbidity Index.2						

3.3. Nomogram Construction and Model Performance

A nomogram was constructed based on the final multivariable model to enable individualized prediction of 28-day mortality (Fig. 4). The model showed good discrimination, with an AUC of 0.747 in the training cohort and 0.753 in the validation cohort (Fig. 5A). At the optimal cutoff of 0.259, the model achieved a high negative predictive value (training: 0.86, 95% CI: 0.82–0.90; validation: 0.85, 95% CI: 0.79–0.91), indicating strong ability to correctly identify survivors (Supplementary Table 2). Calibration analysis showed good agreement between predicted and observed risks, with no evidence of lack of fit in either cohort (Fig. 5B-C). Decision curve analysis demonstrated a positive net benefit across a wide range of threshold probabilities in both cohorts (Fig. 6).

3.4. Model Interpretability Using SHAP Analysis

The SHAP beeswarm plot showed that fluid balance on ICU day 3 was the strongest predictor of mortality at the population level. Age, SOFA score, and Charlson Comorbidity Index also contributed notably. CRRT initiation after 72 hours had a smaller overall contribution but was consistently associated with higher predicted mortality when present (Fig. 7).

3.5. Identification of Fluid Balance Trajectories and Baseline Characteristics Across Classes

Group-based trajectory modeling identified five distinct fluid balance trajectories during the first three ICU days. Model fit improved as the number of classes increased, and the five-class model offered the best balance between goodness of fit and parsimony (AIC = 8600.594; BIC = 8728.440). Classification performance was excellent, with an odds of correct classification of 82.49 and an average posterior probability of 0.908. Class sizes ranged from 13.30% to 39.44% (Supplementary Table 2).

The identified trajectories were labeled according to their longitudinal patterns (Fig. 8):

Class 1, moderate negative balance with gradual upward trend;

Class 2, persistent moderate positive balance;

Class 3, stable near-zero balance;

Class 4, moderate positive balance with rapid correction;

Class 5, marked positive balance with rapid de-resuscitation.

Baseline characteristics differed significantly across trajectory classes (Table 3). Class 2 had the highest illness severity, greatest CRRT use, and highest 28-day mortality. In contrast, Class 1 had the lowest SOFA scores and 28-day mortality. Class 3 was the largest group and showed a near-zero fluid balance pattern. It had intermediate levels of inflammatory burden, illness severity, and 28-day mortality, and was therefore used as the reference trajectory. Classes 4 and 5 had higher illness severity at admission, but their 28-day mortality was substantially lower than that of Class 2, reflecting more rapid correction of fluid balance.

Table 3
Baseline Characteristics of Study Participants Stratified by 3-Day Fluid Balance Trajectories

Variables	Total (n = 639)	Class 1 (n = 85)	Class 2 (n = 106)	Class 3 (n = 252)	Class 4 (n = 135)	Class 5 (n = 61)	Statistic	P
Demographic variables								
Age, years	70.88 ± 11.12	68.72 ± 11.56	71.62 ± 11.83	70.96 ± 11.21	71.18 ± 9.83	71.61 ± 11.51	F = 1.02	0.399
Weight, kg	84.92 ± 27.96	87.01 ± 34.38	78.40 ± 26.14	91.66 ± 27.88	82.44 ± 25.07	70.96 ± 17.87	F = 9.80	< .001*
Gender, n(%)							χ^2=9.44	0.051
Male	315 (49.30)	36 (42.35)	56 (52.83)	128 (50.79)	74 (54.81)	21 (34.43)		
Female	324 (50.70)	49 (57.65)	50 (47.17)	124 (49.21)	61 (45.19)	40 (65.57)		
Race, n(%)							χ^2=0.54	0.969
White	397 (62.13)	54 (63.53)	63 (59.43)	158 (62.70)	83 (61.48)	39 (63.93)		
Others	242 (37.87)	31 (36.47)	43 (40.57)	94 (37.30)	52 (38.52)	22 (36.07)		
Vital signs								
HR, beats/min	92.57 ± 20.30	92.60 ± 18.13	92.72 ± 21.20	91.81 ± 18.98	91.45 ± 20.54	97.85 ± 25.51	F = 1.23	0.298
MAP, mmHg	92.55 ± 239.34	88.22 ± 16.49	80.25 ± 16.43	84.53 ± 17.69	127.30 ± 519.59	76.18 ± 22.12	F = 0.93	0.446
RR, times/min	21.21 ± 6.50	21.31 ± 6.05	21.43 ± 6.70	21.45 ± 6.53	21.00 ± 6.72	20.15 ± 6.24	F = 0.56	0.689
Spo2, %	95.82 ± 4.18	95.06 ± 5.53	96.19 ± 3.52	95.52 ± 3.77	96.37 ± 4.26	96.26 ± 4.39	F = 1.99	0.094
Scores								
Sofa	5.93 ± 3.42	4.81 ± 2.94	6.75 ± 3.49	5.13 ± 3.00	6.59 ± 3.52	7.89 ± 3.92	F = 14.64	< .001*
Charlson	6.34 ± 2.60	6.47 ± 3.07	6.63 ± 2.56	6.40 ± 2.54	6.17 ± 2.48	5.77 ± 2.43	F = 1.30	0.268
Comorbidities								
Hypertension, n(%)							χ^2=2.73	0.603
No	360 (56.34)	53 (62.35)	59 (55.66)	144 (57.14)	74 (54.81)	30 (49.18)		

Table Footnotes: F: ANOVA, #: Kruskal-waills test, χ^2: Chi-square test, -: Fisher exact; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

Variables	Total (n = 639)	Class 1 (n = 85)	Class 2 (n = 106)	Class 3 (n = 252)	Class 4 (n = 135)	Class 5 (n = 61)	Statistic	P
Yes	279 (43.66)	32 (37.65)	47 (44.34)	108 (42.86)	61 (45.19)	31 (50.82)		
Diabetes, n(%)							χ^2=10.03	0.040*
No	443 (69.33)	54 (63.53)	72 (67.92)	165 (65.48)	107 (79.26)	45 (73.77)		
Yes	196 (30.67)	31 (36.47)	34 (32.08)	87 (34.52)	28 (20.74)	16 (26.23)		
Heart failure, n(%)							χ^2=22.22	< .001*
No	322 (50.39)	27 (31.76)	62 (58.49)	118 (46.83)	76 (56.30)	39 (63.93)		
No	317 (49.61)	58 (68.24)	44 (41.51)	134 (53.17)	59 (43.70)	22 (36.07)		
Acute renal failure, n(%)							χ^2=9.09	0.059
No	322 (50.39)	55 (64.71)	47 (44.34)	121 (48.02)	68 (50.37)	31 (50.82)		
Yes	317 (49.61)	30 (35.29)	59 (55.66)	131 (51.98)	67 (49.63)	30 (49.18)		
Cirrhosis, n(%)							-	0.986
No	610 (95.46)	81 (95.29)	102 (96.23)	240 (95.24)	128 (94.81)	59 (96.72)		
Yes	29 (4.54)	4 (4.71)	4 (3.77)	12 (4.76)	7 (5.19)	2 (3.28)		
Stroke, n(%)							χ^2=4.92	0.296
No	592 (92.64)	76 (89.41)	101 (95.28)	234 (92.86)	122 (90.37)	59 (96.72)		
Yes	47 (7.36)	9 (10.59)	5 (4.72)	18 (7.14)	13 (9.63)	2 (3.28)		
Treatments								
Rxglucocorticoids, n(%)							χ^2=1.79	0.775
No	291 (45.54)	39 (45.88)	52 (49.06)	112 (44.44)	64 (47.41)	24 (39.34)		
Yes	348 (54.46)	46 (54.12)	54 (50.94)	140 (55.56)	71 (52.59)	37 (60.66)		
Dopamine, n(%)							-	0.460
No	615 (96.24)	82 (96.47)	100 (94.34)	245 (97.22)	131 (97.04)	57 (93.44)		

Table Footnotes: F: ANOVA, #: Kruskal-waills test, χ^2: Chi-square test, -: Fisher exact; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

Variables	Total (n = 639)	Class 1 (n = 85)	Class 2 (n = 106)	Class 3 (n = 252)	Class 4 (n = 135)	Class 5 (n = 61)	Statistic	P
Yes	24 (3.76)	3 (3.53)	6 (5.66)	7 (2.78)	4 (2.96)	4 (6.56)		
Epinephrine, n(%)							χ^2=74.54	< .001*
No	291 (45.54)	62 (72.94)	35 (33.02)	142 (56.35)	40 (29.63)	12 (19.67)		
Yes	348 (54.46)	23 (27.06)	71 (66.98)	110 (43.65)	95 (70.37)	49 (80.33)		
Crrt, n(%)							χ^2=30.50	< .001*
No	596 (93.27)	84 (98.82)	91 (85.85)	240 (95.24)	131 (97.04)	50 (81.97)		
Yes	43 (6.73)	1 (1.18)	15 (14.15)	12 (4.76)	4 (2.96)	11 (18.03)		
Ventilation, n(%)							-	0.025*
No	16 (2.50)	1 (1.18)	8 (7.55)	5 (1.98)	2 (1.48)	0 (0.00)		
Yes	623 (97.50)	84 (98.82)	98 (92.45)	247 (98.02)	133 (98.52)	61 (100.00)		
Incidence of CRRT after 72h, n(%)							-	0.020*
No	613 (95.93)	84 (98.82)	101 (95.28)	241 (95.63)	133 (98.52)	54 (88.52)		
Yes	26 (4.07)	1 (1.18)	5 (4.72)	11 (4.37)	2 (1.48)	7 (11.48)		
Fluid Balance Dynamics								
Fluid balance on Day 1, %	1.97 ± 3.81	-2.63 ± 1.33	2.47 ± 2.08	0.10 ± 1.08	4.20 ± 1.58	10.29 ± 2.67	F = 725.41	< .001*
Fluid balance on Day 2, %	0.21 ± 2.19	-1.67 ± 1.35	2.72 ± 1.77	-0.24 ± 1.10	-0.44 ± 1.69	1.81 ± 3.28	F = 107.58	< .001*
Fluid balance on Day 3, %	-0.51 ± 1.94	-1.60 ± 1.30	1.57 ± 1.86	-0.61 ± 1.15	-1.38 ± 1.68	-0.31 ± 2.98	F = 60.51	< .001*
Rate of fluid balance change, %	-1.24 ± 2.07	0.51 ± 1.01	-0.45 ± 1.43	-0.36 ± 0.83	-2.79 ± 1.05	-5.30 ± 2.05	F = 337.89	< .001*
Cumulative fluid balance over 3 days, %	1.67 ± 5.78	-5.90 ± 2.01	6.76 ± 3.20	-0.75 ± 1.89	2.38 ± 3.36	11.79 ± 5.88	F = 414.29	< .001*
Laboratory parameters								
Creatinine, mg/dL	1.28 ±	1.17 ±	1.44 ±	1.28 ±	1.29 ±	1.17 ±	F = 1.33	0.257

Table Footnotes: F: ANOVA, #: Kruskal-waills test, χ^2: Chi-square test, -: Fisher exact; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

Variables	Total (n = 639)	Class 1 (n = 85)	Class 2 (n = 106)	Class 3 (n = 252)	Class 4 (n = 135)	Class 5 (n = 61)	Statistic	P
	0.93	0.78	1.20	0.83	0.99	0.85		
Pt, seconds	15.75 ± 7.82	16.30 ± 9.18	15.17 ± 6.42	15.55 ± 7.35	16.06 ± 8.45	16.18 ± 8.57	F = 0.39	0.817
Inrpt	1.47 ± 0.92	1.50 ± 0.90	1.40 ± 0.66	1.43 ± 0.74	1.57 ± 1.36	1.48 ± 0.77	F = 0.71	0.585
Ptt, seconds	37.01 ± 23.18	38.41 ± 23.79	35.65 ± 19.89	34.79 ± 19.84	39.62 ± 27.89	40.85 ± 28.09	F = 1.60	0.173
White blood cells,10^9/L	12.77 ± 7.23	10.52 ± 6.05	12.66 ± 6.32	11.90 ± 6.58	14.60 ± 7.90	15.61 ± 9.35	F = 7.82	< .001*
Red blood cells, 10^9/L	3.69 (3.15, 4.22)	3.77 (3.16,4.38)	3.65 (3.13,4.19)	3.77 (3.21,4.23)	3.61 (3.10,4.16)	3.42 (3.06,3.94)	χ^2=8.35#	0.079
RDW, %	15.42 ± 2.35	15.88 ± 2.80	15.78 ± 2.69	15.46 ± 2.29	14.89 ± 1.85	15.17 ± 2.12	F = 3.40	0.009*
Sodium, mmol/L	139.00 ± 5.37	138.72 ± 5.76	138.56 ± 5.33	139.07 ± 5.52	139.20 ± 4.73	139.48 ± 5.64	F = 0.41	0.798
Potassium, mmol/L	4.43 ± 0.83	4.41 ± 0.91	4.42 ± 0.87	4.44 ± 0.80	4.48 ± 0.83	4.31 ± 0.71	F = 0.42	0.794
Calciumtotal, mg/dL	8.33 ± 0.81	8.59 ± 0.54	8.26 ± 0.96	8.50 ± 0.73	8.17 ± 0.71	7.71 ± 0.94	F = 17.39	< .001*
Glucose, mg/dL	155.65 ± 65.46	152.35 ± 70.57	154.54 ± 67.03	160.69 ± 65.17	150.62 ± 65.92	152.49 ± 55.37	F = 0.67	0.614
Aniongap, mmol/L	13.99 ± 3.99	13.49 ± 4.01	15.21 ± 4.67	13.90 ± 3.56	13.61 ± 3.40	13.79 ± 5.12	F = 3.21	0.013*
Base excess, mmol/L	1.52 ± 5.65	5.44 ± 5.99	0.28 ± 5.40	2.03 ± 4.83	0.44 ± 5.43	-1.54 ± 6.03	F = 19.87	< .001*
Outcome								
28-day mortality, n(%)							χ^2=14.11	0.007*
No	484 (75.74)	70 (82.35)	66 (62.26)	196 (77.78)	107 (79.26)	45 (73.77)		
Yes	155 (24.26)	15 (17.65)	40 (37.74)	56 (22.22)	28 (20.74)	16 (26.23)		

Table Footnotes: F: ANOVA, #: Kruskal-waills test, χ^2: Chi-square test, -: Fisher exact; *: $p < 0.05$. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HR, heart rate; MAP, mean arterial Pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; SOFA, sequential organ failure assessment; Charlson, charlson comorbidity index; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDW, red cell distribution width; CRRT, continuous renal replacement therapy.

3.6. Association Between Fluid Balance Trajectories and 28-Day Mortality

Kaplan-Meier analysis showed significant differences in 28-day survival across the five trajectory classes (log-rank P = 0.0023). Trajectory class 2 had the poorest survival (Fig. 9). Using class 3 as the reference, Cox regression analyses showed that class 2 was consistently associated with increased 28-day mortality across sequentially adjusted models. In the fully adjusted

model, trajectory class 2 remained independently associated with higher mortality risk (HR: 1.73, 95% CI: 1.12–2.67; P = 0.014). No significant associations were observed for the other classes (Table 4).

Table 4
Association Between Fluid Balance Trajectory Classes and 28-Day Mortality: Unadjusted and Multivariable-Adjusted Cox Proportional Hazards Models

Variables	Model1		Model2		Model3		Model4	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Class								
3	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.94 (1.29 ~ 2.91)	**0.001**	1.79 (1.18 ~ 2.71)	**0.006**	1.85 (1.22 ~ 2.81)	**0.004**	1.73 (1.12 ~ 2.67)	**0.014**
1	0.77 (0.44 ~ 1.37)	0.380	0.76 (0.43 ~ 1.36)	0.358	0.84 (0.47 ~ 1.51)	0.566	0.87 (0.49 ~ 1.57)	0.654
4	0.91 (0.58 ~ 1.44)	0.700	0.90 (0.57 ~ 1.43)	0.658	0.98 (0.61 ~ 1.56)	0.933	0.92 (0.56 ~ 1.49)	0.721
5	1.27 (0.73 ~ 2.21)	0.401	1.25 (0.70 ~ 2.26)	0.453	1.21 (0.66 ~ 2.21)	0.538	1.23 (0.66 ~ 2.30)	0.521
HR: Hazard Ratio, CI: Confidence Interval								
Model1: Crude								
Model2: Adjust: Age, Gender, Sofa, Charlson								
Model3: Adjust: Age, Gender, Sofa, Charlson, Acute renal failure, Dopamine, Crrt occurrence 72h								
Model4: Adjust: Age, Gender, Sofa, Charlson, Diabetes, Heart failure, Acute renal failure, Dopamine, Epinephrine, Crrt, Ventilation, Crrt occurrence 72h, White blood cells, Red cell distribution width, Calciumtotal, Aniongap, Base excess								

3.7. Subgroup Analyses

Subgroup analyses demonstrated that the association between trajectory class 2 and increased mortality risk was consistent across strata defined by age, sex, race, and major comorbidities. No significant interactions were detected (all P for interaction > 0.05), indicating no evidence of effect modification (Fig. 10).

4. Discussion

In this retrospective analysis of critically ill patients with AECOPD, we combined interpretable machine learning with trajectory analysis to examine the prognostic significance of early fluid dynamics. Our results provide three clinically relevant insights: (1) Fluid balance on ICU day 3 was a dominant, independent predictor of 28-day mortality. (2) Early fluid evolution was heterogeneous, forming five distinct longitudinal phenotypes. (3) A trajectory of "persistent positive balance" was strongly associated with poor outcomes, whereas trajectories with rapid fluid correction even after initial overload showed survival rates comparable to patients with stable fluid balance. While cumulative fluid overload is a known risk factor in general sepsis and surgical populations [5, 11],our findings highlight the specific temporal importance of Day 3 in AECOPD. Conceptually, the first three days of critical illness bridge the transition from the "Resuscitation" and "Optimization" phases to the "Stabilization" and "De-resuscitation" phases [12, 13]. Fluid balance on Day 3 thus serves as a functional biomarker of two processes: the resolution of shock and the effectiveness of fluid removal.

In our SHAP analysis, fluid balance on ICU day 3 contributed significantly to mortality prediction. This is biologically plausible given the cardiopulmonary pathophysiology of AECOPD. These patients often have right ventricular (RV) dysfunction and pulmonary hypertension [2, 3]. Unlike healthy hearts, the failing right ventricle is highly sensitive to volume overload. Venous congestion can rapidly increase RV afterload and impair gas exchange [4, 7]. Consequently, failure to reach a neutral or negative balance by day 3 likely reflects a state of "fluid lock-in," leading to pulmonary edema and prolonged ventilator dependence. This mirrors findings in ARDS populations, where conservative fluid strategies improve outcomes [8–10].

The use of GBTM allowed us to move beyond static snapshots and identify latent phenotypes, similar to recent studies in AKI [14]. The most striking finding was the divergence between Class 2 (Persistent Positive) and Classes 4/5 (Rapid Correction). Although all three groups initially received substantial fluid volumes, presumably for resuscitation, their outcomes differed markedly.

Class 2 patients, who failed to transition to a negative balance, had the highest mortality. This supports the concept that sustained tissue edema, rather than initial resuscitation volume, drives adverse outcomes [13]. In contrast, patients in Classes 4 and 5 achieved rapid fluid removal, likely through diuretics or spontaneous diuresis, and had survival rates similar to the "Stable Zero" group. This observation aligns with the "de-resuscitation" paradigm proposed by the International Fluid Academy [12] and suggests that in AECOPD, reversibility of fluid overload is a key determinant of survival. Clinicians should actively assess the potential for fluid removal once hemodynamic stability is achieved, rather than accepting cumulative positive balance as inevitable.

Combining GBTM features with prediction models represents a step toward "precision fluid management." Traditional scores like SOFA [18] capture organ dysfunction but miss dynamic nuances of treatment response. Using SHAP, we showed that fluid metrics are not mere confounders but potent drivers of mortality risk.

5. Limitations

This study has several limitations. First, as a retrospective single-center study, causal relationships between fluid removal and survival cannot be definitively established. Second, we were unable to distinguish fluid types or capture detailed diuretic dosages due to data granularity. Third, although we adjusted for major confounders, unmeasured variables such as specific ventilation strategies could still influence outcomes.

6. Conclusion

In critically ill patients with AECOPD, failure to achieve negative fluid balance by ICU day 3 and a trajectory of persistent fluid accumulation are strong, independent predictors of short-term mortality. In contrast, early correction of fluid overload appears protective. These findings support a paradigm shift toward dynamic fluid stewardship in AECOPD, emphasizing active de-resuscitation once the shock phase resolves.

Abbreviations

AECOPD
Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AIC
Akaike Information Criterion
AKI
Acute Kidney Injury
ARDS
Acute Respiratory Distress Syndrome
AUC
Area Under the Receiver Operating Characteristic Curve

BIC
Bayesian Information Criterion
BLRT
Bootstrap Likelihood Ratio Test
CI
Confidence Interval
CRRT
Continuous Renal Replacement Therapy
DCA
Decision Curve Analysis
GBTM
Group-Based Trajectory Modeling
HR
Hazard Ratio
ICD
International Classification of Diseases
ICU
Intensive Care Unit
LASSO
Least Absolute Shrinkage and Selection Operator
MIMIC-IV
Medical Information Mart for Intensive Care IV
NPV
Negative Predictive Value
PPV
Positive Predictive Value
ROC
Receiver Operating Characteristic
RV
Right Ventricular
SHAP
Shapley Additive Explanations
SOFA
Sequential Organ Failure Assessment
SQL
Structured Query Language
VIF
Variance Inflation Factor

Declarations

Ethics approval and consent to participate

This study utilized de-identified data from the MIMIC-IV database. The use of this publicly available database was approved by the Institutional Review Boards of the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The requirement for individual patient consent was waived due to the retrospective design and the anonymized nature of the data. One author (Chufan Dong) completed the required training and obtained authorized access to the database.

Consent for publication

All authors have reviewed the final version of the manuscript and approved its submission for publication.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Yonggui Yang1: Conceptualization, Methodology, Statistical analysis, and Writing – original draft. Chufan Dong1: Data curation and Data preprocessing. Jiuwen Tan1 and Yue Zhang1: Translation and Writing – review & editing. Qing Guo1: Software, Validation, and Visualization. Rui Zhang[1]*: Supervision, Manuscript revision, and Final approval of the version to be published. All authors read and approved the final manuscript.

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Data Availability

The datasets generated and analyzed during the current study are available from the MIMIC-IV database (https://mimic.mit.edu/) upon reasonable request and completion of the required credentialing process. The datasets supporting the conclusions of this article are included within the additional files.

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Figures

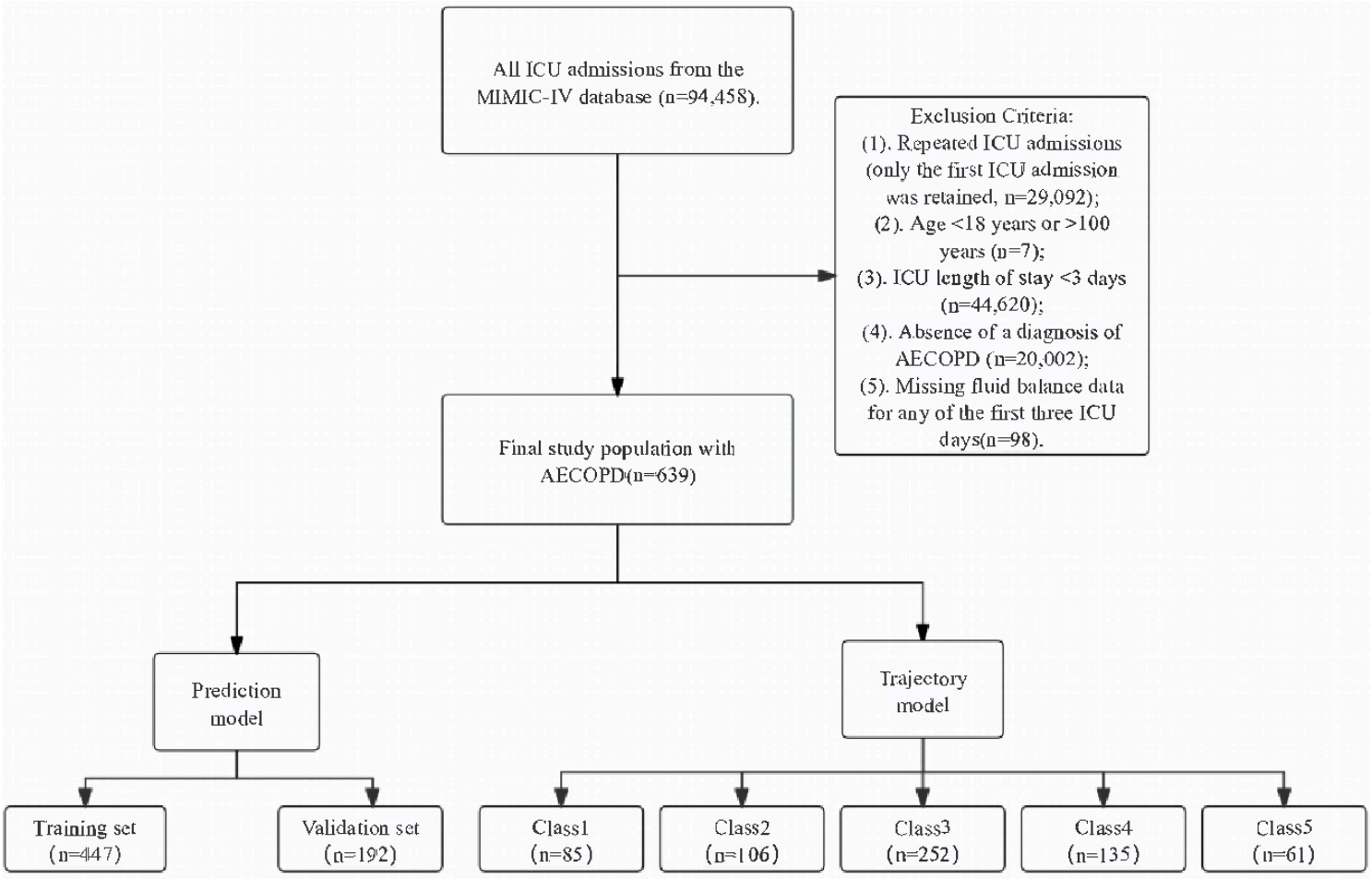


Figure 1

Flow diagram of patient selection.

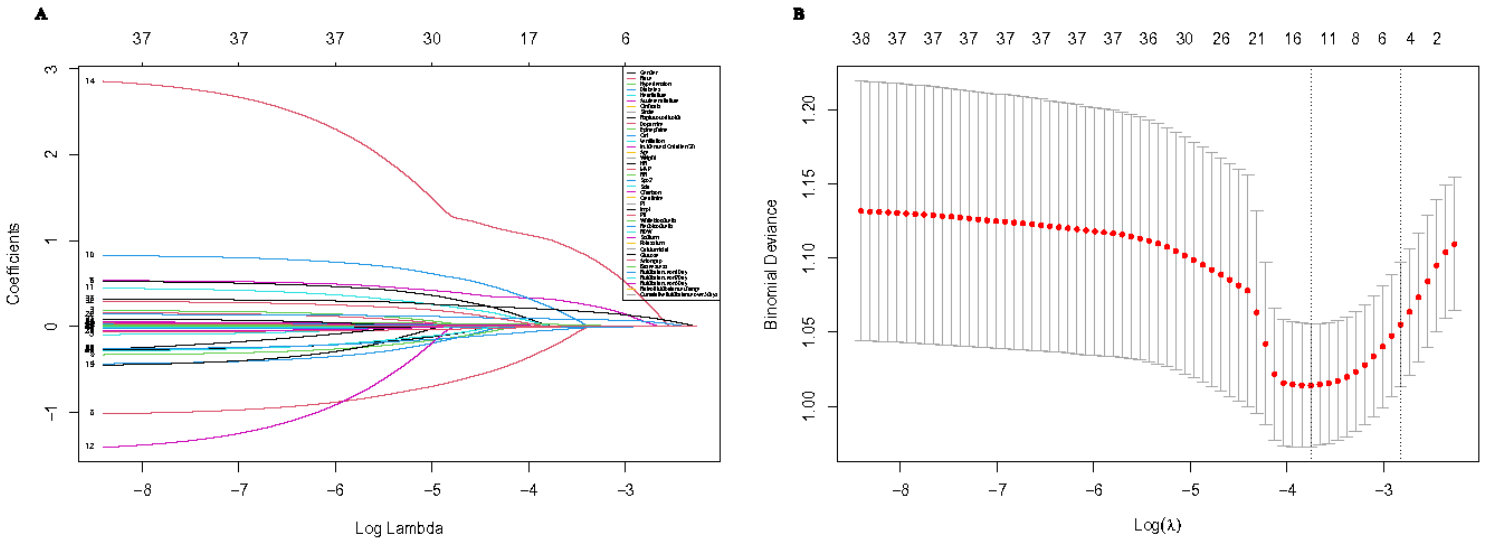


Figure 2

Variables selection from Lasso model. (A) Coefficient profiles of candidate variables across different log(λ) values in the LASSO model. (B) Ten-fold cross-validation for tuning parameter selection in the LASSO model.

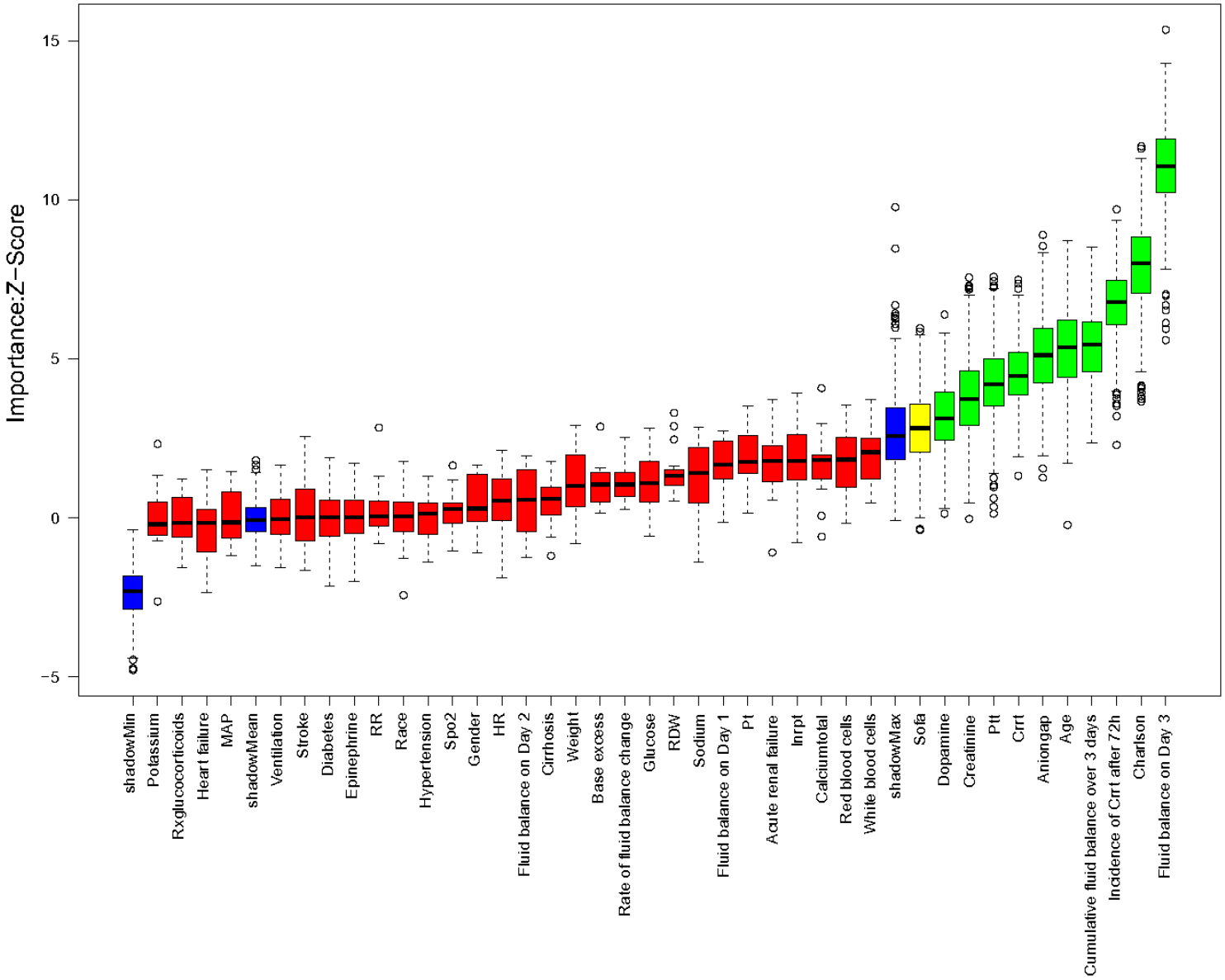


Figure 3

Variables selection from Boruta algorithm. Feature importance ranking derived from the Boruta algorithm.

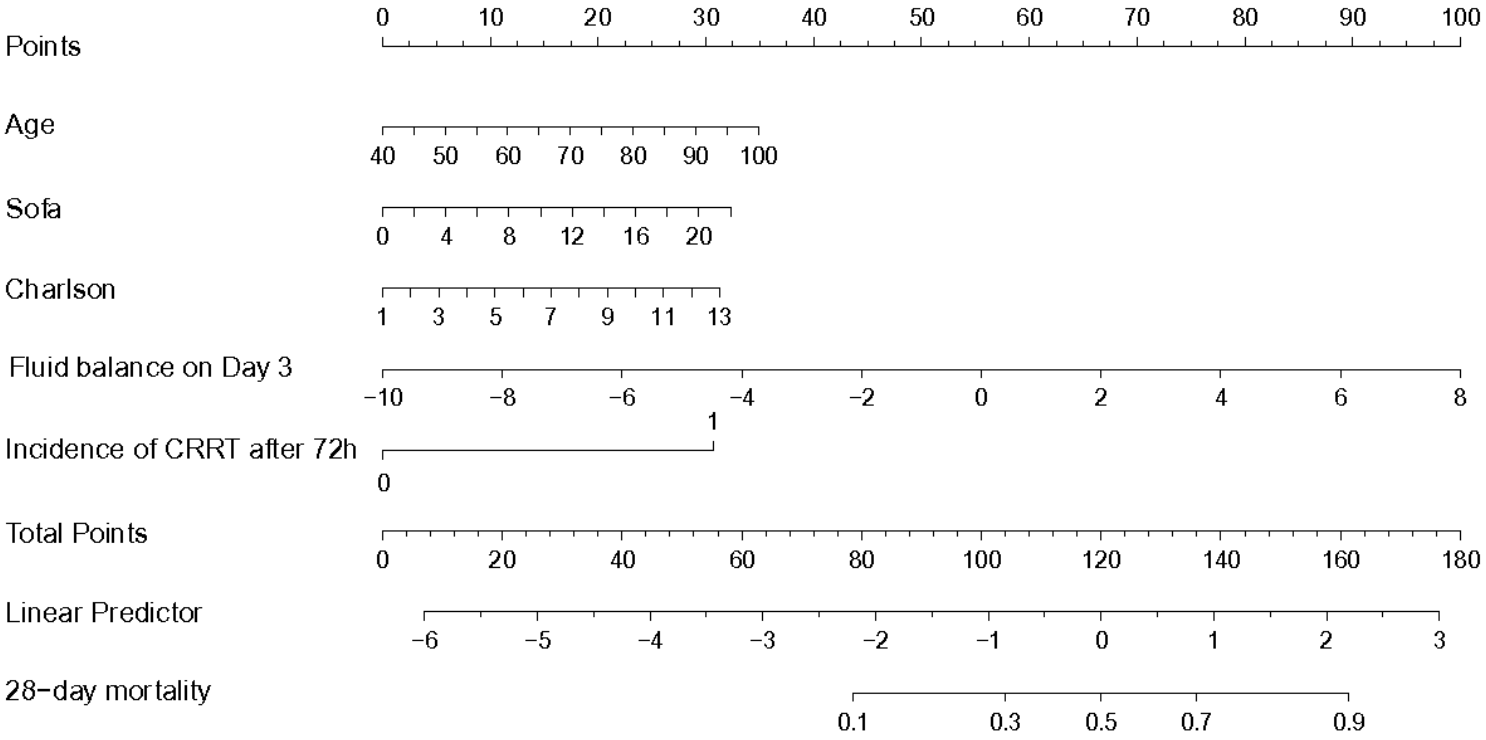


Figure 4

Nomogram for predicting 28-day mortality in patients with AECOPD.

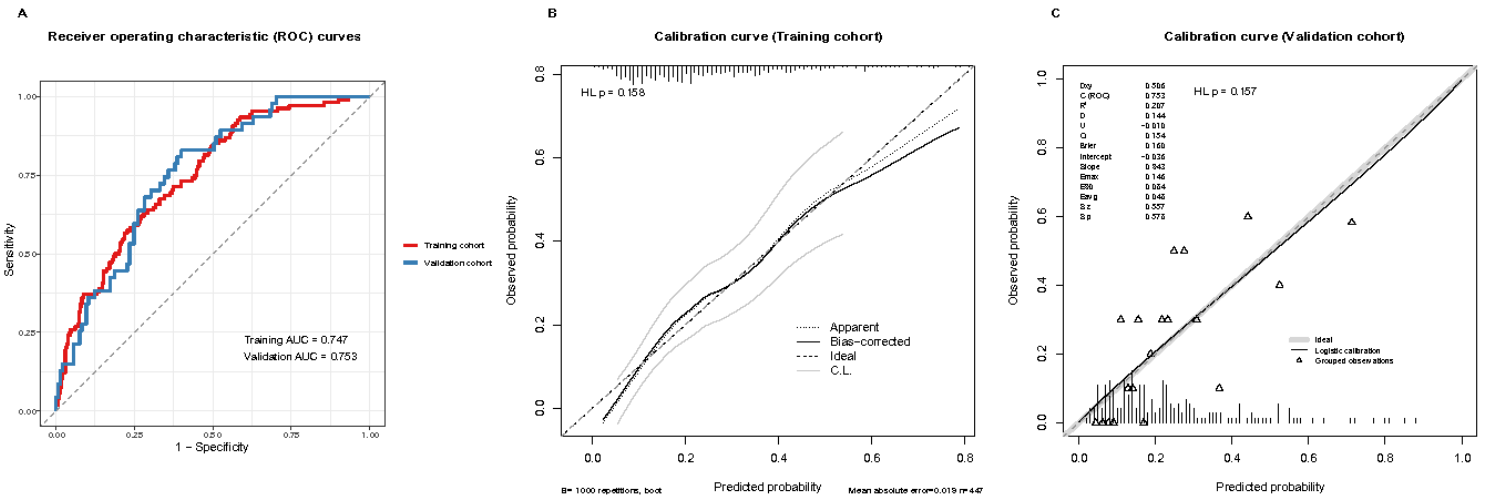


Figure 5

Discrimination and calibration of the prediction model.(A) Receiver operating characteristic (ROC) curves in the training and validation cohorts. (B) Calibration curve for the training cohort. (C) Calibration curve for the validation cohort.

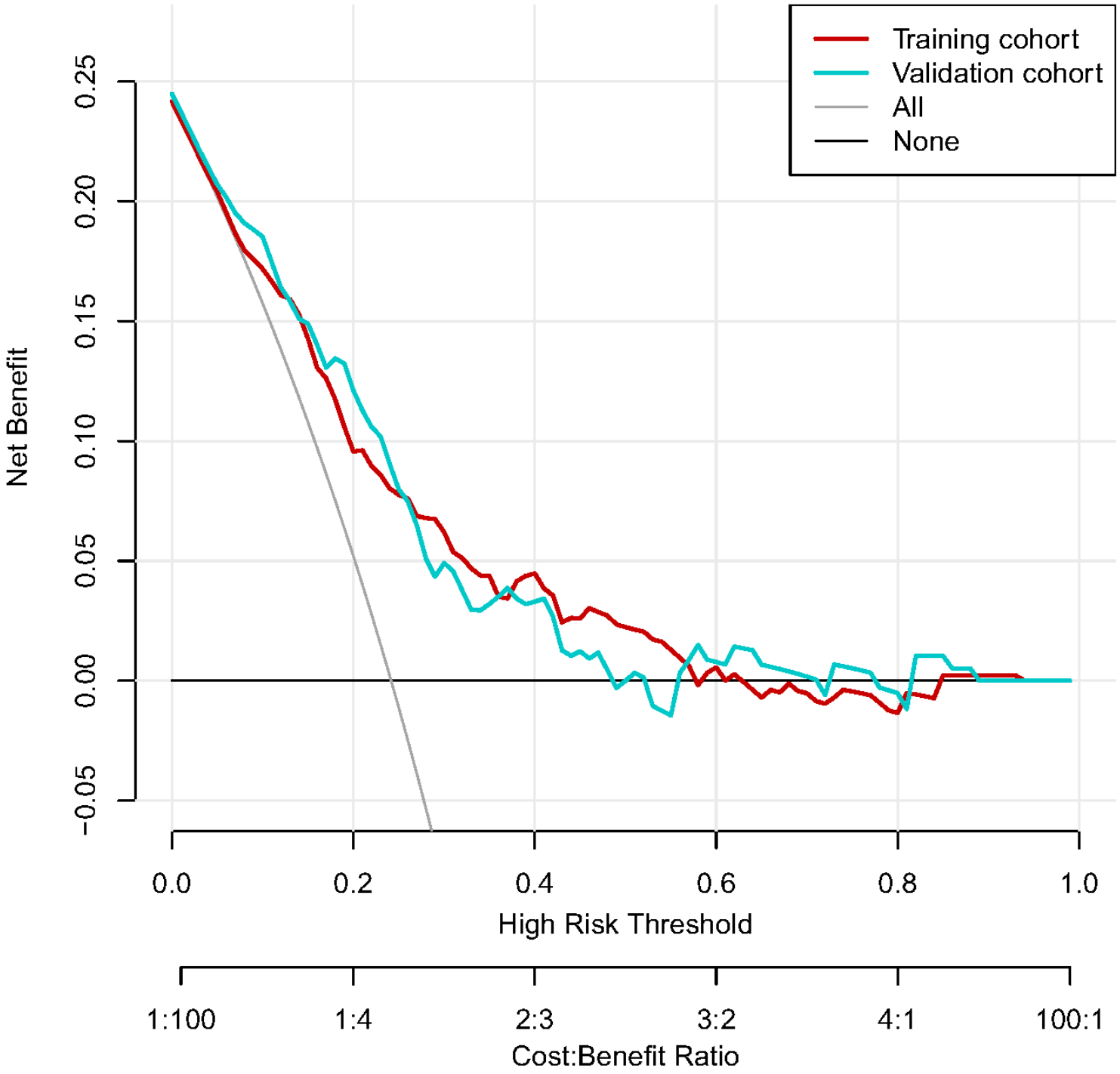


Figure 6

Decision curve analysis demonstrating net clinical benefit across a range of threshold probabilities in the training and validation

cohorts.

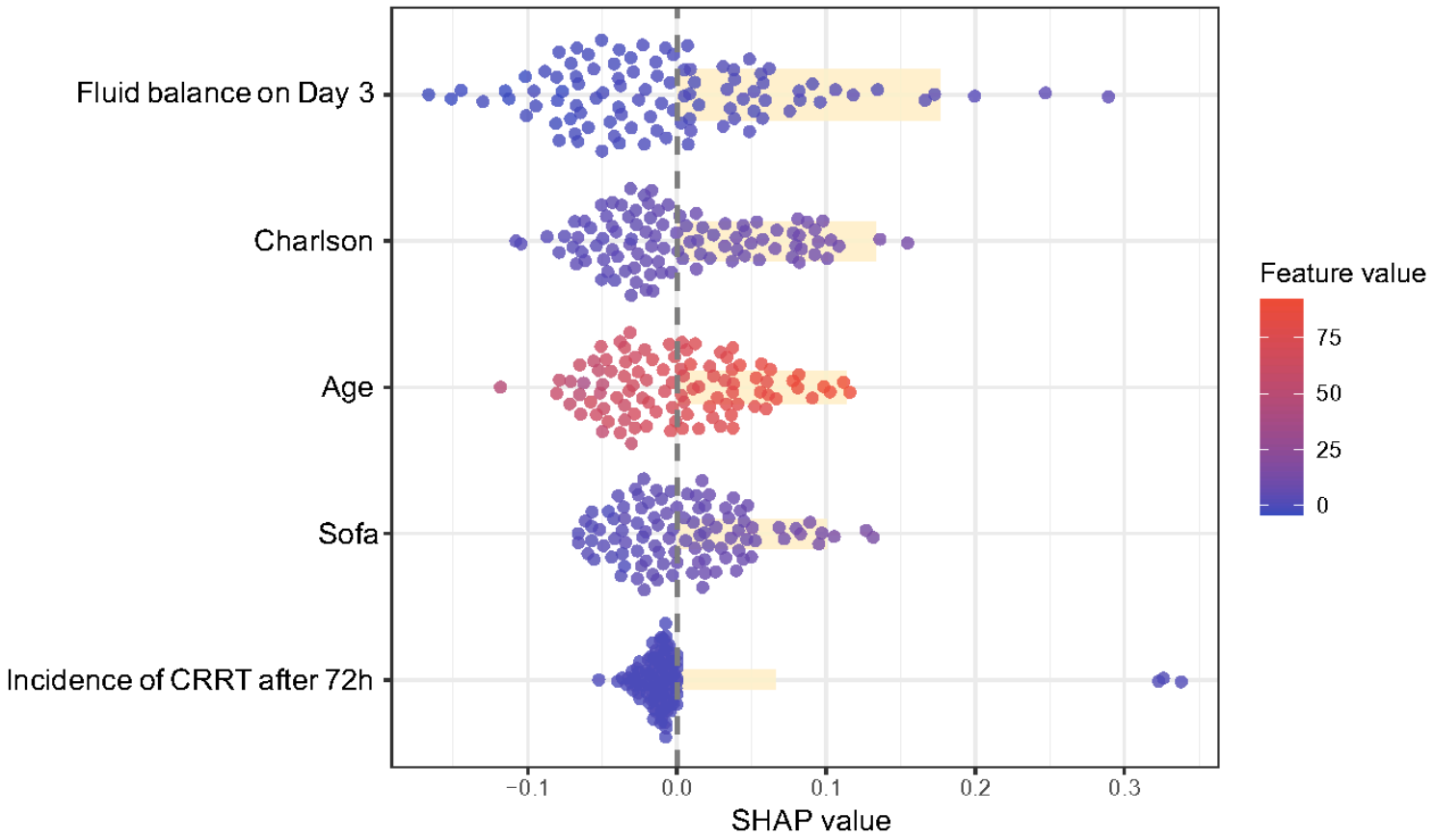


Figure 7

SHAP-based interpretation of the prediction model.SHAP beeswarm plot with global importance overlay showing the relative importance and direction of effects of each predictor on mortality risk.

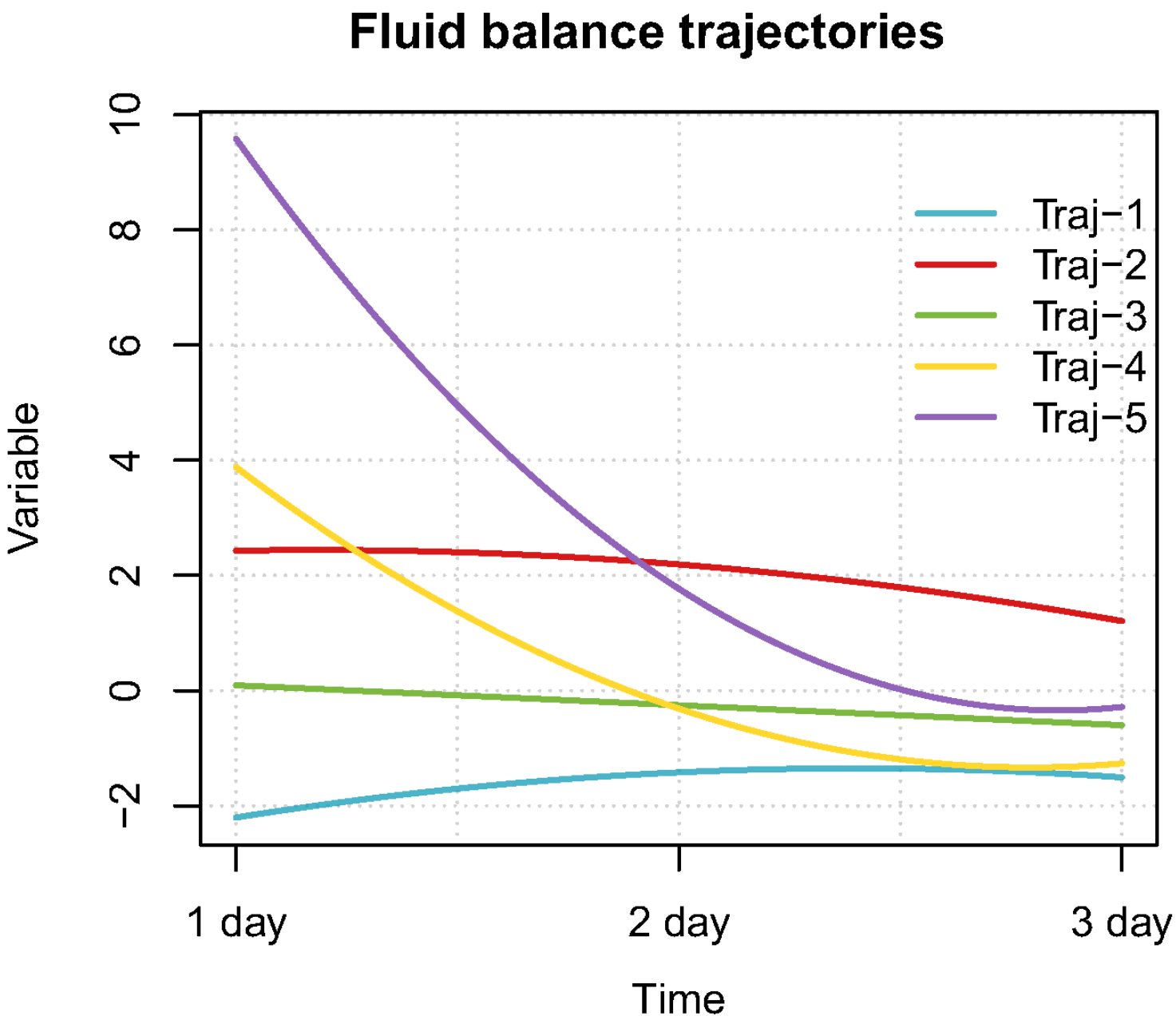


Figure 8

Fluid balance trajectories during the first three ICU days.

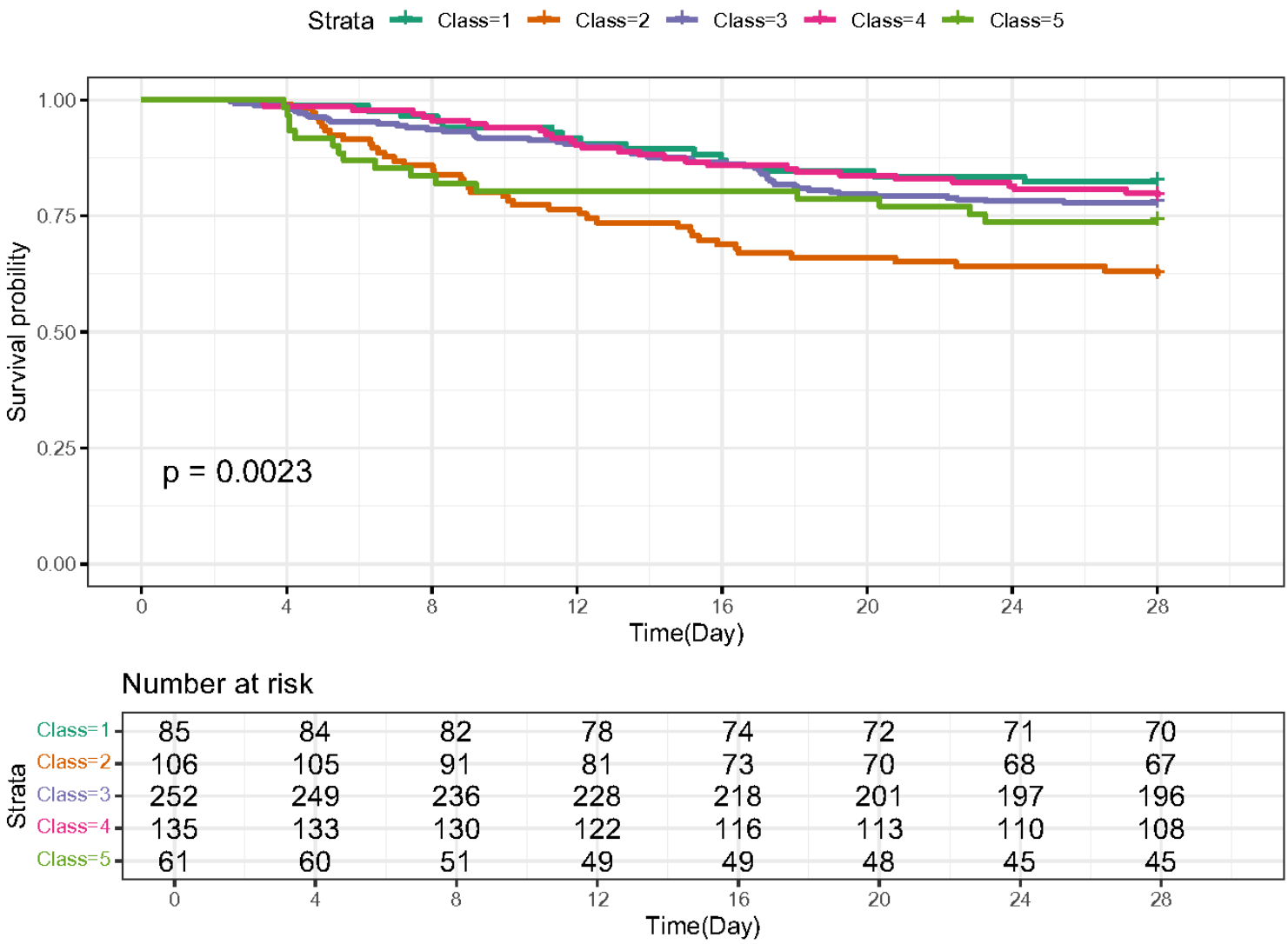


Figure 9

Kaplan–Meier survival curves according to fluid balance trajectory classes.

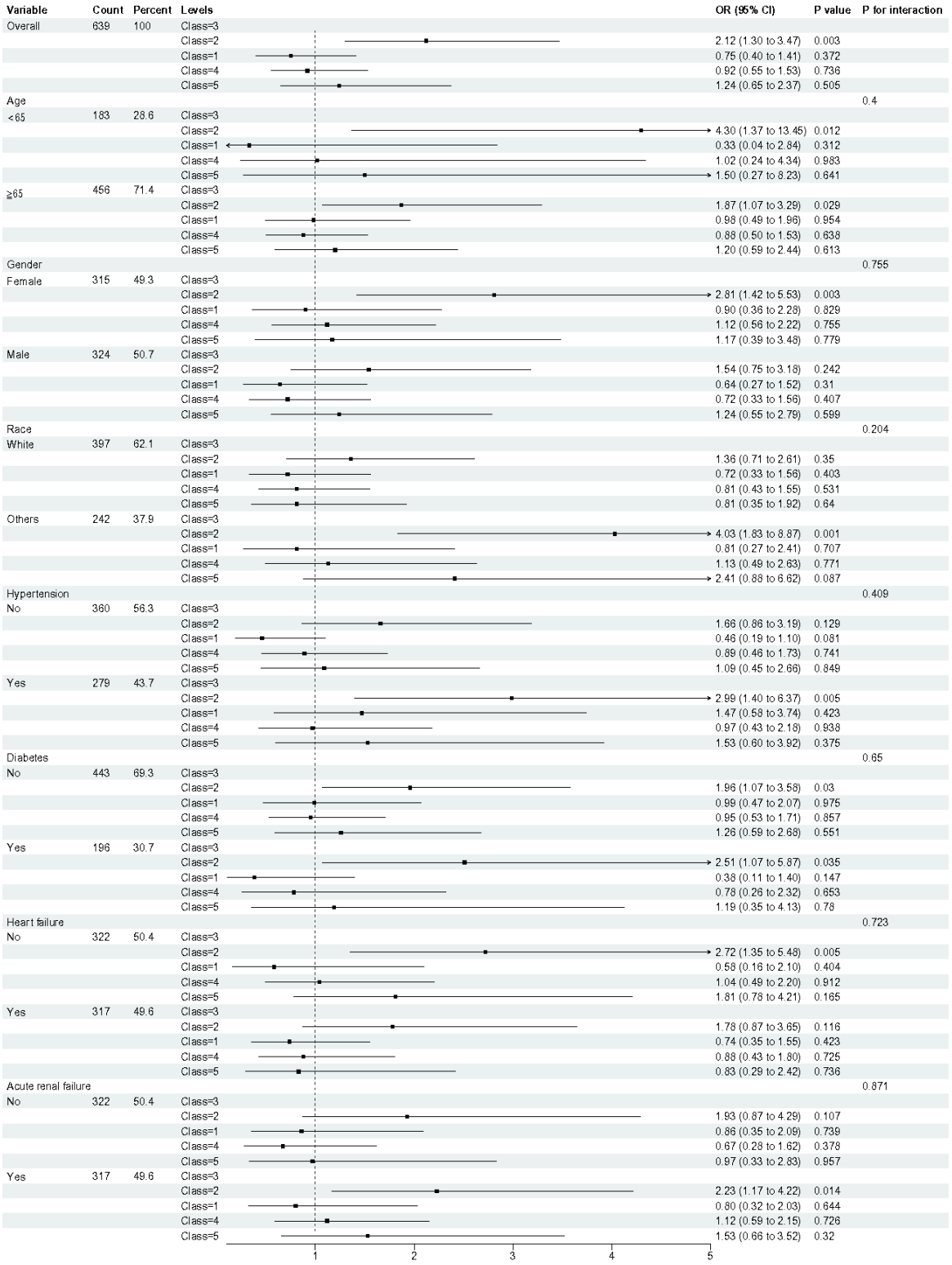


Figure 10

Subgroup analyses of the association between fluid balance trajectories and 28-day mortality.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.BaselineCharacteristicsandHomogeneityTestBetweenTrainingandValidationSets.docx

- SupplementaryTableS2.Confusionmatrixofthepredictionmodelinthetrainingandvalidationcohorts.docx
- SupplementaryTableS3.StatisticsforchoosingthebestnumberofClasses..docx
- SupplementaryTableS4.Unrocesseddataset.xlsx
- SupplementaryTableS5.Processeddataset.csv