

Joint early resuscitation-response phenotypes and post-landmark organ-support transitions in critically ill adults with acute pancreatitis: a multi-database landmark study

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Research Article

Keywords: acute pancreatitis, fluid balance, vasopressors, lactate, multistate model

Posted Date: October 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11259775/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Early resuscitation in critically ill patients with acute pancreatitis involves interdependent fluid administration, vasopressor support, and metabolic response. We sought to identify joint resuscitation-response phenotypes and examine their associations with subsequent organ-support transitions.

Methods

We used MIMIC-IV v3.1 for discovery and model freezing, MIMIC-III CareVue for same-center historical/temporal transport, and screened eICU-CRD v2.0 hospitals for partial multicenter structural transport. Adults with acute pancreatitis who were alive and remained in the ICU at 24 h were eligible. A two-part trajectory model integrated cumulative net fluid balance, vasopressor exposure and positive-dose norepinephrine-equivalent intensity, and lactate response in four 6-h bins. The outcome-blind K3 linear model was frozen before recurrent cause-specific Cox analysis of post-landmark transitions.

Results

The MIMIC-IV cohort included 575 patients: 198 (34.4%) in P1 low-burden/low-lactate, 239 (41.6%) in P2 fluid-predominant with declining lactate, and 138 (24.0%) in P3 high-intensity multimodal burden. Median net fluid balance was 5.1, 47.9, and 88.1 mL/kg, and vasopressor exposure was 24.2%, 14.2%, and 98.6%, respectively. Relative to P1, P2 was not clearly associated with escalation (adjusted hazard ratio [HR] 0.86, 95% CI 0.57–1.32) or alive ICU discharge (HR 0.91, 95% CI 0.75–1.11). P3 was associated with faster escalation (HR 1.80, 95% CI 1.22–2.65) and slower alive ICU discharge (HR 0.68, 95% CI 0.55–0.84). Assignment certainty remained high in MIMIC-III ($n = 181$) and screened eICU ($n = 152$, 47 hospitals); eICU supported structural transport only because P3 and deaths were sparse.

Conclusions

A frozen joint 24-h phenotype distinguished fluid-predominant patients with declining lactate from patients with concurrent fluid, vasopressor, and lactate burden. The high-intensity phenotype was associated with subsequent support escalation and delayed alive ICU discharge. These observational phenotypes may support structured monitoring but do not identify optimal fluid or vasopressor treatment.

Introduction

Acute pancreatitis spans a broad clinical spectrum, and persistent organ failure defines the patients at greatest risk of prolonged critical illness and death. Early intravenous fluid therapy remains central to

management, but contemporary guidance emphasizes goal-directed reassessment rather than indiscriminate volume expansion [1, 2]. The WATERFALL trial and subsequent analyses reinforced the safety concerns of aggressive fluid strategies in unselected patients, while more recent evidence continues to refine how intensity should be adapted to severity and response [3–5]. These findings make the clinical problem less about a universal volume target and more about recognizing whether fluid accumulation occurs alongside circulatory support requirements and a favorable or unfavorable metabolic response.

Observational analyses in acute pancreatitis have usually examined one dimension at a time. Fluid-balance trajectories and fluid-balance indices have been associated with outcomes [6–8]; early vasopressor use has been evaluated in MIMIC-IV [9]; and lactate clearance has been investigated as a prognostic marker [10]. Other studies have identified dynamic subphenotypes from vital signs, hematocrit and blood urea nitrogen, or single laboratory trajectories [11–13]. These studies demonstrate the value of repeated measurements, but they do not answer whether joint patterns of fluid burden, vasopressor exposure and intensity, and lactate response distinguish clinically different early resuscitation states.

A second limitation is that many studies reduce the ICU course to one terminal outcome. Mortality and length of stay are important, but they do not distinguish escalation of organ support from de-escalation or alive discharge. Multistate methods can represent these competing and recurrent processes explicitly [14–16]. A landmark design can also separate an early exposure window from later outcomes, although it necessarily changes the target population to patients who survive and remain in the ICU to the landmark.

We therefore used MIMIC-IV to identify and freeze outcome-blind joint 0–24-h resuscitation-response phenotypes in critically ill adults with acute pancreatitis. We then examined associations with post-landmark organ-support transitions, evaluated same-center historical/temporal transport in MIMIC-III CareVue, and assessed partial multicenter structural transport in eICU after hospital-level infusion-interface screening. We hypothesized that a multimodal high-burden phenotype, rather than fluid accumulation alone, would be associated with a greater rate of subsequent support escalation and a lower rate of alive ICU discharge.

Methods

Study design and data sources

This retrospective, multi-database, observational landmark study followed STROBE reporting principles [17]. MIMIC-IV v3.1, which contains source admissions from 2008–2022, was used for phenotype discovery, model freezing, primary association analysis, and sensitivity analyses [18]. MIMIC-III v1.4 spans 2001–2012; this study was restricted to CareVue-derived ICU stays from the earlier clinical-information-system era and used them only for same-center historical/temporal transport [19]. Because

dates are deidentified and shifted, a narrow boundary-period overlap with MIMIC-IV cannot be excluded. eICU-CRD v2.0, covering 2014–2015, provided a multicenter structural-transport assessment after screening hospitals for infusion-interface completeness [20]. We did not pool databases or re-estimate a common cross-database effect.

The scientific estimand was the grouped cause-specific transition rate ratio for P2 or P3 versus P1 among adults with acute pancreatitis who were alive and remained in the ICU at 24 h, conditional on their current support state, transition-specific baseline hazard, and prespecified covariates. This estimand does not apply to patients who died or left the ICU before 24 h.

Cohort construction

Acute pancreatitis admissions were identified using ICD-9 code 5770 or ICD-10 codes beginning with K85. We linked acute-pancreatitis-coded hospital admissions to ICU stays, retained the first ICU stay within each hospitalization, restricted the cohort to adults, retained the first qualifying acute pancreatitis ICU hospitalization per patient, and required ICU entry within 0–24 h after hospital admission. The landmark-eligible population comprised patients alive and remaining in the ICU at 24 h. The primary phenotype cohort additionally required a valid body weight, quantifiable fluid and vasopressor data across all four 6-h bins, and lactate measured in at least one bin.

Of 7,481 acute-pancreatitis-coded hospital admissions, 1,398 had ICU care, comprising 1,686 ICU stays; retaining the first ICU stay per hospitalization removed 288 additional stay-level records, and all 1,398 retained hospitalizations were adult. Retaining the first acute pancreatitis ICU hospitalization per patient yielded 1,280 patients. We excluded 255 patients whose ICU timing fell outside the prespecified 0–24-h entry window (253 entered after 24 h and 2 had ICU time recorded before hospital admission), leaving 1,025. A further 162 patients left the ICU alive and 19 died before the 24-h landmark, leaving 844 landmark-eligible patients. Phenotype-marker requirements excluded 63 patients with invalid or unavailable weight, 13 with insufficient quantifiable fluid input/output, none for incomplete quantitative NEE, and 193 with no observed lactate bin, yielding the primary cohort of 575 (Fig. 1). Nested sensitivity cohorts included 372 patients with lactate observed in at least two bins and 223 with lactate observed in at least three bins. No a priori sample-size target was imposed; all admissions meeting the prespecified criteria in the fixed database versions were included.

Exposure window and marker construction

The exposure time zero was ICU admission. Cumulative markers were evaluated in four bins covering 0–6, > 6–12, > 12–18, and > 18–24 h. Cumulative net fluid balance was systemic fluid input minus audited measured output, normalized to admission weight (mL/kg). Pre-ICU carry-forward, circuit priming or anticoagulant volumes, and non-systemic irrigation were excluded. Intermittent hemodialysis net output

and patient-level continuous renal replacement therapy removal were included; total circuit effluent was not treated as patient net output.

Vasopressor exposure included norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin. Positive doses were converted to an updated norepinephrine-equivalent dose (NEE) framework [21]: $\text{norepinephrine} + \text{epinephrine} + \text{phenylephrine}/10 + \text{dopamine}/100 + \text{vasopressin in U/min} \times 2.5$, expressed in $\mu\text{g/kg/min}$. In MIMIC-IV, the absence of a vasopressor record was coded as zero; every positive record had to have a recoverable dose and unit. NEE was represented by a Bernoulli exposure component and a conditional log-Gaussian positive-dose component to avoid forcing a zero-inflated distribution into one Gaussian trajectory.

For lactate, the median observed value within each 6-h bin was used. Lactate was log-transformed and standardized. Unmeasured bins were omitted from the observed-data likelihood rather than coded as normal or filled by interpolation or last observation carried forward. The fluid trajectory was inverse-hyperbolic-sine transformed and standardized. Standardization parameters were estimated in the discovery cohort and frozen for transport analyses.

Joint trajectory model and phenotype freezing

We fitted two-part joint latent-class trajectory candidates with two to four classes and linear or quadratic time terms. Thirty starting values were used for each candidate. Selection considered Bayesian information criterion, convergence, minimum class proportion, entropy, average posterior probability of assignment (APPA), patient-level bootstrap stability, out-of-bag adjusted Rand index (ARI), and stability in serial- and dense-lactate refits. Outcomes were not used for model selection, class ordering, or naming.

The K3 linear model (K3_d1; BIC 12,024.17) was frozen before outcome modeling. It assigned 198, 239, and 138 patients to the three groups, had entropy 0.929 and class-specific APPA values of 0.963, 0.964, and 0.983, and completed all 100 bootstrap replicates. Median out-of-bag ARI was 0.874; ARI values in serial- and dense-lactate refits were 0.814 and 0.717. A K4 linear candidate had the lowest BIC (11,661.24) but was ineligible under the prespecified minimum-class gate because its smallest class comprised 57 of 575 patients (9.9%, below 10%). The admissible K4 quadratic candidate (BIC 11,687.93) failed the bootstrap stability gate; its weakest class had a median out-of-bag Jaccard index of 0.648 and a fifth percentile of 0.025. The three-class interpretation was therefore retained for stability and parsimony rather than information-criterion fit alone.

Phenotypes were named descriptively: P1 low-burden/low-lactate, P2 fluid-predominant with declining lactate, and P3 high-intensity multimodal burden. Names describe marker patterns and do not judge treatment quality.

Organ-support states and outcomes

Beginning at the 24-h landmark, we reconstructed organ-support state in 6-h intervals. Advanced support comprised vasopressors, invasive mechanical ventilation, and renal replacement therapy. States were no support, one concurrent support, or multiple concurrent supports. Alive ICU discharge and ICU death were distinct absorbing states. Death occurring at or before ICU outtime was classified as ICU death; otherwise ICU outtime was classified as alive ICU discharge.

The four prespecified grouped transition outcomes were escalation to higher support, de-escalation to lower support, alive ICU discharge, and ICU death. A patient could contribute repeated nonfatal transitions before an absorbing event. Observed state occupancy through seven post-landmark days was descriptive, whereas the Cox models used the complete post-landmark ICU course.

Baseline variables and missing data

Adjustment variables were selected before outcome modeling based on temporal precedence, clinical confounding logic, missingness, and the event budget. They included age per 10 years, sex, prior Charlson score excluding age per 2 points, primary acute pancreatitis diagnosis, emergency or urgent admission, first mean arterial pressure (MAP) during 0–6 h per 10 mmHg, blood urea nitrogen (BUN) nearest ICU admission within ± 6 h per 10 mg/dL, hospital-to-ICU delay per 6 h, and the categorical MIMIC-IV calendar-period group (anchor_year_group: 2008–2010 through 2020–2022). We did not use numeric anchor_year as calendar time because patient dates are independently shifted during deidentification. Race/ethnicity was described but was not a prespecified core confounder; its grouped Other/unknown category was common. Laboratory variables with substantial missingness were also not added to the primary adjustment set. Variables accumulated during the 24-h exposure window, including organ support and severity scores, were not treated as baseline confounders.

MAP was missing in 9 of 575 patients (1.6%) and BUN in 59 (10.3%). These two covariates were multiply imputed using chained equations with predictive mean matching, 20 imputations, and Rubin pooling. Exposures and outcomes were not imputed. A complete-case model included 514 patients and 1,567 transition events.

Lactate was observed in 1,292 of 2,300 patient-bin records and missing in 1,008 (43.8%). Because measurement density increased with vasopressor exposure, multiple support, and mortality, missing lactate was treated as an informative measurement process rather than missing completely at random. Serial- and dense-lactate refits were therefore used as primary missingness sensitivity analyses.

Statistical analysis

Continuous variables were summarized as median (interquartile range) and categorical variables as n (%). Descriptive between-phenotype P values used Kruskal–Wallis, chi-square, or simulated Fisher exact tests as appropriate. We also reported the maximum pairwise standardized mean difference.

The primary association model was a transition-stratified recurrent-event cause-specific Cox model. Each exact transition had its own baseline hazard. Phenotype effects were grouped a priori as escalation, de-escalation, alive ICU discharge, and ICU death, while covariate effects were shared. Patient-clustered robust variances accounted for repeated transitions. P1 was the reference. Hazard ratios (HRs) are conditional transition-rate ratios, not absolute risks or causal effects. The primary event budget was 1,809 events: 477 escalations, 757 de-escalations, 527 alive ICU discharges, and 48 ICU deaths. ICU-death estimates were treated as secondary because of sparse events.

Proportional-hazards assumptions were assessed using scaled Schoenfeld residuals. The global test was significant ($P = 0.013$), but phenotype terms were not. A sensitivity model added age and Charlson interactions with $\log(1 + t)$. To propagate classification uncertainty, we performed 100 posterior pseudo-class draws; each draw was paired cyclically with one of the 20 completed covariate-imputation datasets, and robust within-fit and between-draw variance were combined using Rubin-style rules. Additional analyses included unadjusted and complete-case models; semi-Markov clock-reset models; posterior-probability thresholds of 0.80 and 0.90; primary-diagnosis, early-circulatory-dysfunction, and strict shock-like subgroups; hospital-to-ICU entry-window restrictions; a 12-h landmark using the partial frozen likelihood; alternative fluid and lactate operationalizations; and exclusion of first-24-h renal replacement therapy.

The frozen discovery parameters and standardization rules were applied without outcome-based refitting to MIMIC-III and eICU. MIMIC-III models adjusted for age, sex, and primary acute pancreatitis diagnosis. eICU hospitals were screened for infusion-interface completeness before absence of a vasopressor record could approximate zero; mL/h rates without recoverable concentration information were not converted to $\mu\text{g/kg/min}$. Because P3 and deaths were sparse, eICU outcome comparisons remained descriptive.

Analyses used Python 3.11.15 with NumPy 2.4.3, pandas 2.3.3, and SciPy 1.17.1, and R 4.6.1 with survival 3.8-6 and mice 3.19.0. Two-sided $P < 0.05$ was used without multiplicity adjustment; emphasis was placed on effect estimates, 95% CIs, and consistency across prespecified analyses rather than isolated P values.

Ethics and data governance

MIMIC-IV, MIMIC-III, and eICU contain deidentified data available to credentialed users under data-use agreements [18–20]. The source databases were established under their original institutional review-board approvals and waivers of informed consent. The present secondary analysis involved no participant contact or intervention and provided the investigators with no direct identifiers. Accordingly, additional approval by the Ethics Committee of the First Affiliated Hospital of Hunan Traditional Chinese Medical College (Hunan Provincial Hospital of Traditional Chinese Medicine) and additional individual informed consent were not required. The analysis complied with the applicable PhysioNet credentialing

and data-use conditions, no patient-level data are included in the manuscript package, and no attempt was made to re-identify any individual.

Results

Cohort and baseline characteristics

Among 844 patients alive and in the ICU at 24 h, 575 met all phenotype-evaluability requirements (Fig. 1). Median age was 58.0 years, 245 (42.6%) were female, 186 (32.3%) had acute pancreatitis coded as the primary diagnosis, and 500 (87.0%) had an emergency or urgent admission (Table 1). Race/ethnicity was White in 340 (59.1%), Black in 63 (11.0%), Asian in 16 (2.8%), Hispanic/Latino in 25 (4.3%), and other/unknown in 131 (22.8%). P3 patients were older, had lower initial MAP, and had higher BUN and creatinine than the other groups; these descriptive imbalances supported adjusted analyses but were not used to redefine the frozen phenotypes.

Table 1
Baseline characteristics of the MIMIC-IV discovery cohort by frozen phenotype

Characteristic	Overall (N = 575)	P1 Low-burden (N = 198)	P2 Fluid-predominant (N = 239)	P3 High-intensity (N = 138)	P value	Max pairwise SMD
Age, years	58.0 (45.0–70.0)	56.0 (46.2–68.8)	55.0 (43.0–68.0)	60.5 (51.0–74.8)	0.013	0.30
Female sex	245 (42.6%)	78 (39.4%)	103 (43.1%)	64 (46.4%)	0.436	0.14
Race/ethnicity: White	340 (59.1%)	117 (59.1%)	155 (64.9%)	68 (49.3%)	0.004	0.36
Black	63 (11.0%)	16 (8.1%)	30 (12.6%)	17 (12.3%)		
Asian	16 (2.8%)	5 (2.5%)	6 (2.5%)	5 (3.6%)		
Hispanic/Latino	25 (4.3%)	5 (2.5%)	13 (5.4%)	7 (5.1%)		
Other/unknown	131 (22.8%)	55 (27.8%)	35 (14.6%)	41 (29.7%)		
Primary AP diagnosis	186 (32.3%)	65 (32.8%)	99 (41.4%)	22 (15.9%)	< 0.001	0.56
Emergency/urgent admission	500 (87.0%)	183 (92.4%)	200 (83.7%)	117 (84.8%)	0.018	0.27
Hospital-to-ICU interval, h	1.1 (0.0–2.2)	0.1 (0.0–1.8)	1.3 (0.0–2.2)	1.1 (0.0–2.3)	0.004	0.12
Prior Charlson score	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.774	0.02
Congestive heart failure	44 (7.7%)	19 (9.6%)	14 (5.9%)	11 (8.0%)	0.338	0.14
Chronic pulmonary disease	48 (8.3%)	15 (7.6%)	19 (7.9%)	14 (10.1%)	0.675	0.09
Diabetes	53 (9.2%)	16 (8.1%)	28 (11.7%)	9 (6.5%)	0.193	0.18
Renal disease	36 (6.3%)	15 (7.6%)	12 (5.0%)	9 (6.5%)	0.542	0.11
Liver disease	42 (7.3%)	12 (6.1%)	21 (8.8%)	9 (6.5%)	0.508	0.10

Characteristic	Overall (N = 575)	P1 Low-burden (N = 198)	P2 Fluid-predominant (N = 239)	P3 High-intensity (N = 138)	P value	Max pairwise SMD
Malignancy	23 (4.0%)	7 (3.5%)	10 (4.2%)	6 (4.3%)	0.916	0.04
First MAP within 0–6 h, mmHg	86.0 (73.0–99.8)	86.0 (73.0–99.0)	90.0 (79.5–103.5)	76.0 (67.0–88.5)	< 0.001	0.57
Missing	9 (1.6%)	2 (1.0%)	0 (0.0%)	7 (5.1%)		
BUN at ICU admission ± 6 h, mg/dL	22.0 (13.0–40.0)	20.0 (11.0–42.5)	20.0 (12.0–36.2)	27.5 (18.8–49.2)	< 0.001	0.36
Missing	59 (10.3%)	26 (13.1%)	19 (7.9%)	14 (10.1%)		
Creatinine at ICU admission ± 6 h, mg/dL	1.20 (0.80–2.20)	1.10 (0.70–2.00)	1.10 (0.80–1.80)	1.70 (1.10–3.20)	< 0.001	0.42
Missing	57 (9.9%)	25 (12.6%)	19 (7.9%)	13 (9.4%)		
Hematocrit at ICU admission ± 6 h, %	34.3 (30.0–39.5)	32.6 (28.4–38.0)	35.6 (31.0–40.5)	35.0 (30.2–41.6)	< 0.001	0.42
Missing	77 (13.4%)	31 (15.7%)	36 (15.1%)	10 (7.2%)		
White blood cell count, 10 ³ /μL	12.6 (8.9–18.2)	12.6 (9.1–18.2)	12.9 (9.0–17.9)	12.2 (7.7–19.0)	0.802	0.09
Missing	85 (14.8%)	32 (16.2%)	39 (16.3%)	14 (10.1%)		
Platelet count, 10 ³ /μL	182 (126–250)	197 (138–298)	186 (124–249)	153 (110–209)	< 0.001	0.47
Missing	84 (14.6%)	31 (15.7%)	39 (16.3%)	14 (10.1%)		
Total bilirubin, mg/dL	1.1 (0.6–3.0)	1.0 (0.5–2.8)	1.1 (0.6–3.0)	1.4 (0.7–3.6)	0.226	0.14
Missing	151 (26.3%)	52 (26.3%)	59 (24.7%)	40 (29.0%)		

Characteristic	Overall (N = 575)	P1 Low-burden (N = 198)	P2 Fluid-predominant (N = 239)	P3 High-intensity (N = 138)	P value	Max pairwise SMD
Albumin, g/dL	2.9 (2.5–3.4)	3.0 (2.6–3.6)	3.1 (2.5–3.5)	2.7 (2.4–3.3)	0.008	0.46
Missing	269 (46.8%)	91 (46.0%)	106 (44.4%)	72 (52.2%)		
AP, acute pancreatitis; BUN, blood urea nitrogen; ICU, intensive care unit; MAP, mean arterial pressure; SMD, standardized mean difference.						
P values are descriptive (Kruskal–Wallis, chi-square, or simulated Fisher exact test as appropriate). Max pairwise SMD is the largest standardized difference across the three phenotypes.						
Values are median (interquartile range) or n (%). Percentages use nonmissing values as denominators; missing counts are shown explicitly.						

Frozen resuscitation-response phenotypes

P1 included 198 patients (34.4%), P2 239 (41.6%), and P3 138 (24.0%). Median cumulative net fluid balance at 24 h was 5.1 mL/kg (IQR – 6.5 to 14.2) in P1, 47.9 (35.3–66.3) in P2, and 88.1 (51.4–126.1) in P3 (Table 2; Fig. 2). Vasopressor exposure occurred in 24.2%, 14.2%, and 98.6%, respectively. Maximum NEE was 0.000, 0.000, and 0.351 µg/kg/min, and maximum lactate was 1.4, 2.0, and 4.1 mmol/L.

Table 2
Early resuscitation-response markers, 24-hour landmark state, and outcomes by phenotype

Characteristic	Overall (N = 575)	P1 Low- burden (N = 198)	P2 Fluid- predominant (N = 239)	P3 High- intensity (N = 138)	P value	Max pairwise SMD
Body weight, kg	83.9 (70.3– 100.0)	86.8 (75.0– 106.4)	80.1 (69.0– 97.5)	83.8 (70.0– 98.8)	0.012	0.27
Cumulative fluid input, mL/kg	63.1 (39.3– 96.6)	32.7 (21.6– 44.8)	73.8 (55.3– 95.4)	108.6 (73.7– 155.7)	< 0.001	1.61
Cumulative measured output, mL/kg	22.7 (12.5– 37.9)	26.7 (15.6– 46.2)	20.7 (13.2– 33.4)	19.3 (8.3– 35.5)	< 0.001	0.41
Cumulative net fluid balance, mL/kg	36.3 (12.2– 67.2)	5.1 (-6.5– 14.2)	47.9 (35.3– 66.3)	88.1 (51.4– 126.1)	< 0.001	2.27
Any vasopressor during 0–24 h	218 (37.9%)	48 (24.2%)	34 (14.2%)	136 (98.6%)	< 0.001	1.70
Maximum NEE, µg/kg/min	0.000 (0.000– 0.155)	0.000 (0.000– 0.000)	0.000 (0.000– 0.000)	0.351 (0.250– 0.575)	< 0.001	1.33
Maximum lactate, mmol/L	1.9 (1.3– 3.3)	1.4 (1.0– 1.9)	2.0 (1.4–3.0)	4.1 (2.3– 6.5)	< 0.001	1.20
Observed lactate 6-h bins, n	2 (1–3)	1 (1–2)	2 (1–3)	4 (3–4)	< 0.001	1.74
Lactate observed in ≥ 2 bins	372 (64.7%)	89 (44.9%)	155 (64.9%)	128 (92.8%)	< 0.001	1.03
Minimum MAP during 0–6 h, mmHg	69.0 (58.0– 80.9)	70.0 (60.0– 82.0)	74.0 (64.0– 85.0)	57.0 (50.0– 66.0)	< 0.001	1.07
Missing	9 (1.6%)	2 (1.0%)	0 (0.0%)	7 (5.1%)		
Organ-support state at 24 h: No support	291 (50.6%)	111 (56.1%)	171 (71.5%)	9 (6.5%)	< 0.001	1.47
Single support	152 (26.4%)	59 (29.8%)	64 (26.8%)	29 (21.0%)		
Multiple support	132 (23.0%)	28 (14.1%)	4 (1.7%)	100 (72.5%)		
Maximum posterior probability	1.000 (0.995– 1.000)	1.000 (0.995– 1.000)	0.999 (0.989– 1.000)	1.000 (1.000– 1.000)	< 0.001	0.24

Characteristic	Overall (N = 575)	P1 Low- burden (N = 198)	P2 Fluid- predominant (N = 239)	P3 High- intensity (N = 138)	P value	Max pairwise SMD
Post-landmark ICU stay, days	2.9 (1.0– 8.8)	2.7 (0.8– 7.5)	2.2 (1.0–5.3)	7.6 (2.7– 18.0)	< 0.001	0.61
ICU death	48 (8.3%)	7 (3.5%)	11 (4.6%)	30 (21.7%)	< 0.001	0.55
In-hospital death	75 (13.0%)	13 (6.6%)	22 (9.2%)	40 (29.0%)	< 0.001	0.59
NEE, norepinephrine-equivalent dose; MAP, mean arterial pressure. Organ support comprised vasopressors, invasive mechanical ventilation, and renal replacement therapy.						
Values are median (interquartile range) or n (%). The fluid, vasopressor, and lactate variables defined the trajectory model and are descriptive rather than treatment-effect estimates.						

The P2 pattern was not an intermediate version of P3. P2 combined progressive fluid accumulation with infrequent vasopressor exposure and declining lactate. P3 combined the greatest fluid accumulation with near-universal vasopressor exposure and persistently higher lactate. At 24 h, multiple concurrent supports were present in 14.1% of P1, 1.7% of P2, and 72.5% of P3 patients. Median maximum posterior probability was at least 0.999 in each group.

Post-landmark state occupancy and transition associations

Observed state occupancy diverged after the landmark (Fig. 3). P3 patients remained more frequently in multiple-support states and accumulated alive ICU discharge more slowly. Median post-landmark ICU stay was 2.7 days in P1, 2.2 days in P2, and 7.6 days in P3. Crude ICU mortality was 3.5%, 4.6%, and 21.7%, and crude in-hospital mortality was 6.6%, 9.2%, and 29.0%, respectively. These absolute summaries were unadjusted.

In adjusted recurrent-event models, P2 was not clearly associated with escalation to higher support (HR 0.86, 95% CI 0.57–1.32; P = 0.499), de-escalation (HR 0.78, 95% CI 0.57–1.06; P = 0.112), alive ICU discharge (HR 0.91, 95% CI 0.75–1.11; P = 0.349), or ICU death (HR 1.81, 95% CI 0.73–4.51; P = 0.203) compared with P1 (Table 3; Fig. 4a).

Table 3

Adjusted grouped cause-specific hazards for post-landmark organ-support transitions

Transition group	Repeated events, P1/P2/P3	P2 vs P1, HR (95% CI)	P value (P2)	P3 vs P1, HR (95% CI)	P value (P3)
Escalation to higher support	121/111/245	0.86 (0.57–1.32)	0.499	1.80 (1.22–2.65)	0.003
De-escalation to lower support	205/153/399	0.78 (0.57–1.06)	0.112	1.01 (0.77–1.31)	0.960
Alive ICU discharge	191/228/108	0.91 (0.75–1.11)	0.349	0.68 (0.55–0.84)	< 0.001
ICU death	7/11/30	1.81 (0.73–4.51)	0.203	1.95 (0.86–4.42)	0.109

ICU-death estimates are sparse (48 ICU-death events across phenotypes) and should not be interpreted as definitive evidence of mortality association.

Adjusted for age, sex, prior Charlson score, primary AP diagnosis, emergency/urgent admission, initial MAP, baseline BUN, ICU admission delay, and the actual MIMIC-IV calendar-period group. MAP and BUN were multiply imputed ($m = 20$).

P1 Low-burden is the reference. Hazard ratios are conditional on current support state and exact transition-specific baseline hazards; repeated transitions use patient-clustered robust variance.

P3 was associated with faster escalation (HR 1.80, 95% CI 1.22–2.65; $P = 0.003$) and slower alive ICU discharge (HR 0.68, 95% CI 0.55–0.84; $P < 0.001$). The de-escalation rate did not differ clearly (HR 1.01, 95% CI 0.77–1.31; $P = 0.960$). The ICU-death estimate was imprecise (HR 1.95, 95% CI 0.86–4.42; $P = 0.109$) and did not establish an adjusted mortality association.

Sensitivity analyses

The direction of the P3 escalation and alive-discharge estimates was maintained in unadjusted, complete-case, time-varying-confounder, semi-Markov, posterior-certainty, posterior pseudo-class, and most population-restriction analyses (Supplementary Table S4; Supplementary Figure S3). In 100 posterior pseudo-class draws, the corresponding pooled estimates were HR 1.84 (95% CI 1.24–2.75) and HR 0.68 (95% CI 0.55–0.85). In the strict shock-like subgroup, the P3 escalation estimate was null and imprecise rather than directionally concordant (HR 0.97, 95% CI 0.55–1.71; $P = 0.925$). Restricted shock-like subgroups had wide CIs because of sparse events, and one ICU-death contrast was structurally non-estimable because one comparison group had zero events; no infinite HR was substituted.

A 12-h landmark analysis included 589 patients and reduced survivor selection time. P3 versus P1 was associated with in-hospital mortality (OR 6.53, 95% CI 3.42–12.44) and slower alive ICU discharge (HR 0.43, 95% CI 0.34–0.55), while P2 estimates remained near the null (Supplementary Table S5).

Agreement between 12- and 24-h assignments was moderate (ARI 0.653), indicating that the two landmarks did not define identical constructs.

Phenotype assignments were nearly unchanged when the last rather than median lactate was used within each bin (ARI 0.989), and remained stable after excluding first-24-h renal replacement therapy. Output-events-only net fluid retained high agreement (ARI 0.917), whereas input-only cumulative fluid (ARI 0.555) and especially interval rather than cumulative balance (ARI 0.343) changed the classification more substantially (Supplementary Figure S5). The interval analysis therefore represented construct sensitivity, not merely measurement noise.

Historical/temporal and multicenter structural transport

Applying the frozen model to MIMIC-III CareVue classified 51 of 181 patients as P1, 85 as P2, and 45 as P3; mean posterior probabilities were 0.955, 0.948, and 0.965 (Table 4; Supplementary Table S6). Compared with P1, P3 was associated with higher in-hospital mortality (adjusted OR 5.74, 95% CI 1.96–16.76; P = 0.001) and slower alive ICU discharge (adjusted HR 0.55, 95% CI 0.35–0.87; P = 0.011). P2 estimates were not clearly different from P1. Because MIMIC-III and MIMIC-IV derive from the same center, these findings support historical/temporal transport rather than independent external validation.

Table 4

Adjusted associations in the MIMIC-III CareVue historical/temporal transport cohort

Outcome	Measure	N (events)	P2 vs P1 (95% CI)	P value (P2)	P3 vs P1 (95% CI)	P value (P3)
In-hospital mortality	OR	181 (39)	1.34 (0.45–3.98)	0.594	5.74 (1.96–16.76)	0.001
Alive ICU discharge	HR	181 (152)	0.94 (0.64–1.38)	0.757	0.55 (0.35–0.87)	0.011
OR, odds ratio; HR, cause-specific hazard ratio.						
Models were adjusted for age, sex, and primary AP diagnosis. The three phenotype groups contained 51, 85, and 45 patients; mean posterior probabilities were 0.955, 0.948, and 0.965, respectively.						
MIMIC-III CareVue is a same-center historical/temporal validation cohort, not an independent external cohort. P1 is the reference.						

In eICU, 152 patients from 47 hospitals passed the full cohort and hospital-interface criteria: 123 were P1, 20 P2, and 9 P3 (Supplementary Table S7). Mean posterior probabilities were 0.983, 0.951, and 0.925. Profile correlations with the discovery trajectories were 0.955 for cumulative net fluid, 0.982 for vasopressor exposure probability, 0.937 for marginal NEE, and 0.911 for lactate. However, phenotype prevalence shifted markedly, P3 included only nine patients, and only 12 hospital deaths occurred (zero in P2 and two in P3). We therefore did not fit an adjusted eICU outcome model. eICU supported partial multicenter structural transport only (Fig. 4c-d; Supplementary Figure S4).

Discussion

Principal findings

In this outcome-blind landmark study, the joint early trajectories of cumulative net fluid, vasopressor exposure and intensity, and lactate response identified three analytically stable phenotypes. The clinically important distinction was not simply low versus high fluid balance. P2 accumulated substantially more fluid than P1 but had infrequent vasopressor exposure, declining lactate, very little multiple support at 24 h, and post-landmark transition rates that were not clearly different from P1. P3 combined high fluid burden with near-universal vasopressor exposure and higher lactate; it was associated with faster subsequent support escalation and slower alive ICU discharge. This pattern was stable across multiple analytic choices and retained high classification certainty across MIMIC eras and screened eICU hospitals; these findings do not establish fixed biological subtypes.

Relation to previous work

Our findings extend, rather than replace, recent trajectory and subphenotype studies in acute pancreatitis. Fluid-balance and fluid-therapy trajectories have shown that cumulative exposure patterns

are heterogeneous and associated with mortality [6, 7]. Multicenter analyses have also linked fluid-balance indices with outcomes [8]. Dynamic subphenotypes based on vital signs or hematocrit and BUN have demonstrated cross-cohort heterogeneity and potentially different clinical courses [11–13]. Separately, early vasopressor exposure and lactate clearance have been associated with prognosis [9, 10], and a large registry analysis has addressed ICU mortality or prolonged stay as a prediction target [22].

The present study differs in four linked design features: it models fluid burden, zero-inflated vasopressor exposure/intensity, and lactate response jointly; freezes the model without using outcomes; starts outcome analysis at a prespecified 24-h landmark; and decomposes the later ICU course into recurrent escalation, de-escalation, alive discharge, and ICU death. The strict literature search found no prior report combining all four features, although generic claims of being the first trajectory or subphenotype study would be incorrect.

Interpretation

P2 and P3 illustrate why fluid accumulation cannot be interpreted in isolation. One plausible interpretation is that P2 represents patients receiving substantial fluid with limited vasopressor requirement and a resolving metabolic signal, whereas P3 captures persistent circulatory dysfunction, treatment intensity, and illness severity simultaneously. This interpretation is consistent with the trajectory geometry and subsequent support course, but it is not a demonstrated biological mechanism. Fluid and vasopressor markers were treatment-linked, and unmeasured indications for therapy remain major competing explanations.

The P3 escalation and alive-discharge associations were more precise than the ICU-death association. This difference supports the use of organ-support transitions as process outcomes, but it does not diminish mortality as a patient-important endpoint. Rather, only 48 ICU deaths occurred, limiting precision. Similarly, the P3 de-escalation HR was close to one. A higher rate of escalation and lower rate of alive discharge can coexist without a lower de-escalation rate because patients enter different support states, contribute repeated transitions, and face competing absorbing outcomes.

Clinical and research implications

The frozen phenotype is best viewed as a structured 24-h review framework. It may help identify patients whose combined fluid, vasopressor, and lactate course warrants intensified reassessment or monitoring. It is not a treatment algorithm and does not identify an optimal fluid amount or vasopressor dose. Formal incremental comparisons with simple markers, SOFA, or APACHE were not performed, so predictive superiority and clinical utility remain unproven.

Prospective evaluation should apply the frozen parameters without outcome-based refitting in independent multicenter data. Such work should test bedside availability, calibration of absolute transition risks, incremental information beyond established severity measures, and whether phenotype-triggered monitoring changes care processes. The marked eICU prevalence shift also indicates that interface completeness and local practice patterns must be assessed before transport is assumed.

Strengths and limitations

Strengths include outcome-blind model freezing; explicit treatment of the zero-inflated NEE process; separation of the exposure and outcome windows; repeated-event multistate analysis; direct examination of informative lactate measurement; extensive marker, population, landmark, and model sensitivities; and transparent separation of same-center temporal transport from partial multicenter structural transport. All displayed numbers were linked to aggregate source data and deterministic numeric and rendering quality checks.

Several limitations are important. First, the 24-h landmark excludes early deaths and early ICU discharges; findings apply only to patients alive and still in the ICU at 24 h. The 12-h analysis reduced but did not eliminate landmark selection and defined a partly different phenotype construct. Second, diagnostic codes did not reproduce a clinical Atlanta-classification adjudication, and residual misclassification is possible. Third, treatment indication, clinician intent, bedside volume responsiveness, onset time, necrosis burden, and other severity information were unavailable or not harmonized. Residual and time-dependent confounding therefore precludes causal treatment interpretation.

Fourth, the imputation model deliberately excluded post-landmark outcomes; this may have reduced efficiency or congeniality, and complete-case consistency provides only partial reassurance. Lactate measurement was informative and 43.8% of patient-bin lactate records were unobserved. Omitting unmeasured bins from the likelihood and refitting denser-measurement cohorts addressed some consequences but did not prove missing-at-random assumptions. The baseline-covariate imputation model deliberately excluded post-landmark outcomes; complete-case consistency reduced, but did not remove, concern about imputation-model congeniality. Fifth, 6-h snapshots may miss brief support episodes, and fluid records remain sensitive to interface and output definitions. Sixth, the discovery sample was modest and ICU-death events were sparse. Seventh, MIMIC-III is not geographically independent, a narrow boundary-period overlap with MIMIC-IV cannot be excluded after date deidentification, and eICU could support only partial structural transport because of infusion-unit constraints, phenotype-prevalence shift, and sparse P3 and mortality events. Finally, we did not assess incremental prediction, decision-curve utility, or whether phenotype-guided action improves outcomes.

Conclusions

Joint 0–24-h fluid, vasopressor, and lactate trajectories identified a fluid-predominant phenotype with declining lactate and a distinct high-intensity multimodal phenotype in critically ill adults with acute pancreatitis. The high-intensity phenotype was associated with faster post-landmark organ-support escalation and slower alive ICU discharge, whereas the fluid-predominant phenotype was not clearly different from the low-burden phenotype. These findings support prospective evaluation of a monitoring-oriented response framework but do not establish causal treatment effects or optimal resuscitation targets.

Abbreviations

AP

acute pancreatitis

APPA

average posterior probability of assignment

ARI

adjusted Rand index

BIC

Bayesian information criterion

BUN

blood urea nitrogen

CI

confidence interval

HR

hazard ratio

ICU

intensive care unit

IQR

interquartile range

MAP

mean arterial pressure

NEE

norepinephrine-equivalent dose

OR

odds ratio

RRT

renal replacement therapy

SMD

standardized mean difference

STROBE

Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of deidentified data from MIMIC-IV, MIMIC-III, and the eICU Collaborative Research Database obtained through PhysioNet under the applicable credentialing and data-use agreements. The source databases were established under their original institutional review-board approvals and waivers of informed consent. The present analysis involved no direct participant contact or intervention and provided the investigators with no direct identifiers. Accordingly, additional approval by the Ethics Committee of the First Affiliated Hospital of Hunan Traditional Chinese Medical College (Hunan Provincial Hospital of Traditional Chinese Medicine) and additional individual informed consent were not required. No attempt was made to re-identify any individual.

Consent for publication

Not applicable. The manuscript contains no identifiable individual-level information.

Availability of data and materials

Patient-level MIMIC-IV, MIMIC-III, and eICU data cannot be redistributed by the authors and are available to credentialed users through PhysioNet under the applicable data-use agreements. Aggregate identifier-free source data underlying the manuscript tables and figures are included in the supplementary delivery set. Analysis code can be shared subject to author approval and the source-database data-use agreements.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this work.

Authors' contributions

JJL conceptualized the study, curated and analyzed the data, developed the methodology and software, prepared the visualizations, and wrote the original draft. YY contributed to the methodology and validation and critically revised the manuscript. LF contributed to validation and critically revised the manuscript. XP contributed to the study conception, supervised and administered the project, validated the interpretation, and critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for the work.

Acknowledgements

Not applicable.

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Figures

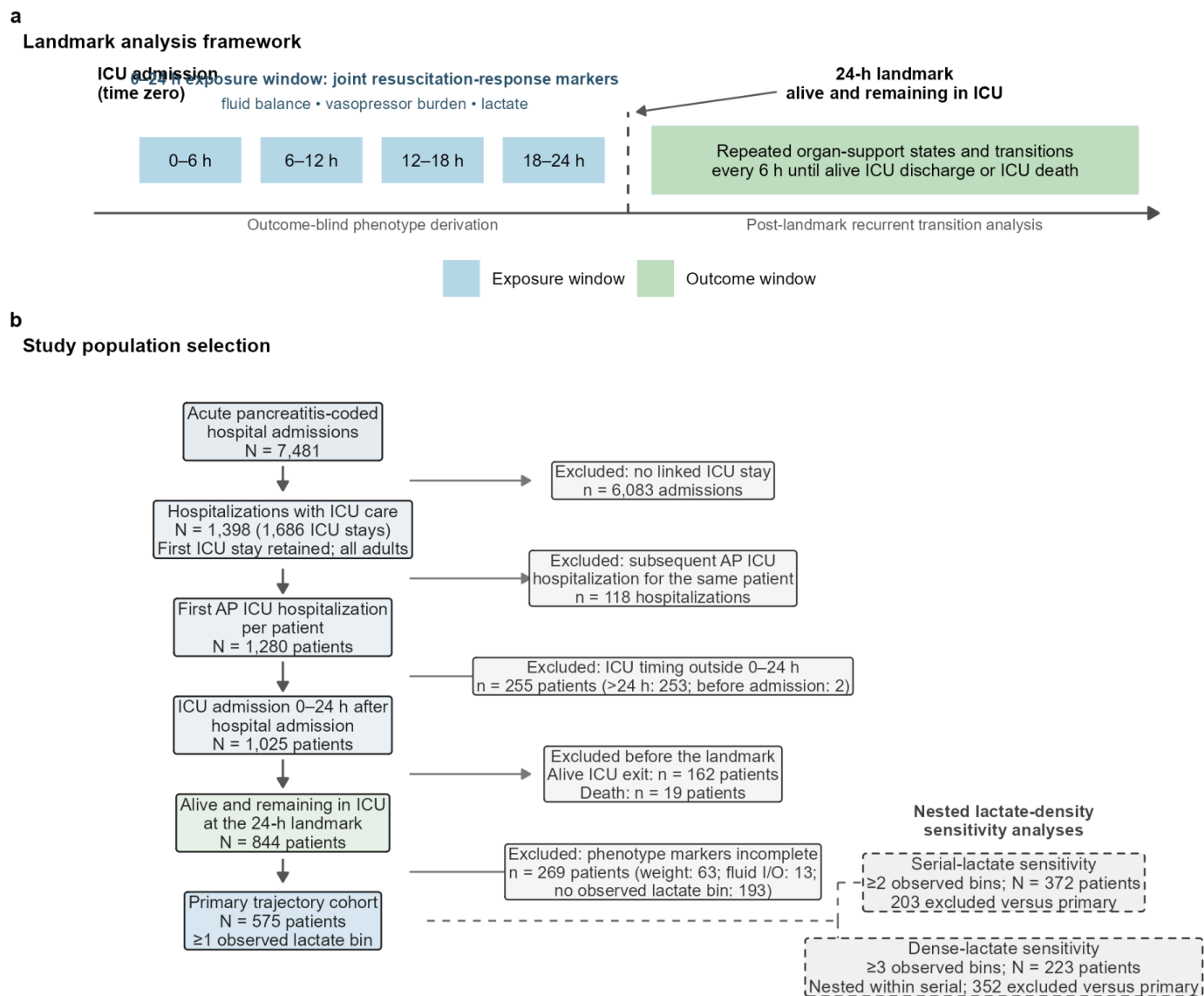


Figure 1

Landmark analysis framework and study population selection

(a) The outcome-blind exposure window began at ICU admission and comprised four consecutive 6-hour bins of cumulative net fluid balance, vasopressor exposure/intensity, and lactate response. The 24-hour landmark included only patients alive and remaining in the ICU; post-landmark organ-support states and transitions were assessed every 6 hours until alive ICU discharge or ICU death. (b) Of 7,481 acute-pancreatitis-coded hospital admissions, 1,398 had ICU care, representing 1,686 ICU stays; the first ICU stay per hospitalization was retained, and all were adults. After retaining the first acute pancreatitis ICU hospitalization per patient, applying the 0–24-hour hospital-to-ICU entry window, and excluding 162 alive ICU exits and 19 deaths before the landmark, 844 patients were landmark eligible. A further 269 patients lacked phenotype-marker evaluability because of invalid or unavailable weight ($n=63$), insufficient

quantifiable fluid input/output (n=13), or no observed lactate bin (n=193), leaving 575 in the primary trajectory cohort. The serial-lactate (at least two observed bins; N=372) and dense-lactate (at least three observed bins; N=223) cohorts were displayed as sensitivity-analysis branches from the primary cohort; the dense cohort was nested within the serial cohort. N denotes included units at each stage and n denotes stage-specific exclusions; after patient-level deduplication, N values denote patients. AP, acute pancreatitis; ICU, intensive care unit; I/O, input/output.

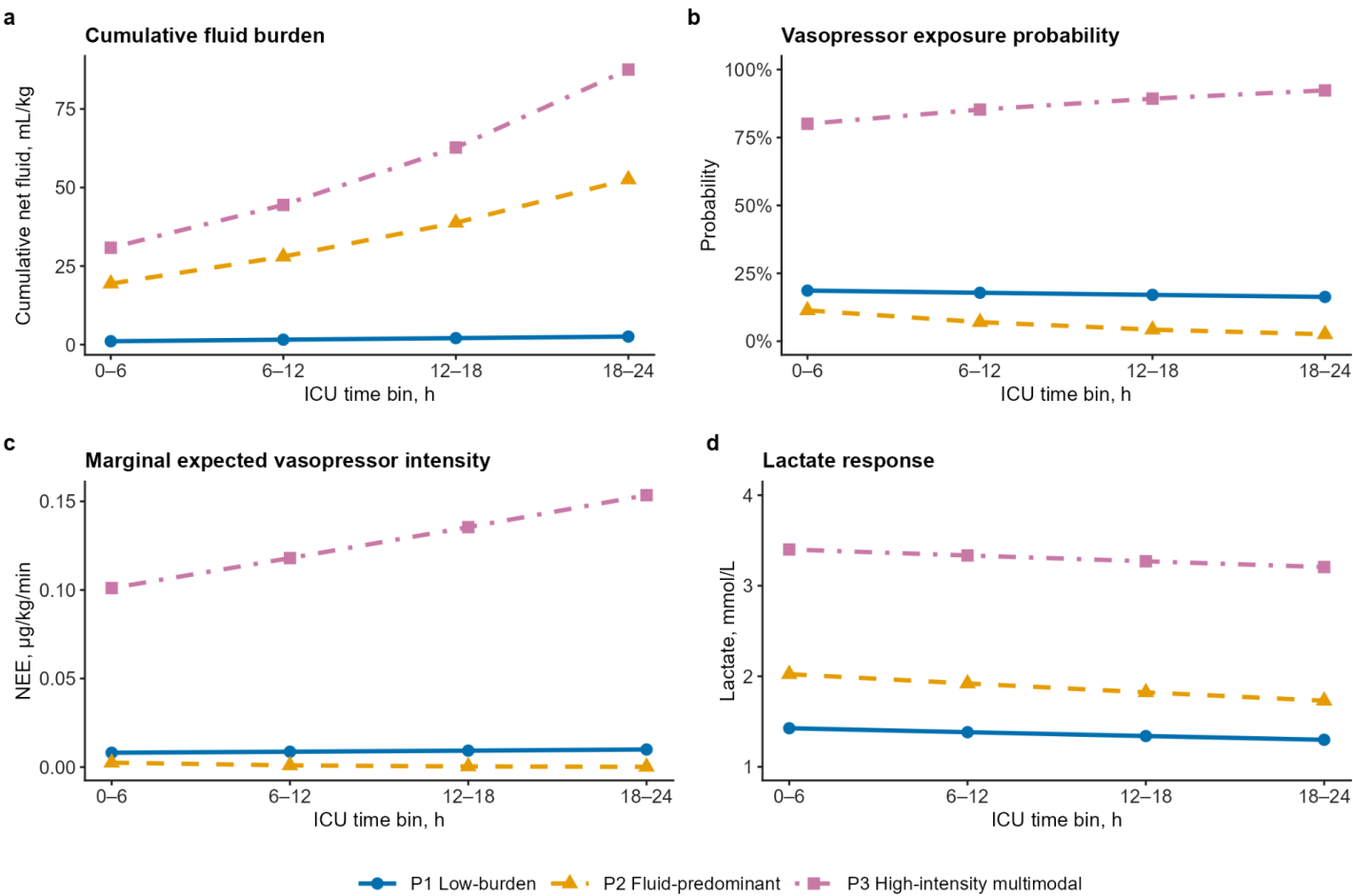


Figure 2

Frozen joint early resuscitation-response trajectories

Outcome-blind trajectories for the three frozen phenotypes across the first 24 ICU hours. Panels show cumulative net fluid balance normalized to body weight, probability of vasopressor exposure, marginal expected NEE, and lactate response. Lines connect model-predicted values at the midpoints of the four 6-hour bins.

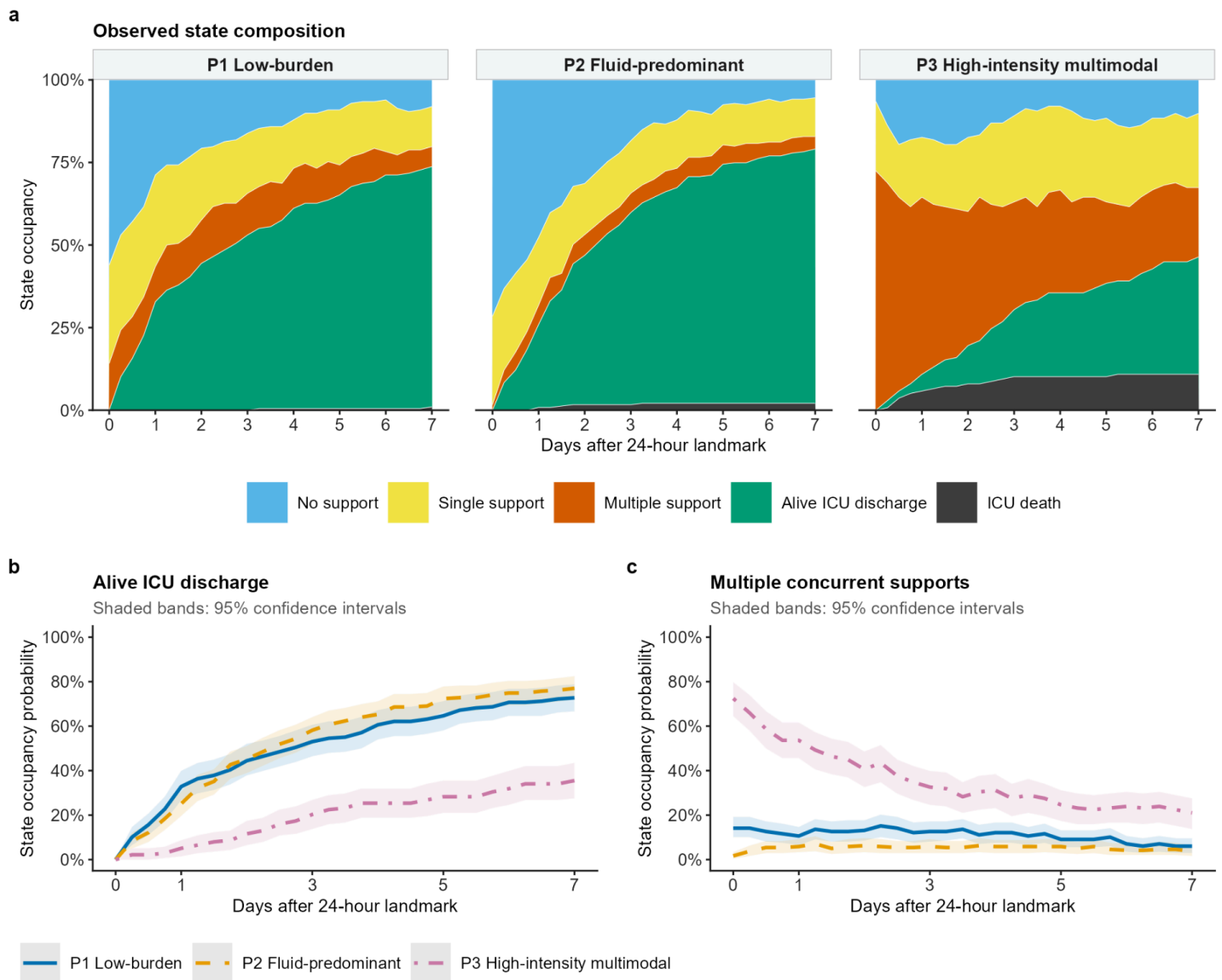


Figure 3

Post-landmark organ-support state occupancy

Observed organ-support state occupancy after the 24-hour landmark. Stacked probabilities of no support, single support, multiple concurrent supports, alive ICU discharge, and ICU death are shown separately by phenotype, with focused plots for alive ICU discharge and multiple support during the first seven days. Occupancy is descriptive and is not an adjusted treatment effect.

eICU panels assess structural transportability only; adjusted outcome validation was not attempted.

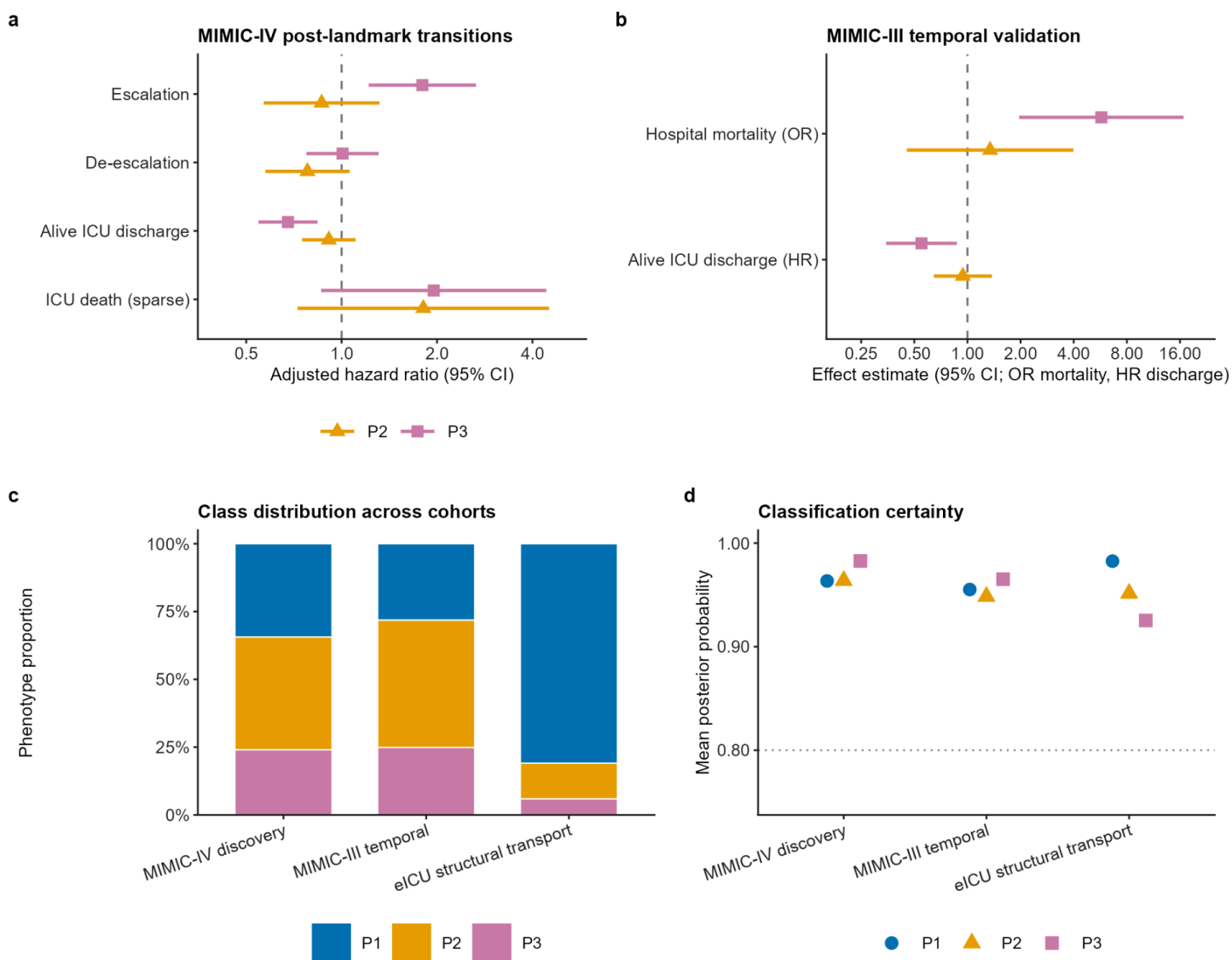


Figure 4

Adjusted associations and cross-cohort transportability

(a) Adjusted grouped cause-specific hazard ratios for post-landmark transitions in MIMIC-IV. (b) Adjusted associations with in-hospital mortality and alive ICU discharge after applying the frozen phenotypes in MIMIC-III CareVue. (c) Phenotype distribution and (d) mean posterior classification probability across MIMIC-IV, MIMIC-III, and screened eICU. MIMIC-III represents same-center historical/temporal transport; eICU represents partial multicenter structural transport only.

Supplementary Files

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- [SupplementaryMaterialTablesS1S8FiguresS1S5v1.docx](#)