

Persistent Positive Fluid Balance Within the First 48 Hours and In-Hospital Mortality in Critically Ill Patients With COPD Complicated by Pulmonary Hypertension

A multicenter cohort study using MIMIC-IV and eICU

Author information: to be completed by the authors.

Running title: Fluid balance in COPD-PH

Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) complicated by pulmonary hypertension (PH) represent a high-risk population with limited evidence regarding early ICU fluid management. We investigated whether persistent positive fluid balance during the first 48 hours after ICU admission was associated with in-hospital mortality.

Methods: We performed a retrospective multicenter cohort study using MIMIC-IV as the discovery cohort and eICU as the external validation cohort. Adult ICU patients with diagnosis-coded COPD complicated by PH were included. The main exposure was persistent positive fluid balance, defined as positive net fluid balance on both day 1 and day 2 after ICU admission. The primary outcome was in-hospital mortality. Multivariable logistic regression with multiple imputation was used as the primary analysis. Propensity score overlap weighting, stabilized inverse probability of treatment weighting (IPTW), complete-case analysis, nonlinear spline analysis, and clinically relevant subgroup analyses were performed.

Results: The analysis included 1,891 ICU stays (1,493 from MIMIC-IV and 398 from eICU), with 348 in-hospital deaths. Persistent positive 48-hour fluid balance occurred in 484 patients (25.6%). Crude mortality was higher in the persistent positive group than in the non-persistent positive group (30.0% vs 14.4%). In the main multiply imputed multivariable model, persistent positive fluid balance was associated with higher in-hospital mortality in MIMIC-IV (OR 1.45, 95% CI 1.01-2.07; $P=0.043$) and in eICU (OR 1.88, 95% CI 1.06-3.32; $P=0.030$), with a fixed-effect pooled OR of 1.56 (95% CI 1.15-2.11; $P=0.004$). The association remained robust after overlap weighting, stabilized IPTW, and complete-case analysis. Subgroup analyses showed directionally consistent associations across all examined strata.

Conclusions: Among ICU patients with diagnosis-coded COPD complicated by PH, persistent positive fluid balance during the first 48 hours was independently associated with higher in-hospital mortality and externally validated in eICU. Persistent early positive fluid balance may represent a high-risk dynamic fluid phenotype rather than a causal treatment effect.

Keywords: COPD; pulmonary hypertension; fluid balance; intensive care unit; MIMIC-IV; eICU; mortality; multiple imputation.

Introduction

Pulmonary hypertension due to lung diseases and/or hypoxia is classified as group 3 PH in contemporary guidelines, and COPD is one of the major underlying lung diseases in this category [1]. COPD complicated by PH is clinically important because pulmonary vascular disease may amplify hypoxemia, right ventricular afterload, systemic congestion, and vulnerability during acute illness [2,3].

Prior hemodynamic and observational data suggest that COPD-PH is associated with worse clinical trajectories and increased mortality compared with COPD without PH [3,4].

Early fluid management in critically ill patients with PH is challenging. While fluid administration may be necessary in true hypovolemia or shock, excessive preload can worsen right ventricular dilatation, ventricular interdependence, tricuspid regurgitation, systemic venous congestion, and renal dysfunction [9-11]. In broader ICU populations, positive fluid balance and fluid overload have repeatedly been associated with adverse outcomes [7,8,12,13]. However, evidence specific to critically ill patients with COPD complicated by PH remains sparse.

Most database studies in COPD or PH have focused on mortality prediction or static laboratory biomarkers. A clinically actionable question is whether early dynamic fluid patterns identify high-risk patients. We therefore evaluated the association between persistent positive fluid balance during the first 48 hours after ICU admission and in-hospital mortality among diagnosis-coded COPD-PH patients in MIMIC-IV, with external validation in the multicenter eICU database [5,6].

Methods

Study design and data sources

This was a retrospective multicenter cohort study based on two publicly available, de-identified ICU databases: MIMIC-IV and eICU [5,6]. MIMIC-IV was used as the discovery cohort, and eICU was used as the external validation cohort. The reporting framework was aligned with the STROBE statement for observational studies [14]. Because both databases contain de-identified data with established data-use agreements, additional institutional review board approval was not required for this secondary analysis.

Study population

We included adult ICU patients with diagnosis-coded COPD complicated by PH. COPD and PH were identified using International Classification of Diseases diagnosis codes and diagnosis text harmonized across MIMIC-IV and eICU. For MIMIC-IV, the first ICU stay within the index hospitalization was retained. The main COPD definition excluded emphysema-only codes, while expanded COPD/emphysema definitions were assessed during feasibility screening. Patients without sufficient early fluid balance information or outcome information were excluded from the modeling dataset.

Exposure definition

The primary exposure was persistent positive fluid balance within the first 48 hours after ICU admission, defined as net fluid balance greater than 0 mL during both the first 24-hour period and the second 24-hour period. Net fluid balance was calculated as total documented input minus total documented output. In MIMIC-IV, input events were restricted to volume entries documented in mL to avoid mixing medication dose units with fluid volume. In eICU, stool-like count records were excluded from output calculation. Continuous 24-hour net fluid balance was winsorized at the 1st and 99th percentiles and analyzed as a secondary exposure.

Outcome

The primary outcome was in-hospital mortality, harmonized across MIMIC-IV and eICU.

Covariates

Candidate covariates included age, sex, early vital signs, early laboratory values, comorbidities, acute diagnoses, and early ICU treatments. The main adjusted model included age, sex, heart rate,

respiratory rate, SpO₂, white blood cell count, blood urea nitrogen, creatinine, sodium, bicarbonate, heart failure, chronic kidney disease, pneumonia, sepsis, mechanical ventilation within 24 hours, vasopressor use within 24 hours, and diuretic use within 24 hours. Variables with excessive missingness or inconsistent availability across the two databases were not used in the primary model.

Missing data

Missing covariates were handled using multiple imputation by chained equations separately within each database [15,16]. The outcome and main exposure were not imputed. Variables with high missingness were removed from the primary model, and complete-case analysis was performed as a sensitivity analysis.

Statistical analysis

Baseline characteristics were summarized by exposure group. Continuous variables were presented as medians and interquartile ranges, and categorical variables as counts and percentages. The primary association between persistent positive 48-hour fluid balance and in-hospital mortality was evaluated using multivariable logistic regression after multiple imputation. Cohort-specific estimates from MIMIC-IV and eICU were combined using fixed-effect inverse-variance meta-analysis. Propensity score overlap weighting and stabilized IPTW were used to assess robustness to measured confounding [17,18]. Natural cubic spline analysis was used to explore nonlinearity for continuous 24-hour net fluid balance [19]. Prespecified subgroup analyses were performed by age, sex, heart failure, chronic kidney disease, pneumonia, sepsis, mechanical ventilation, vasopressor use, and diuretic use. Interaction terms were used to estimate P values for effect modification.

Results

Study population. The final modeling dataset included 1,891 ICU stays: 1,493 from MIMIC-IV and 398 from eICU. In-hospital mortality was 17.5% in MIMIC-IV and 21.9% in eICU. Persistent positive 48-hour fluid balance was observed in 484 patients (25.6%).

Study flow and analytical framework

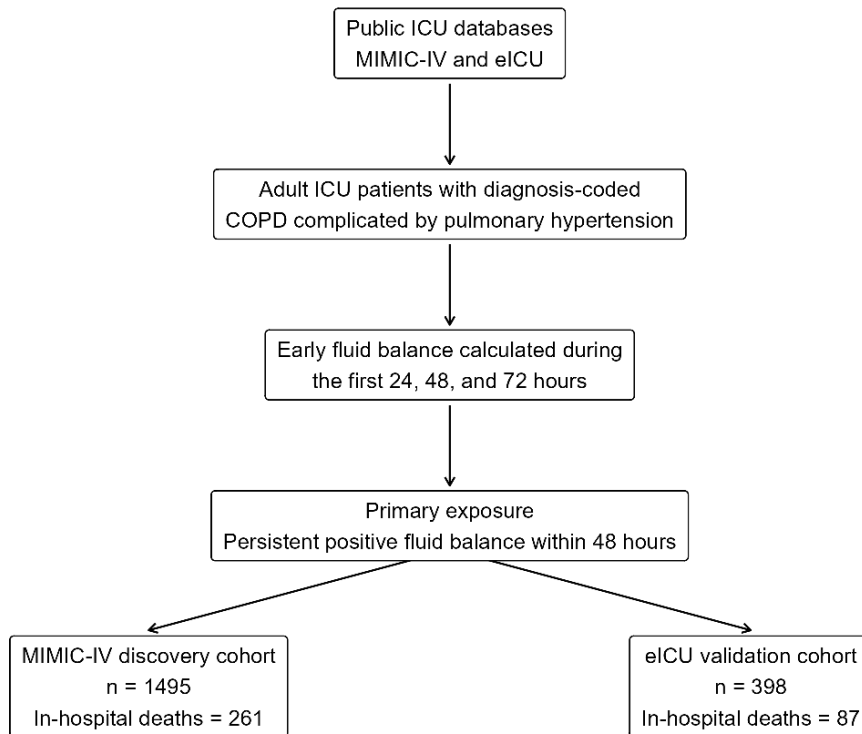


Figure 1. Study design and analytical framework.

Baseline characteristics. Compared with non-persistent positive fluid balance, the persistent positive group had higher heart rate, higher white blood cell count, higher creatinine, higher blood urea nitrogen, and a greater burden of acute illness markers including sepsis, mechanical ventilation, and vasopressor use. These imbalances support the need for multivariable adjustment and propensity score-based sensitivity analyses.

Table 1. Baseline characteristics stratified by persistent positive 48-hour fluid balance.

Table	Variable	Overall	Non-persistent positive	Persistent positive 48h	P value	SMD	Missing
Combined	Database: eICU	398 (21.0%)	282 (20.0%)	116 (24.0%)	0.078	0.095	0 (0.0%)
Combined	Male sex	824 (43.6%)	591 (42.0%)	233 (48.1%)	0.022	0.123	0 (0.0%)
Combined	Age, years	71.0 [62.0, 79.0]	70.0 [61.0, 78.0]	71.0 [63.0, 79.0]	0.068	0.109	0 (0.0%)
Combined	Heart rate, beats/min	89.0 [77.0, 103.0]	88.0 [76.0, 102.0]	91.0 [78.0, 107.0]	0.003	0.169	5 (0.3%)
Combined	Respiratory rate, breaths/min	20.0 [16.0, 25.0]	20.0 [17.0, 25.0]	20.0 [16.0, 25.0]	0.886	0.038	58 (3.1%)
Combined	SpO2, %	95.0 [89.0, 98.0]	95.0 [88.0, 98.0]	95.0 [90.0, 99.0]	0.012	0.069	6 (0.3%)
Combined	White blood cell count	10.2 [7.3, 13.9]	9.8 [7.2, 13.2]	11.3 [7.8, 15.4]	<0.001	0.233	56 (3.0%)
Combined	Hemoglobin	10.4 [8.8, 12.1]	10.5 [8.9, 12.4]	10.1 [8.5, 11.7]	0.001	0.147	52 (2.7%)
Combined	Platelet count	198.0 [148.0, 263.0]	201.0 [149.0, 266.5]	190.0 [144.2, 255.8]	0.035	0.042	54 (2.9%)
Combined	RDW	15.9 [14.6, 17.8]	15.9 [14.6, 17.7]	16.1 [14.8, 18.1]	0.174	0.034	70 (3.7%)
Combined	Blood urea nitrogen	28.0 [18.0, 45.5]	27.0 [18.0, 45.0]	30.0 [19.0, 46.0]	0.026	0.059	36 (1.9%)
Combined	Creatinine	1.2 [0.9, 2.0]	1.2 [0.8, 1.8]	1.4 [0.9, 2.5]	<0.001	0.391	34 (1.8%)
Combined	Sodium	139.0 [135.0, 141.0]	139.0 [135.0, 141.0]	138.5 [136.0, 142.0]	0.123	0.126	36 (1.9%)
Combined	Potassium	4.3 [3.9, 4.8]	4.3 [3.9, 4.7]	4.3 [3.9, 4.8]	0.288	0.081	32 (1.7%)
Combined	Chloride	100.0 [96.0, 105.0]	100.0 [95.0, 104.0]	101.5 [97.0, 106.0]	<0.001	0.278	37 (2.0%)
Combined	Bicarbonate	26.0 [22.0, 31.0]	27.0 [23.0, 31.0]	25.0 [21.0, 28.0]	<0.001	0.314	29 (1.5%)
Combined	Glucose	131.0 [105.0, 169.0]	130.0 [104.0, 170.0]	132.0 [107.0, 165.0]	0.939	0.062	22 (1.2%)
Combined	Heart failure	1390 (73.5%)	1054 (74.9%)	336 (69.4%)	0.021	0.122	0 (0.0%)
Combined	Coronary artery disease	818 (43.3%)	603 (42.9%)	215 (44.4%)	0.585	0.032	0 (0.0%)
Combined	Hypertension	1511 (79.9%)	1125 (80.0%)	386 (79.8%)	0.975	0.005	0 (0.0%)
Combined	Diabetes	728 (38.5%)	550 (39.1%)	178 (36.8%)	0.396	0.048	0 (0.0%)
Combined	Chronic kidney disease	793 (41.9%)	564 (40.1%)	229 (47.3%)	0.006	0.146	0 (0.0%)
Combined	Atrial fibrillation	950 (50.2%)	704 (50.0%)	246 (50.8%)	0.805	0.016	0 (0.0%)
Combined	Pneumonia	553 (29.2%)	376 (26.7%)	177 (36.6%)	<0.001	0.212	0 (0.0%)
Combined	Sepsis	388 (20.5%)	213 (15.1%)	175 (36.2%)	<0.001	0.481	0 (0.0%)
Combined	Mechanical ventilation within 24h	814 (43.0%)	533 (37.9%)	281 (58.1%)	<0.001	0.404	0 (0.0%)
Combined	Vasopressor use within 24h	497 (26.3%)	276 (19.6%)	221 (45.7%)	<0.001	0.555	0 (0.0%)
Combined	Diuretic use within 24h	986 (52.1%)	823 (58.5%)	163 (33.7%)	<0.001	0.498	0 (0.0%)
Combined	Systemic steroid use within 24h	583 (30.8%)	433 (30.8%)	150 (31.0%)	0.974	0.005	0 (0.0%)

Note: Continuous variables are median [IQR]; categorical variables are n (%). The outcome variable was removed from the baseline table and is reported in the Results.

Primary analysis. Crude in-hospital mortality was 30.0% in the persistent positive group and 14.4% in the non-persistent positive group. In the multiply imputed main adjusted model, persistent positive fluid balance was associated with higher in-hospital mortality in MIMIC-IV (OR 1.45, 95% CI 1.01-2.07; $P=0.043$) and eICU (OR 1.88, 95% CI 1.06-3.32; $P=0.030$). The fixed-effect pooled OR was 1.56 (95% CI 1.15-2.11; $P=0.004$).

Table 2. Main and sensitivity analyses for persistent positive 48-hour fluid balance and in-hospital mortality.

Analysis	Cohort	OR (95% CI)	P value
Main multivariable model with multiple imputation	MIMIC-IV	1.45 (1.01–2.07)	0.043
Main multivariable model with multiple imputation	eICU	1.88 (1.06–3.32)	0.030
Main multivariable model with multiple imputation	Fixed-effect pooled	1.56 (1.15–2.11)	0.004
Overlap weighting after multiple imputation	MIMIC-IV	1.40 (1.09–1.80)	0.008
Stabilized IPTW after multiple imputation	MIMIC-IV	1.41 (1.04–1.90)	0.026
Overlap weighting after multiple imputation	eICU	1.64 (1.05–2.56)	0.031
Stabilized IPTW after multiple imputation	eICU	1.83 (1.11–3.02)	0.018
Overlap weighting after multiple imputation	Fixed-effect pooled	1.45 (1.17–1.81)	<0.001
Stabilized IPTW after multiple imputation	Fixed-effect pooled	1.51 (1.17–1.95)	0.002
Complete-case sensitivity analysis	MIMIC-IV	1.53 (1.07–2.20)	0.020
Complete-case sensitivity analysis	eICU	1.68 (0.87–3.26)	0.122
Complete-case sensitivity analysis	Fixed-effect pooled	1.57 (1.14–2.15)	0.005

Note: MI, multiple imputation; IPTW, inverse probability of treatment weighting.

Persistent positive fluid balance within 48 hours and in-hospital mortality

Main analysis and sensitivity analyses

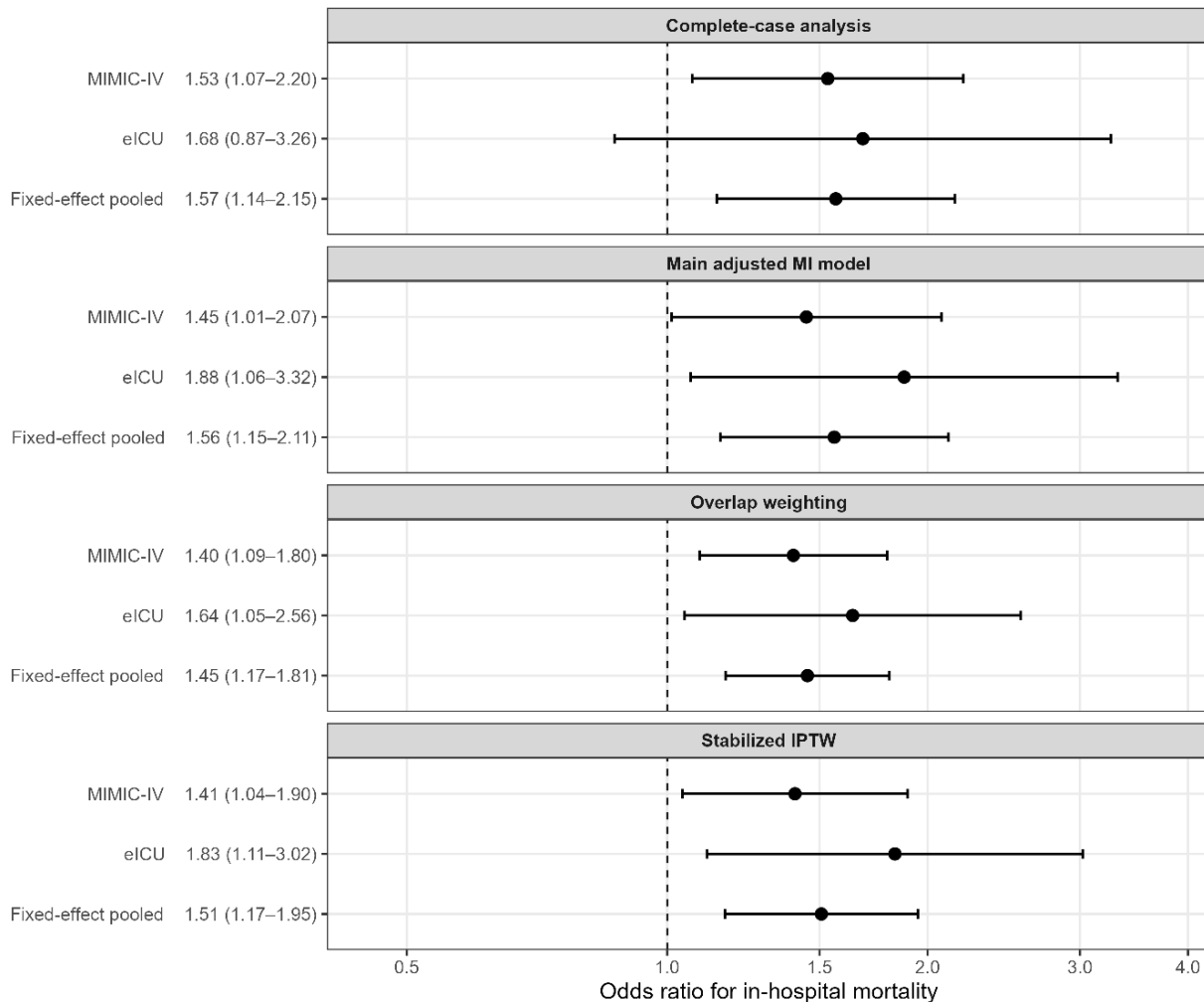


Figure 2. Association between persistent positive 48-hour fluid balance and in-hospital mortality across main and sensitivity analyses.

Sensitivity analyses. The association remained directionally consistent after propensity score overlap weighting and stabilized IPTW. The fixed-effect pooled OR was 1.45 (95% CI 1.17-1.81; $P < 0.001$) after overlap weighting and 1.51 (95% CI 1.17-1.95; $P = 0.002$) after stabilized IPTW. Complete-case analysis yielded a pooled OR of 1.57 (95% CI 1.14-2.15; $P = 0.005$). Heterogeneity was negligible in the weighted analyses ($I^2 = 0\%$).

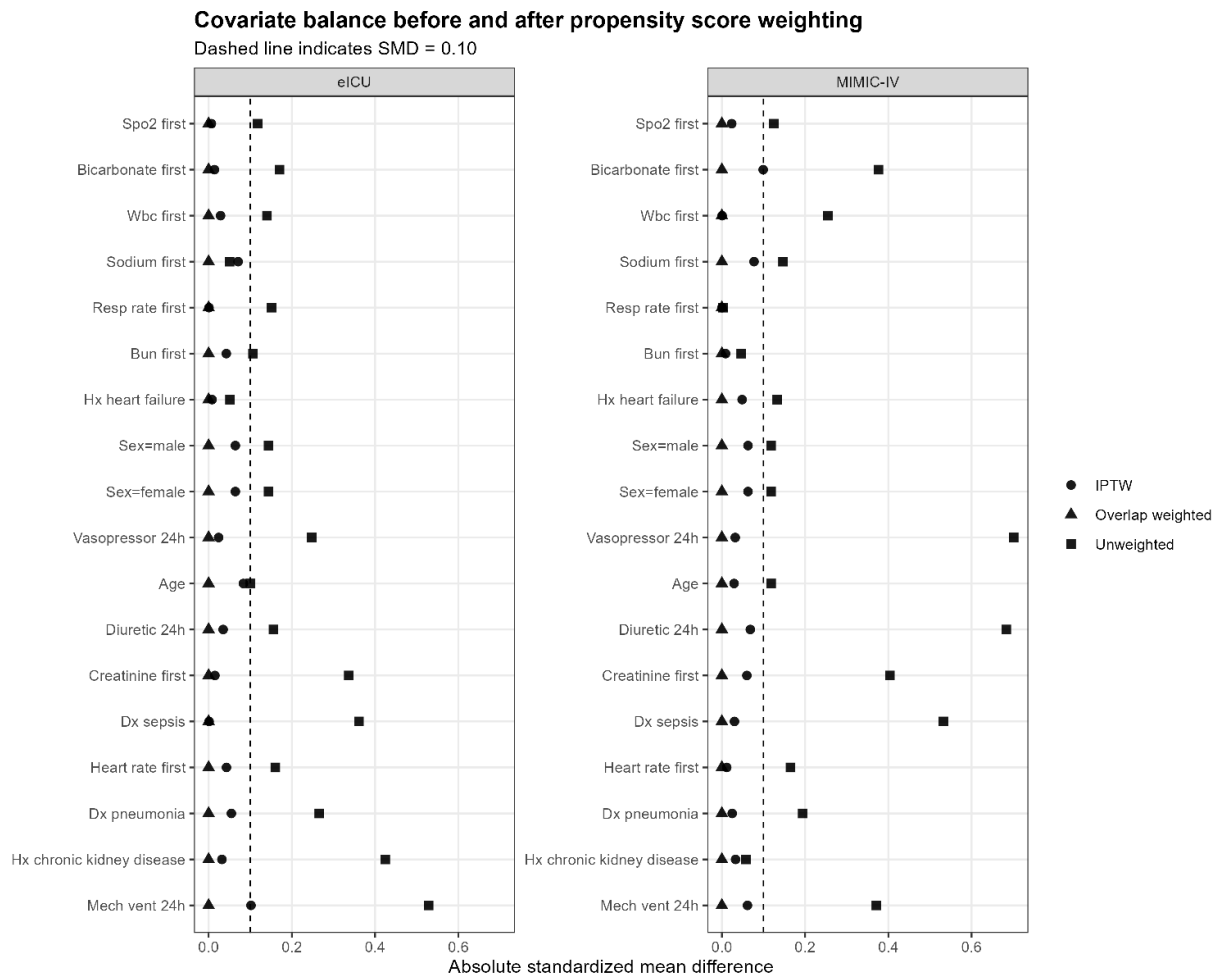


Figure 3. Covariate balance before and after propensity score weighting.

Subgroup analyses. The association between persistent positive fluid balance and in-hospital mortality was directionally consistent across all examined subgroups, with all pooled subgroup ORs greater than 1. A nominal interaction was observed for vasopressor use, but this finding should be interpreted cautiously given multiple subgroup comparisons and the observational design.

Table 3. Subgroup analyses of persistent positive 48-hour fluid balance.

Subgroup	Level	OR (95% CI)	P value	P for interaction
Age	Age <75 years	1.43 (0.96–2.14)	0.081	0.603
Age	Age ≥75 years	2.00 (1.23–3.26)	0.005	0.603
Diuretic use	Diuretic use: No	1.88 (1.25–2.83)	0.002	0.347
Diuretic use	Diuretic use: Yes	1.26 (0.77–2.06)	0.354	0.347
Pneumonia	Pneumonia: No	1.40 (0.93–2.08)	0.103	0.655
Pneumonia	Pneumonia: Yes	1.91 (1.14–3.21)	0.014	0.655
Sepsis	Sepsis: Yes	1.20 (0.70–2.06)	0.503	0.162
Sepsis	Sepsis: No	1.76 (1.20–2.58)	0.004	0.162
Chronic kidney disease	Chronic kidney disease: Yes	1.45 (0.92–2.28)	0.114	0.508
Chronic kidney disease	Chronic kidney disease: No	1.73 (1.12–2.68)	0.013	0.508
Heart failure	Heart failure: Yes	1.42 (0.99–2.04)	0.057	0.759
Heart failure	Heart failure: No	2.29 (1.24–4.23)	0.008	0.759
Mechanical ventilation	Mechanical ventilation: No	1.97 (1.22–3.19)	0.006	0.956
Mechanical ventilation	Mechanical ventilation: Yes	1.43 (0.94–2.17)	0.098	0.956
Sex	Sex: Female	2.01 (1.33–3.05)	<0.001	0.189
Sex	Sex: Male	1.27 (0.79–2.06)	0.322	0.189
Vasopressor use	Vasopressor use: No	2.02 (1.38–2.97)	<0.001	0.048
Vasopressor use	Vasopressor use: Yes	1.08 (0.64–1.83)	0.770	0.048

Note: P for interaction values were derived from interaction models. Nominal interactions should be interpreted cautiously because multiple subgroup comparisons were performed.

Subgroup analyses of persistent positive 48-hour fluid balance

Fixed-effect pooled estimates from MIMIC-IV and eICU

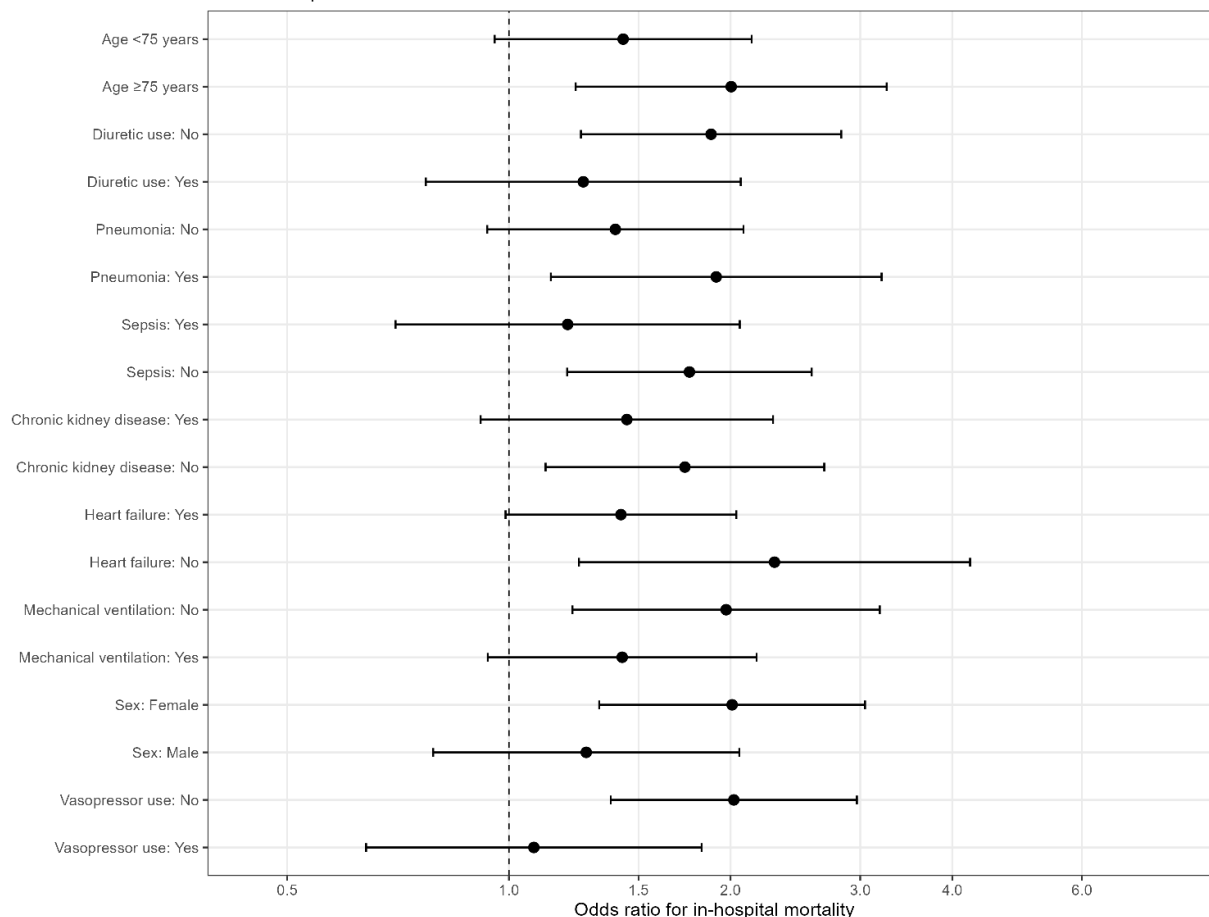
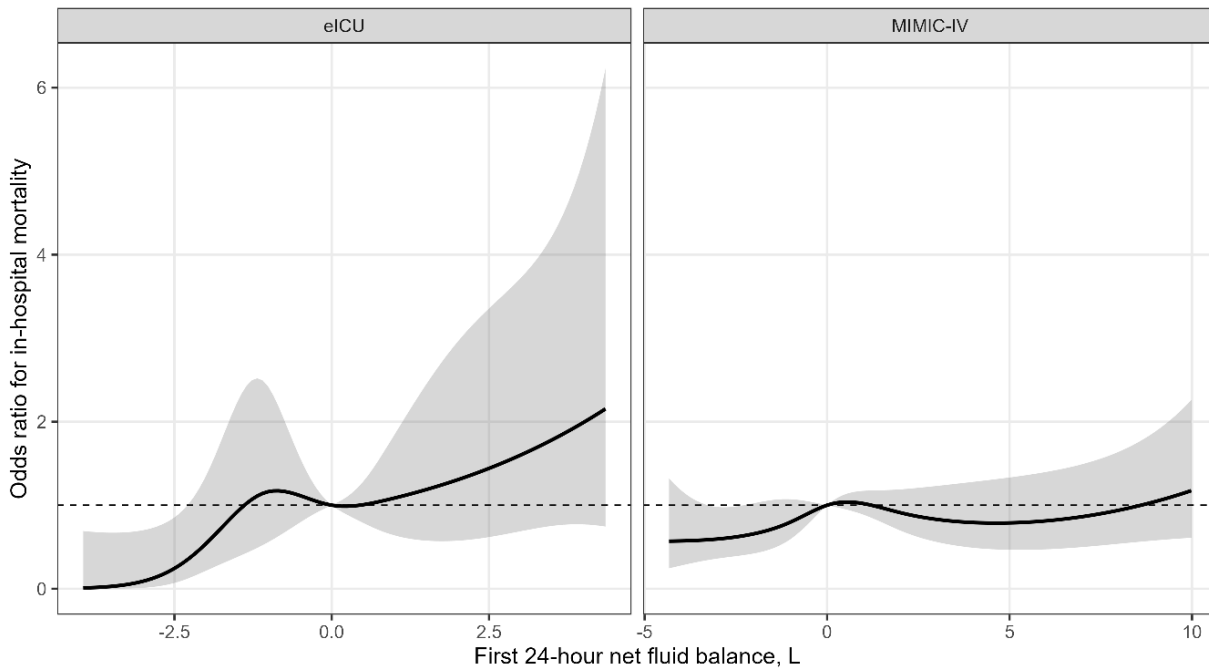


Figure 4. Subgroup analyses of persistent positive 48-hour fluid balance.

Exploratory nonlinear analysis. Natural cubic spline analysis of continuous 24-hour net fluid balance showed wider confidence intervals and less stable patterns than the 48-hour dynamic exposure. Therefore, continuous 24-hour fluid balance was considered exploratory and is presented in the Supplementary Figure.

Nonlinear association between 24-hour net fluid balance and mortality

Natural cubic spline; exploratory secondary analysis



Supplementary Figure S1. Exploratory nonlinear association between 24-hour net fluid balance and in-hospital mortality.

Discussion

In this multicenter analysis of ICU patients with diagnosis-coded COPD complicated by PH, persistent positive fluid balance during the first 48 hours was independently associated with higher in-hospital mortality. The association was observed in MIMIC-IV and externally validated in eICU. It also remained robust in propensity score weighting and complete-case sensitivity analyses. These findings suggest that persistent early positive fluid balance may identify a high-risk dynamic fluid phenotype in COPD-PH critical illness.

The clinical relevance of this finding is biologically plausible. COPD-PH patients may have limited right ventricular reserve and increased vulnerability to changes in preload and afterload. Excessive positive fluid balance may aggravate right ventricular dilatation, venous congestion, renal dysfunction, and impaired gas exchange. Prior critical care literature has linked fluid overload with adverse outcomes in heterogeneous ICU populations [7,8,12,13]. Our study extends this concept to a clinically distinct COPD-PH ICU subgroup and emphasizes a dynamic 48-hour pattern rather than a single static fluid measurement.

The finding should not be interpreted as proof that fluid restriction or aggressive deresuscitation reduces mortality. Positive fluid balance may reflect severity of illness, oliguria, shock, clinician response to hemodynamic instability, or early renal dysfunction. Although we adjusted for major measured confounders and performed propensity score analyses, residual confounding remains possible. Thus, persistent positive fluid balance should be viewed as a risk marker and a potential target for future prospective investigation.

The study has several strengths. First, it focused on a clinically meaningful high-risk subgroup rather than a general ICU population. Second, MIMIC-IV and eICU provided independent discovery and external validation cohorts. Third, the exposure definition was deliberately dynamic and clinically interpretable. Fourth, the analytic strategy included multiple imputation, multivariable adjustment, propensity score weighting, complete-case sensitivity analysis, and subgroup analysis.

Several limitations should be acknowledged. First, COPD and PH were identified using diagnosis codes and diagnosis text; right heart catheterization, echocardiographic pulmonary artery pressure, and detailed right ventricular function were unavailable. Therefore, the cohort should be described as diagnosis-coded COPD complicated by PH. Second, fluid balance records are subject to measurement error and database-specific documentation practices. Third, the eICU cohort was smaller than MIMIC-IV, limiting precision in some analyses. Fourth, we evaluated in-hospital mortality only and did not assess long-term survival after discharge. Finally, observational data cannot establish causality.

Conclusions

Among critically ill patients with diagnosis-coded COPD complicated by PH, persistent positive fluid balance during the first 48 hours after ICU admission was independently associated with higher in-hospital mortality and externally validated in eICU. Persistent positive 48-hour fluid balance may represent a high-risk dynamic fluid phenotype and should prompt careful reassessment of volume status, renal function, and hemodynamic trajectory. Prospective studies are needed to determine whether individualized fluid management strategies can improve outcomes in this population.

Data availability

All data used in this study were obtained from publicly available, de-identified critical care databases: MIMIC-IV and eICU. Access requires completion of the relevant data-use agreements and credentialing procedures.

Ethics statement

This study used publicly available de-identified databases. The original database projects received appropriate ethical approvals and data were released under data-use agreements. No protected health information was used in this secondary analysis.

Funding

To be completed by the authors.

Conflicts of interest

The authors declare no conflicts of interest. To be confirmed by the authors.

Author contributions

To be completed according to the target journal requirements.

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