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Early Cumulative Fluid Balance Trajectories and Mortality in Sepsis with Reduced Right Ventricular Systolic Function: A Retrospective Cohort Study

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Abstract

Background

Patients with sepsis and reduced right ventricular (RV) systolic function present particular challenges for fluid management. We investigated early cumulative fluid balance trajectories and their associations with mortality and ventilator-free days in this population.

Methods

This retrospective cohort study used MIMIC-IV version 3.1. Adults with sepsis and echocardiographically documented reduced RV systolic function who remained alive and in the ICU for 72 hours after sepsis onset were included. Group-based trajectory modelling identified patterns of weight-normalised cumulative fluid balance measured at 6-hour intervals during these 72 hours. The primary outcome was 28-day all-cause mortality; secondary outcomes were ICU mortality, in-hospital mortality, and 28-day ventilator-free days. Cox models evaluated mortality from the 72-hour landmark, adjusting for demographic characteristics, comorbidities, initial severity, cardiac and renal function, haemodynamics, and initial ventilation.

Results

Among 1,042 patients, five trajectories were identified: persistent negative (T1), mild negative (T2), mild positive (T3), moderate positive (T4), and high positive (T5) balance. Overall, 338 patients (32.4%) died within 28 days. Twenty-eight-day mortality ranged from 25.9% in T1 to 43.0% in T5. Compared with T1, T5 was associated with higher 28-day mortality after full adjustment (HR 2.01, 95% CI 1.34–3.02; $P < 0.001$). Corresponding adjusted HRs were 1.97 (95% CI 1.19–3.27) for ICU mortality and 2.25 (95% CI 1.45–3.48) for in-hospital mortality. Median 28-day ventilator-free days decreased across T1–T5, from 25.75 to 10.59 days (global $P < 0.001$).

Conclusions

Early cumulative fluid balance trajectories were associated with outcomes in patients with sepsis and reduced RV systolic function. High positive balance identified a pattern associated with greater mortality and fewer ventilator-free days, highlighting the prognostic relevance of longitudinal fluid balance assessment in this population.

Background

Sepsis and septic shock are life-threatening syndromes commonly encountered in intensive care units (ICUs), and fluid resuscitation remains central to early haemodynamic management [1, 2]. Recent

Surviving Sepsis Campaign guidelines recommend early crystalloid resuscitation, ongoing assessment of fluid responsiveness, and consideration of active fluid removal after initial resuscitation in septic shock [1]. These recommendations underscore a central clinical dilemma in fluid management: inadequate resuscitation may compromise tissue perfusion, whereas persistent fluid overload may exacerbate tissue oedema and organ dysfunction [3]. Observational studies have linked positive cumulative fluid balance and fluid overload to adverse outcomes in patients with sepsis [4, 5, 6]. In a MIMIC-IV cohort of 11,437 patients, the association between fluid balance and mortality varied over time; a positive balance on ICU day 1 was associated with lower in-hospital mortality, whereas fluid overload from day 3 onwards was associated with higher mortality [7]. However, cumulative measures over 24 hours, 72 hours, or 7 days do not fully capture the rate, persistence, or direction of fluid accumulation. Characterising these temporal patterns may provide a more informative description of fluid exposure during early critical illness.

Trajectory analysis provides a framework for examining this temporal heterogeneity. Studies of circulatory failure and sepsis have identified distinct fluid balance patterns associated with different mortality risks [8, 9]. These findings support evaluating the evolution of fluid balance over time, rather than relying on a single time-point measurement. However, existing studies have primarily examined broad critically ill or sepsis populations. The patterns and prognostic implications of early fluid balance remain insufficiently characterised in patients with sepsis and reduced right ventricular (RV) systolic function. RV physiology provides a rationale for examining fluid tolerance within this subgroup [10, 11]. The thin-walled right ventricle is particularly sensitive to acute changes in loading conditions. Inflammation, myocardial depression, hypoxic pulmonary vasoconstriction, and mechanical ventilation can impair RV performance during sepsis. Excessive volume loading may promote RV dilatation and leftward septal displacement, compromising left ventricular filling and cardiac output. A retrospective cohort study linked RV dysfunction in sepsis with greater organ support requirements and lower 30-day survival [12], while a meta-analysis found that the pooled incidence of RV dysfunction peaked within 48 hours of sepsis onset and declined by 72 hours, with RV dysfunction associated with higher mortality [13]. Together with the time-dependent associations of fluid balance [7], these observations support examining fluid dynamics during the first 72 hours after sepsis onset.

We therefore used the MIMIC-IV database to identify early cumulative fluid balance trajectories among adults with sepsis and reduced RV systolic function who remained alive and in the ICU during the first 72 hours after sepsis onset. The primary endpoint was 28-day all-cause mortality. This study aimed to identify high-risk fluid balance patterns and inform future research on individualised fluid management in this population.

Methods

Data sources and study population

This retrospective cohort study used MIMIC-IV version 3.1, which contains deidentified clinical data from Beth Israel Deaconess Medical Center in Boston, Massachusetts, United States, covering the period 2008–2022 [14]. Clinical records were linked to echocardiographic information using patient, hospital admission, and ICU stay identifiers.

We included patients who met the following criteria: (1) age ≥ 18 years; (2) sepsis with documented reduced right ventricular systolic function on echocardiography within 12 hours before or after sepsis onset; and (3) survival and continued ICU residence throughout the first 72 hours after sepsis onset. Sepsis onset was used as time zero (T0). Reduced right ventricular systolic function included mild, moderate, or severe global reduction, unspecified depressed function, and regional dysfunction. For patients with multiple eligible ICU stays, the earliest eligible stay was retained.

Patients were excluded if they died or were discharged from the ICU or hospital during the 72-hour assessment period, had incomplete fluid balance data for the 12 consecutive 6-hour intervals, or lacked a valid baseline body weight of 20–300 kg. Patients receiving renal replacement therapy during the assessment period were retained. The final cohort comprised 1,042 patients. The patient selection process is shown in Fig. 1.

Data collection and missing data

For each eligible patient, we extracted demographic characteristics, comorbidities, vital signs, laboratory measurements, echocardiographic findings, and organ support. Baseline variables included the Sequential Organ Failure Assessment (SOFA) score at sepsis onset, left ventricular ejection fraction, creatinine, and initial invasive ventilation. Vital signs were summarized over the 6 hours preceding sepsis onset, and laboratory measurements were represented by the last available values within the 24 hours preceding sepsis onset. The primary outcome was all-cause mortality within 28 days after sepsis onset; secondary outcomes included ICU mortality, in-hospital mortality, and 28-day ventilator-free days.

Laboratory variables with more than 40% missing values were excluded, whereas structurally missing values were retained as missing. Missing covariates were imputed using multiple imputation by chained equations, generating 50 imputed datasets [15]. Adjusted estimates were pooled using Rubin's rules. Baseline characteristics were summarized using observed data. Missingness of baseline variables before imputation is reported in Table S3.

Fluid balance assessment

Fluid input and output were summarized in consecutive 6-hour intervals during the first 72 hours after sepsis onset. Input included intravenous fluids, blood products, nutrition, and other recorded volumes. Continuous infusions were allocated according to their overlap with each 6-hour interval. Cumulative fluid balance (CFB) was calculated using the following formula:

$$CFB\,(t)\;=\;\frac{Cumulative\;input(0-t)\;-\;Cumulative\;output(0-t)}{Baseline\;body\;weight}$$

Fluid volumes were measured in milliliters and normalized to baseline body weight in kilograms, yielding CFB in mL/kg at t = 6, 12, …, 72 hours. Baseline weight was obtained from a valid measurement at sepsis onset or, if unavailable, admission or first-day records.

For fully observed intervals, the absence of eligible volume records was treated as zero recorded volume; incomplete intervals were considered missing. Urine output was counted once within total output. Fluid balance reflected documented volumes, and complete capture of RRT net ultrafiltration could not be confirmed.

Group-based trajectory analysis

Group-based trajectory modelling was used to identify distinct patterns of cumulative fluid balance during the first 72 hours after sepsis onset. Gaussian finite-mixture models were fitted to 12 measurements obtained at 6-hour intervals. Models with two to six groups and quadratic or cubic time functions were evaluated using 30 initializations per model.

Final selection was restricted to models with no more than five groups, each comprising ≥ 5% of patients, average posterior probabilities ≥ 0.70, and entropy ≥ 0.70. Among eligible models, the model with the lowest Bayesian information criterion was selected, with trajectory interpretability also considered. Patients were assigned to the group with the highest posterior probability. Groups were labelled T1–T5 in ascending order of observed median cumulative fluid balance at 72 hours. Model selection statistics are presented in Table S1.

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges and compared using the Kruskal–Wallis test. Categorical variables were presented as counts and percentages and compared using Pearson’s chi-squared or Fisher’s exact test, as appropriate. Monte Carlo estimation with 200,000 samples was used for larger sparse contingency tables.

Survival analyses began at the 72-hour landmark, with 28-day mortality measured from sepsis onset. Kaplan–Meier curves were compared using the log-rank test. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), with T1 as the reference group. Model 1 was unadjusted. Model 2 adjusted for age, sex, and Charlson comorbidity index. Model 3 additionally adjusted for SOFA score at sepsis onset, left ventricular ejection fraction, baseline creatinine, preceding 6-hour mean arterial pressure, and initial invasive ventilation. ICU and in-hospital mortality were analysed using cause-specific Cox models, with censoring at live ICU or hospital discharge.

Exploratory subgroup analyses of 28-day mortality were stratified by age (< 65/≥65 years), sex, left ventricular ejection fraction (< 40%/≥40%), chronic renal disease, initial acute kidney injury, and initial invasive ventilation. Analyses were performed using Python and R version 4.5.2. Two-sided P values < 0.05 were considered statistically significant.

Results

Trajectory identification and selection

The quadratic five-class model was selected, with a Bayesian information criterion of 114,241.8 and entropy of 0.980. Average posterior probabilities ranged from 0.985 to 0.993, and each class accounted for more than 13% of the cohort. Model comparison statistics are presented in Table S1.

Trajectory 1 showed persistent negative fluid balance and included 166 patients (15.9%). Trajectory 2 showed mild negative balance and included 243 patients (23.3%). Trajectories 3, 4, and 5 showed mild, moderate, and high positive balance, respectively, including 281 (27.0%), 210 (20.2%), and 142 patients (13.6%). Median recorded cumulative fluid balance at 72 hours was − 76.7, − 16.7, 28.4, 93.3, and 215.5 mL/kg across Trajectories 1–5 (Fig. 2).

Baseline characteristics

Baseline characteristics are summarized in Table 1. Median age ranged from 68.2 to 70.5 years across trajectories (P = 0.301). Sex distribution differed across groups, with male patients accounting for 66.3% in Trajectory 1 and 55.6% in Trajectory 5 (overall P = 0.038). ICU type and baseline weight also differed (both P < 0.001).

Table 1
Baseline characteristics and clinical outcomes by cumulative fluid balance trajectory

Variables	Class	Class	Class	Class	Class	p-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	
	Persistent negative	Mild negative	Mild positive	Moderate positive	High positive	
	N = 166	N = 243	N = 281	N = 210	N = 142	
Demographics and ICU admission						
Age, years	70.5 (61.5, 78.4)	70.0 (58.9, 78.6)	69.3 (59.3, 79.2)	70.1 (58.9, 77.9)	68.2 (55.0, 77.3)	0.301[1]
Sex, n (%)						0.038[2]
Male	110 (66.3%)	165 (67.9%)	185 (65.8%)	121 (57.6%)	79 (55.6%)	
Female	56 (33.7%)	78 (32.1%)	96 (34.2%)	89 (42.4%)	63 (44.4%)	
ICU type, n (%)						< 0.001[3]
Med-Surg ICU	14 (8.4%)	20 (8.2%)	30 (10.7%)	19 (9.0%)	16 (11.3%)	
Cardiac ICU	112 (67.5%)	142 (58.4%)	119 (42.3%)	84 (40.0%)	43 (30.3%)	
MICU	24 (14.5%)	60 (24.7%)	102 (36.3%)	80 (38.1%)	55 (38.7%)	
SICU	13 (7.8%)	15 (6.2%)	28 (10.0%)	21 (10.0%)	26 (18.3%)	
Other	3 (1.8%)	6 (2.5%)	2 (0.7%)	6 (2.9%)	2 (1.4%)	
Weight, kg	80.0 (69.0, 97.6)	85.6 (71.4, 104.0)	86.0 (71.0, 101.0)	76.3 (61.8, 91.0)	74.5 (61.0, 91.3)	< 0.001[1]
Cardiovascular and physiologic status						
Heart rate, beats/min	89.9 (77.0, 103.4)	92.3 (77.9, 103.9)	93.8 (77.0, 110.0)	94.0 (79.4, 107.6)	97.2 (85.0, 116.5)	0.019[1]
Mean arterial pressure, mmHg	78.1 (70.0, 86.5)	79.0 (70.6, 86.0)	76.8 (69.9, 86.0)	77.9 (68.1, 87.0)	75.0 (67.2, 84.5)	0.106[1]
SpO_2, %	96.5 (94.1, 98.5)	96.5 (94.3, 98.5)	97.0 (94.5, 99.0)	97.0 (94.4, 99.2)	97.0 (94.4, 99.0)	0.312[1]

Variables	Class	Class	Class	Class	Class	p-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	
	Persistent negative	Mild negative	Mild positive	Moderate positive	High positive	
	N = 166	N = 243	N = 281	N = 210	N = 142	
Demographics and ICU admission						
LVEF, %	30.0 (20.0, 47.5)	30.0 (20.0, 55.0)	35.0 (25.0, 55.0)	39.0 (25.0, 55.0)	40.0 (25.0, 55.0)	0.003[1]
Right ventricular dysfunction, n (%)						0.327[2]
Mild global	55 (33.1%)	72 (29.6%)	75 (26.7%)	60 (28.6%)	40 (28.2%)	
Moderate global	34 (20.5%)	61 (25.1%)	65 (23.1%)	46 (21.9%)	29 (20.4%)	
Severe global	36 (21.7%)	35 (14.4%)	46 (16.4%)	29 (13.8%)	31 (21.8%)	
Depressed, unspecified	17 (10.2%)	45 (18.5%)	58 (20.6%)	45 (21.4%)	24 (16.9%)	
Regional	24 (14.5%)	30 (12.3%)	37 (13.2%)	30 (14.3%)	18 (12.7%)	
Laboratory measurements before sepsis onset						
WBC, ×10⁹/L	11.6 (7.8, 17.0)	12.1 (8.8, 17.1)	12.6 (8.6, 17.0)	12.8 (9.2, 18.4)	12.7 (8.9, 17.9)	0.638[1]
Hemoglobin, g/dL	11.2 (9.2, 13.1)	11.0 (9.2, 13.4)	10.6 (8.9, 12.4)	10.5 (8.9, 12.2)	10.5 (8.8, 12.4)	0.068[1]
Platelets, ×10⁹/L	195 (132, 253)	196 (146, 244)	207 (135, 276)	200 (135, 239)	195 (118, 267)	0.608[1]
BUN, mg/dL	32 (21, 46)	28 (19, 46)	31 (20, 49)	34 (19, 49)	26 (18, 44)	0.573[1]
Creatinine, mg/dL	1.50 (1.10, 2.10)	1.40 (1.00, 2.40)	1.50 (1.00, 2.40)	1.60 (1.00, 2.70)	1.90 (1.10, 3.30)	0.058[1]
Sodium, mmol/L	137.0 (134.0, 140.0)	138.0 (134.0, 141.0)	139.0 (134.0, 142.0)	138.0 (133.0, 140.2)	137.0 (133.0, 140.0)	0.038[1]
Potassium, mmol/L	4.3 (3.8, 5.0)	4.4 (4.0, 5.0)	4.3 (3.8, 4.8)	4.4 (3.9, 4.9)	4.5 (3.9, 5.2)	0.222[1]

Variables	Class	Class	Class	Class	Class	p-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	
	Persistent negative	Mild negative	Mild positive	Moderate positive	High positive	
	N = 166	N = 243	N = 281	N = 210	N = 142	
Demographics and ICU admission						
Chloride, mmol/L	99.0 (96.0, 104.0)	101.0 (96.0, 104.0)	103.0 (98.0, 107.0)	102.0 (97.0, 106.0)	100.0 (96.0, 106.0)	0.002[1]
Bicarbonate, mmol/L	23.0 (19.2, 27.0)	22.0 (19.0, 26.0)	22.0 (18.0, 25.0)	21.5 (18.0, 24.0)	20.0 (16.0, 22.0)	< 0.001[1]
INR	1.45 (1.20, 2.08)	1.50 (1.20, 2.10)	1.40 (1.20, 1.90)	1.40 (1.20, 2.05)	1.50 (1.30, 2.00)	0.516[1]
PT, s	15.9 (13.5, 22.4)	15.8 (13.2, 23.0)	15.3 (13.4, 20.4)	15.6 (13.4, 22.2)	16.7 (13.9, 21.6)	0.612[1]
PTT, s	34.8 (29.6, 46.6)	34.2 (29.2, 49.1)	34.4 (29.1, 49.4)	36.8 (30.0, 50.2)	34.8 (29.6, 42.3)	0.790[1]
Severity of illness						
SOFA score at sepsis onset	3 (2, 5)	3 (2, 6)	4 (2, 6)	4 (2, 6)	5 (3, 7)	< 0.001[1]
APS III score	50 (41, 62)	53 (42, 65)	61 (46, 75)	63 (52, 76)	73 (60, 92)	< 0.001[1]
OASIS score	33 (28, 39)	35 (31, 41)	38 (32, 43)	40 (35, 45)	44 (37, 49)	< 0.001[1]
Charlson comorbidity index	6 (4, 8)	6 (4, 8)	7 (4, 8)	7 (5, 8)	6 (3, 8)	0.187[1]
AKI stage at sepsis onset, n (%)						0.003[3]
Stage 0	133 (81.1%)	192 (79.0%)	234 (84.2%)	162 (78.3%)	100 (71.9%)	
Stage 1	22 (13.4%)	31 (12.8%)	27 (9.7%)	28 (13.5%)	19 (13.7%)	
Stage 2	8 (4.9%)	15 (6.2%)	11 (4.0%)	7 (3.4%)	5 (3.6%)	
Stage 3	1 (0.6%)	5 (2.1%)	6 (2.2%)	10 (4.8%)	15 (10.8%)	

Variables	Class	Class	Class	Class	Class	p-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	
	Persistent negative	Mild negative	Mild positive	Moderate positive	High positive	
	N = 166	N = 243	N = 281	N = 210	N = 142	
Demographics and ICU admission						
Comorbidities						
Myocardial infarction, n (%)	64 (38.6%)	104 (42.8%)	102 (36.3%)	94 (44.8%)	46 (32.4%)	0.099[2]
Congestive heart failure, n (%)	145 (87.3%)	201 (82.7%)	206 (73.3%)	149 (71.0%)	85 (59.9%)	< 0.001[2]
Chronic pulmonary disease, n (%)	61 (36.7%)	83 (34.2%)	84 (29.9%)	67 (31.9%)	48 (33.8%)	0.630[2]
Diabetes, n (%)	63 (38.0%)	108 (44.4%)	123 (43.8%)	82 (39.0%)	47 (33.1%)	0.155[2]
Chronic renal disease, n (%)	52 (31.3%)	93 (38.3%)	110 (39.1%)	86 (41.0%)	55 (38.7%)	0.391[2]
Malignant cancer, n (%)	14 (8.4%)	20 (8.2%)	37 (13.2%)	20 (9.5%)	13 (9.2%)	0.331[2]
Atrial fibrillation/flutter, n (%)	84 (50.6%)	139 (57.2%)	145 (51.6%)	106 (50.5%)	68 (47.9%)	0.414[2]
Pulmonary hypertension, n (%)	55 (33.1%)	63 (25.9%)	58 (20.6%)	38 (18.1%)	30 (21.1%)	0.006[2]
Pulmonary embolism, n (%)	12 (7.2%)	16 (6.6%)	23 (8.2%)	19 (9.0%)	14 (9.9%)	0.778[2]
Early organ support						
Invasive mechanical ventilation at sepsis onset, n (%)	71 (42.8%)	123 (50.6%)	156 (55.5%)	130 (61.9%)	85 (59.9%)	0.002[2]
RRT during 0–72 h, n (%)	8 (4.8%)	27 (11.1%)	46 (16.4%)	54 (25.7%)	83 (58.5%)	< 0.001[2]

Variables	Class	Class	Class	Class	Class	p-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	
	Persistent negative	Mild negative	Mild positive	Moderate positive	High positive	
	N = 166	N = 243	N = 281	N = 210	N = 142	
Demographics and ICU admission						
Outcomes						
28-day mortality, n (%)	43 (25.9)	68 (28.0)	91 (32.4)	75 (35.7)	61 (43.0)	0.009[2]
ICU mortality, n (%)	22 (13.3)	38 (15.6)	63 (22.4)	59 (28.1)	59 (41.5)	< 0.001[2]
In-hospital mortality, n (%)	32 (19.3)	57 (23.5)	82 (29.2)	77 (36.7)	66 (46.5)	< 0.001[2]
Ventilator-free days at day 28, days	25.75 (0–28.00)	25.38 (0–28.00)	23.75 (0–27.00)	20.23 (0–26.07)	10.59 (0–24.41)	< 0.001[1]

Values are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Descriptive statistics and unadjusted group comparisons were calculated from the original non-imputed cohort using available observations; percentages use the nonmissing denominator within each trajectory group. Multiple imputation was reserved for adjusted models. Trajectory 1, Persistent negative; Trajectory 2, Mild negative; Trajectory 3, Mild positive; Trajectory 4, Moderate positive; Trajectory 5, High positive. Laboratory measurements are the last available values during the 24 hours before sepsis onset; heart rate, mean arterial pressure, and SpO_2 summarize the 6 hours before sepsis onset. SOFA, Sequential Organ Failure Assessment; APS III, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; ICU, intensive care unit; AKI, acute kidney injury; RRT, renal replacement therapy; LVEF, left ventricular ejection fraction; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time. [1]Kruskal–Wallis rank-sum test. [2]Pearson's chi-squared test. [3]Fisher's exact test; Monte Carlo estimation with 200,000 samples was used for tables larger than 2 × 2. Ventilator-free days at day 28 were calculated as 28 minus the cumulative recorded duration of invasive ventilation or tracheostomy states during the index ICU stay within 28 days after T0; patients who died within 28 days were assigned zero.

Initial severity differed across fluid balance trajectories. Median SOFA scores were 3, 3, 4, 4, and 5 in Trajectories 1–5, respectively (P < 0.001). APS III and OASIS scores showed corresponding differences (both P < 0.001). Median left ventricular ejection fraction was 30%, 30%, 35%, 39%, and 40% (P = 0.003). The distribution of report-derived right ventricular categories did not differ significantly across groups (P = 0.327).

Initial invasive ventilation was recorded in 42.8%, 50.6%, 55.5%, 61.9%, and 59.9% of patients across trajectories (P = 0.002). RRT use during 0–72 hours increased from 4.8% in Trajectory 1 to 58.5% in

Trajectory 5 (global P < 0.001). Congestive heart failure was more frequent in Trajectory 1 than Trajectory 5 (87.3% versus 59.9%; global P < 0.001). Charlson comorbidity index did not differ significantly (P = 0.187).

Trajectory class and mortality risk

Among the 1,042 patients, 338 (32.4%) died within 28 days after sepsis onset, 241 (23.1%) died in the ICU, and 314 (30.1%) died during hospitalization. Twenty-eight-day mortality increased across T1–T5, with rates of 25.9%, 28.0%, 32.4%, 35.7%, and 43.0%, respectively (P = 0.009). T5 also had the highest ICU and in-hospital mortality, at 41.5% and 46.5%, compared with 13.3% and 19.3% in T1, respectively (both global P < 0.001). Median ventilator-free days at day 28 decreased across T1–T5, from 25.75 to 10.59 days (global P < 0.001; Table 1).

In the fully adjusted Cox model, T5 was associated with higher 28-day mortality than T1 (HR 2.01, 95% CI 1.34–3.02; P < 0.001). This association was also observed in the unadjusted and partially adjusted models (Table 2). T4 was associated with higher 28-day mortality after full adjustment (HR 1.51, 95% CI 1.03–2.21; P = 0.035).

Table 2
Cox regression models for mortality by cumulative fluid balance trajectory

Outcome	Class	Model 1 HR (95% CI); P	Model 2 HR (95% CI); P	Model 3 HR (95% CI); P
28-day mortality	T1	Ref	Ref	Ref
	T2	1.08 (0.74–1.58); 0.686	1.10 (0.75–1.62); 0.618	1.08 (0.73–1.58); 0.705
	T3	1.34 (0.93–1.93); 0.111	1.36 (0.95–1.96); 0.095	1.36 (0.94–1.96); 0.104
	T4	1.50 (1.03–2.19); 0.033	1.55 (1.07–2.27); 0.021	1.51 (1.03–2.21); 0.035
	T5	1.88 (1.27–2.78); 0.002	2.10 (1.42–3.12); <0.001	2.01 (1.34–3.02); <0.001
ICU mortality	T1	Ref	Ref	Ref
	T2	1.11 (0.65–1.87); 0.704	1.05 (0.62–1.78); 0.845	1.06 (0.62–1.79); 0.836
	T3	1.61 (0.99–2.61); 0.055	1.51 (0.93–2.45); 0.099	1.55 (0.95–2.53); 0.080
	T4	1.48 (0.91–2.42); 0.116	1.42 (0.87–2.32); 0.164	1.47 (0.89–2.41); 0.131
	T5	1.79 (1.09–2.92); 0.021	1.87 (1.14–3.08); 0.013	1.97 (1.19–3.27); 0.008
In-hospital mortality	T1	Ref	Ref	Ref
	T2	1.21 (0.79–1.87); 0.382	1.21 (0.78–1.86); 0.397	1.19 (0.77–1.84); 0.436
	T3	1.63 (1.08–2.46); 0.019	1.64 (1.09–2.47); 0.018	1.65 (1.09–2.50); 0.017
	T4	1.80 (1.19–2.72); 0.005	1.85 (1.22–2.79); 0.004	1.83 (1.20–2.78); 0.005
	T5	2.04 (1.33–3.11); <0.001	2.24 (1.46–3.43); <0.001	2.25 (1.45–3.48); <0.001

All risk sets included 1,042 patients. Model 1, unadjusted; Model 2, adjusted for age, sex, and Charlson comorbidity index; Model 3, further adjusted for SOFA at T0, LVEF, baseline creatinine, mean MAP during the preceding 6 hours, and initial invasive ventilation. Models 2 and 3 were pooled across 50 multiply imputed datasets. Ref, T1 reference. Follow-up began at T0 + 72 hours. Day 28 was relative to T0. ICU and in-hospital mortality used cause-specific Cox models with live discharge censored. P values were not adjusted across all outcome/class comparisons. Global class P values compare all five trajectories jointly. Global class P values for Models 1/2/3 were 0.005/<0.001/0.003 for 28-day mortality, 0.062/0.033/0.019 for ICU mortality, and 0.003/<0.001/<0.001 for in-hospital mortality.

Similar associations were observed for ICU and in-hospital mortality. Compared with T1, the fully adjusted HRs for T5 were 1.97 (95% CI 1.19–3.27; P = 0.008) for ICU mortality and 2.25 (95% CI 1.45–3.48; P < 0.001) for in-hospital mortality. T3 and T4 were also associated with higher in-hospital mortality, with adjusted HRs of 1.65 (95% CI 1.09–2.50) and 1.83 (95% CI 1.20–2.78), respectively. The fully adjusted global trajectory tests were significant for 28-day, ICU, and in-hospital mortality (P = 0.003, P = 0.019, and P < 0.001, respectively; Fig. 4).

Kaplan–Meier survival analysis

Kaplan–Meier curves showed differences in 28-day survival across trajectories (log-rank χ^2=15.03, 4 degrees of freedom; P = 0.005; Fig. 3). Trajectory 1 had the highest survival probability at day 28 and Trajectory 5 the lowest. Follow-up began at the 72-hour landmark and ended 28 days after the sepsis reference time.

Subgroup analysis

The T5-versus-T1 point estimates were above 1 across all six exploratory subgroup factors (Fig. 5 and Table S2). Adjusted HRs were 1.91 (95% CI 0.91–4.02) below age 65 and 1.94 (1.19–3.18) at age 65 or above. They were 1.77 (0.87–3.61) in women and 2.35 (1.42–3.87) in men. Corresponding HRs were 1.54 (0.78–3.04) with LVEF ≥ 40% and 2.80 (1.57–5.00) with LVEF < 40%.

Global interaction tests evaluated all five trajectories jointly. Interaction P values were 0.138 for age, 0.290 for sex, and 0.364 for LVEF. They were 0.645 for chronic renal disease, 0.955 for initial AKI, and 0.422 for initial invasive ventilation. Benjamini–Hochberg q values ranged from 0.633 to 0.955. No statistically significant global interaction was observed.

Discussion

This study identified five early cumulative fluid balance trajectories in patients with sepsis and reduced RV systolic function who remained alive and in the ICU at 72 hours. The trajectories ranged from persistent negative balance in T1 to high positive balance in T5. Group-based trajectory modelling characterizes longitudinal exposure patterns and has been applied to clinical risk stratification, including in studies of fluid balance in septic shock [16, 17]. Compared with T1, T5 was associated with approximately twice the hazard of 28-day mortality after full adjustment (HR 2.01, 95% CI 1.34–3.02). The point estimate was 1.88 in the unadjusted model and 2.01 after adjustment for measured demographic, clinical, cardiac, and renal characteristics, showing a consistent association after adjustment for the measured baseline covariates. The findings identify a high positive fluid balance trajectory as a prognostic pattern in this clinically defined population.

The temporal nature of fluid exposure helps contextualise this association. Earlier MIMIC-IV research associated positive balance on the first ICU day with lower mortality, but persistent positive balance later in the admission with higher mortality [7]. Our trajectory groups describe different patterns of

accumulation over the first 72 hours and support examining fluid balance longitudinally. Whether trajectory classification improves prediction over a single cumulative measurement remains uncertain, as this comparison was not performed in the present analysis. The findings are consistent with the broader literature linking fluid overload to adverse outcomes in critical illness and highlighting fluid management challenges in acute kidney injury (AKI) [18, 19].

Right ventricular physiology provides a plausible mechanistic explanation for the association between high positive fluid balance and mortality. The right ventricle operates at low pressure and interacts mechanically with the left ventricle through the interventricular septum and shared pericardial space [20, 21]. Hypoxia, pulmonary vascular injury, and mechanical ventilation may increase pulmonary vascular resistance, while sepsis-related myocardial depression may impair RV contractile reserve [11, 22]. The resulting mismatch between RV performance and pulmonary vascular load can promote acute RV decompensation. Acute cor pulmonale in acute respiratory distress syndrome illustrates the clinical importance of this process [23]. Additional volume loading may increase RV dilatation and pericardial constraint, shifting the septum leftwards and impairing left ventricular filling through diastolic ventricular interdependence [20, 24]. These mechanisms provide biological context for our observations; serial quantitative RV measurements and perfusion assessments were unavailable to test them directly.

Our study extends previous fluid balance research to a population defined by reduced RV systolic function. Earlier studies examined cumulative exposure at selected time points [4, 5, 6, 7], whereas more recent investigations identified trajectories in circulatory failure and general sepsis populations [8, 9]. The present analysis combines a 72-hour exposure window with a landmark design and a specific echocardiographic phenotype. High positive balance was associated with greater initial illness severity, consistent with earlier trajectory studies [8, 9]. Its association with mortality persisted after adjustment for measured baseline severity and organ function. These findings support further evaluation of RV phenotype in studies of fluid tolerance. Whether RV dysfunction modifies the effect of fluid exposure requires direct comparison with patients without RV dysfunction and a formal interaction analysis.

The cardiac characteristics of the highest-risk trajectory warrant further consideration. Compared with T1, T5 had a higher median left ventricular ejection fraction (40% versus 30%) and less recorded congestive heart failure (59.9% versus 87.3%). T5 also had a lower representation of patients from cardiac intensive care units. The distribution of report-derived RV categories did not differ significantly across trajectories ($P = 0.327$). These findings raise the possibility of differing cardiac and haemodynamic substrates across trajectories. However, qualitative RV categories cannot establish equivalent RV severity, and the available data cannot distinguish acute septic myocardial dysfunction from pre-existing RV disease. Standardised measurements, including tricuspid annular plane systolic excursion, fractional area change, and tricuspid annular systolic velocity, would help clarify these phenotypes [25, 26]. The association between high positive fluid balance and mortality was therefore observed in a trajectory with a higher LVEF and a lower recorded prevalence of chronic heart failure.

Associations were also observed for ICU and in-hospital mortality. The fully adjusted HRs for T5 versus T1 were 1.97 (95% CI 1.19–3.27) and 2.25 (95% CI 1.45–3.48), respectively. These findings extend the association beyond the primary 28-day endpoint. In exploratory subgroup analyses, T5-versus-T1 point estimates were above 1 across the assessed strata. Global interaction tests involving all five trajectories found no statistically significant evidence of effect modification by age, sex, ejection fraction, chronic renal disease, initial AKI, or initial ventilation. The high positive balance trajectory also had the lowest median number of ventilator-free days at day 28, reflecting a greater combined burden of mortality and recorded respiratory support in the unadjusted analysis.

Fluid balance trajectories can be derived from routinely recorded fluid inputs and outputs and may help identify patients at higher subsequent risk [16, 17]. However, their association with mortality does not determine whether changing fluid administration or removal improves outcomes. The CLASSIC and CLOVERS trials did not demonstrate an overall mortality advantage for restrictive fluid strategies in their respective populations [27, 28]. Evidence on conservative fluid management and deresuscitation, including the FFAKI feasibility trial, further supports evaluating treatment effects in clearly defined clinical settings [29, 30]. Fluid responsiveness and fluid tolerance also require physiological assessment; static filling pressures alone are insufficient to guide resuscitation [31]. Our findings provide a rationale for trials incorporating RV assessment into patient selection and fluid management strategies. Such trials could evaluate when fluid removal should begin and whether an RV-guided approach improves outcomes [27, 28, 30].

Several limitations should be considered when interpreting these findings. First, the retrospective observational design cannot establish causality. Greater illness severity may increase both fluid requirements and mortality, and adjustment for measured baseline variables does not eliminate residual or time-varying confounding. Second, RV systolic function was classified from qualitative echocardiographic reports rather than standardised quantitative thresholds [25]. Differences in image quality and interpretation may have introduced phenotype misclassification. Echocardiography within 12 hours before or after sepsis onset also does not establish the exact onset of RV dysfunction. The direction and magnitude of bias arising from these timing differences cannot be assumed. Third, RRT was substantially more common in T5 during the exposure window. RRT initiation and fluid removal are clinical decisions related to both illness severity and fluid balance. Trials of RRT timing have produced differing findings, and the KDIGO guideline emphasises clinical indications and the broader clinical context [32, 33, 34, 35]. Incomplete recording of net ultrafiltration could overestimate recorded positive fluid balance; its effect on the trajectory–mortality association is uncertain. Fourth, trajectory classes are statistical groupings rather than biologically validated disease subtypes. Model selection criteria were not prospectively registered, and assigning each patient to one class did not fully propagate classification uncertainty [16]. Fifth, the landmark design restricts inference to patients alive and still in the ICU 72 hours after sepsis onset. The results therefore do not apply directly to patients who died or left the ICU earlier. Pairwise comparisons between trajectory classes and across outcomes were not adjusted for multiplicity, although the six subgroup interaction tests underwent false discovery rate

correction. Finally, cause-specific HRs for ICU and in-hospital death describe instantaneous hazards among patients remaining at risk, rather than cumulative mortality probabilities.

Early cumulative fluid balance trajectories were associated with subsequent outcomes in patients with sepsis and reduced RV systolic function. High positive balance remained associated with greater mortality after adjustment for measured baseline characteristics. These findings support further evaluation of longitudinal fluid balance assessment for risk stratification and of RV-guided fluid management in prospective studies.

Conclusions

Five early cumulative fluid balance trajectories were identified in patients with sepsis and reduced right ventricular systolic function. Among patients alive and in the ICU at 72 hours, the high positive trajectory was associated with higher subsequent mortality than the persistent negative trajectory. This association remained after adjustment for initial severity, cardiac and renal function, comorbidity burden, and initial ventilation. These findings highlight the prognostic relevance of early fluid balance trajectories in sepsis with reduced RV systolic function.

Abbreviations

AKI, acute kidney injury; APS III, Acute Physiology Score III; ARDS, acute respiratory distress syndrome; BIC, Bayesian information criterion; BUN, blood urea nitrogen; CFB, cumulative fluid balance; CHF, congestive heart failure; CI, confidence interval; FAC, fractional area change; FDR, false discovery rate; GBTM, group-based trajectory modeling; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MICE, multiple imputation by chained equations; MIMIC-IV, Medical Information Mart for Intensive Care IV; OASIS, Oxford Acute Severity of Illness Score; PT, prothrombin time; PTT, partial thromboplastin time; RRT, renal replacement therapy; RV, right ventricular; SOFA, Sequential Organ Failure Assessment; SpO_2, peripheral oxygen saturation; T0, sepsis reference time; T1–T5, trajectory 1–trajectory 5; VFD-28, ventilator-free days at day 28; WBC, white blood cell count.

Declarations

Ethics approval and consent to participate

he MIMIC-IV database was approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, with a waiver of informed consent for the use of deidentified data. This study analysed these deidentified records in accordance with the Declaration of Helsinki. Database access was obtained through PhysioNet after completion of the required Collaborative Institutional Training Initiative (CITI) training (Record IDs: 47924316 and 71753331), credentialing, and signing of the data use agreement.

Consent for publication

Not applicable (retrospective database analysis using de-identified data).

Availability of data and materials

MIMIC-IV version 3.1 is available through PhysioNet to credentialed users who have completed the required training and accepted its data use agreement [14]. The version-specific resource is available at https://doi.org/10.13026/kpb9-mt58 [36,37]. Patient-level source and derived datasets remain subject to the PhysioNet access and sharing conditions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

R.Y., L.C. and G.D. designed the study. R.Y. and D.S. extracted, collected, and analyzed the data. J.J. and Y.Z. prepared the tables and figures. R.Y. interpreted the data and wrote the main manuscript text. All authors read and approved the final manuscript.

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Figures

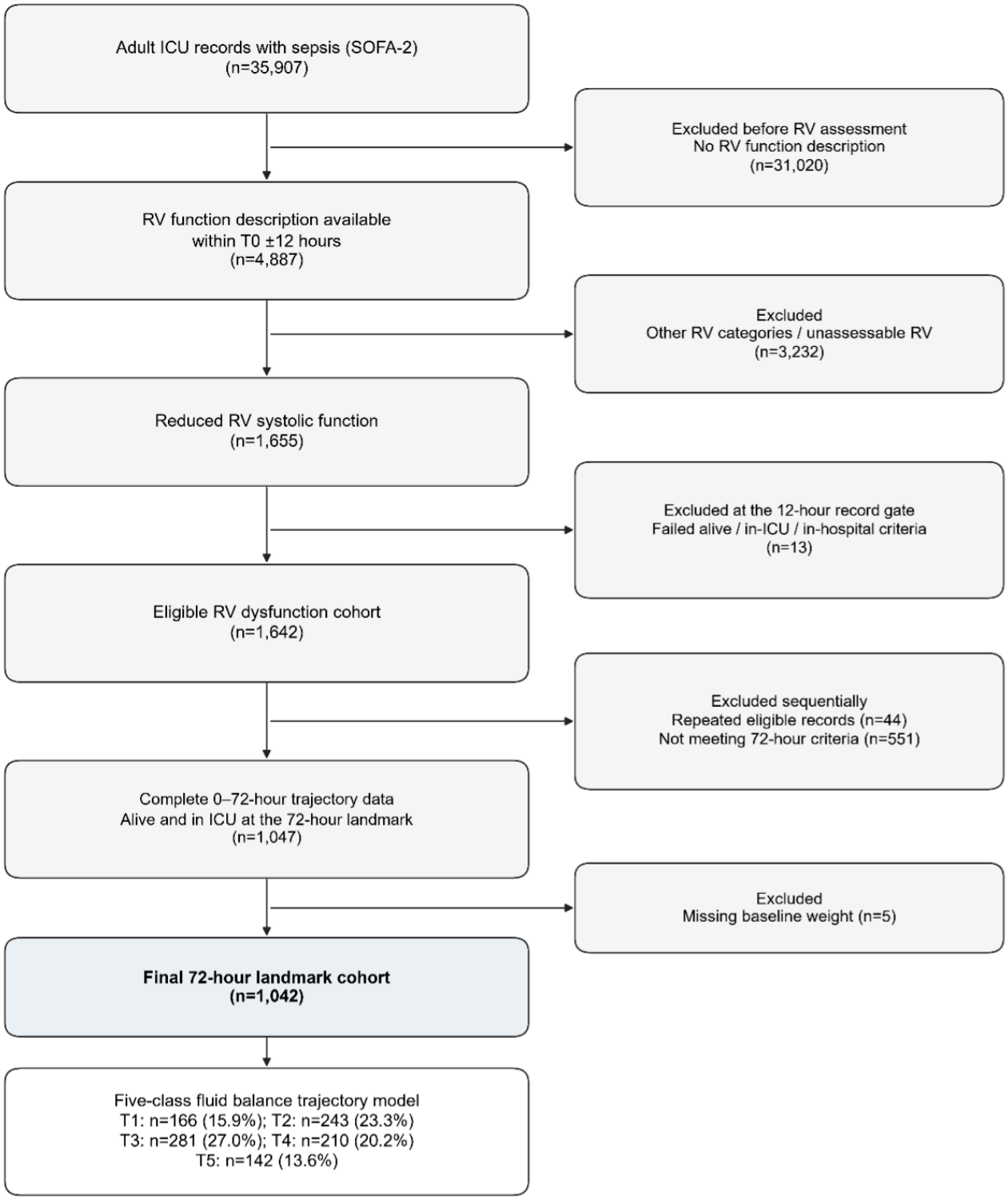


Figure 1

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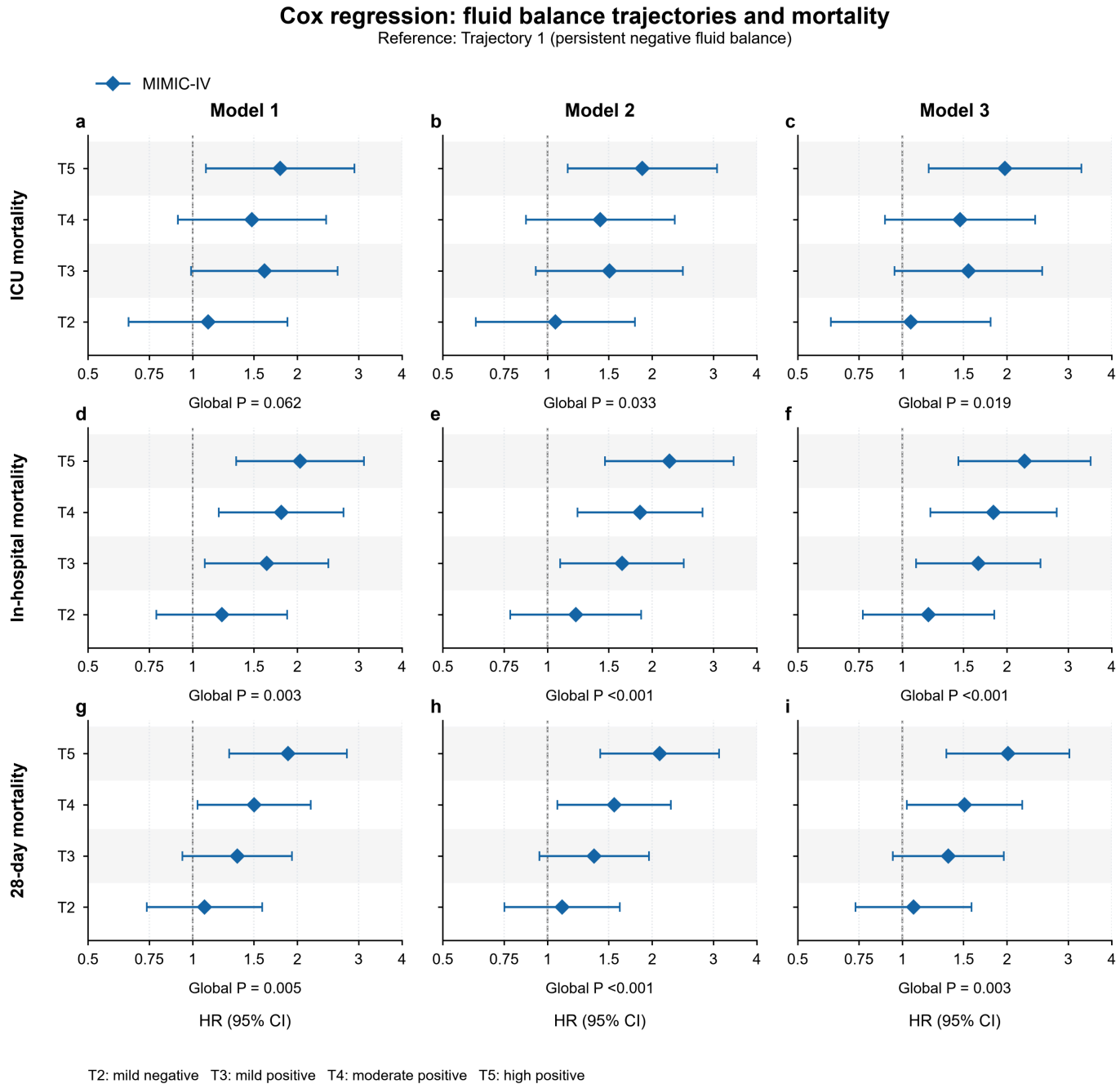


Figure 4

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