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Peripheral edema trajectory over the first ICU week is independently associated with mortality: a retrospective cohort study

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Title page

Title: Peripheral edema trajectory over the first ICU week is independently associated with mortality: a retrospective cohort study

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Abstract

Peripheral edema is among the most frequently recorded physical signs in intensive care, yet is almost always analyzed as a static variable. In MIMIC-IV v3.1 we used a day-3 landmark to classify 18,098 adults with ICU stay ≥ 72 h by the first-week trajectory of any peripheral edema (hand, arm, leg, or pedal; generalized excluded) as never, resolved, persistent, or new onset. The trajectory was independently associated with 28-day mortality (adjusted odds ratios 1.26–1.64 across groups versus never) and with new-onset acute kidney injury, was only partly mediated by cumulative fluid balance, and was confined to patients without sepsis. Combining edema with capillary refill time defined congestion–perfusion phenotypes whose 28-day mortality spanned 16–42%. In an independent MIMIC-III CareVue cohort (n = 6,176), the static any-edema exposure was replicated (adjusted odds ratio 1.44, 95% CI 1.00–2.05; ratio of odds ratios versus MIMIC-IV 0.92, P heterogeneity 0.64). A routinely charted, zero-cost sign therefore carries prognostic information beyond standard variables, though its value lies in risk stratification rather than standalone prediction; standardized prospective charting is a prerequisite for clinical use.

Keywords: peripheral edema; edema trajectory; capillary refill time; prognosis; MIMIC-IV

Introduction

Peripheral edema is among the most frequently documented physical findings in critically ill patients [1]. Despite its ubiquity, it is seldom quantified in prognostic research: it is usually recorded as present or absent at a single time point, or absorbed into proxies such as cumulative fluid balance, and its temporal evolution at the bedside is largely ignored.

Positive fluid balance is reproducibly associated with mortality and organ failure [2, 3], and international consensus now frames fluid accumulation as a multidimensional syndrome requiring dynamic assessment [4]. Yet edema is not merely a passive readout of fluid loading. Capillary leak, endothelial glycocalyx degradation, hypoalbuminemia, venous congestion, and lymphatic drainage all shape where and when fluid becomes visible at the skin [5–7]. Whether a purely observational, zero-cost bedside sign—repeatedly charted by nurses—can encode this physiology is unknown.

A small but influential literature has linked the physical examination of edema with outcome. Danziger and colleagues showed that peripheral edema on the admission examination was independently associated with mortality, with a dose–response across grades [8]; companion analyses linked peripheral edema to central venous pressure and incident acute kidney injury [9] and to right ventricular dysfunction [10]. These studies established edema as a legitimate prognostic sign but left three questions open, which define the present study: (1) *site specificity*—whether a focal, easily observed peripheral site carries the signal, tested by direct comparison with arm, leg, pedal, and generalized edema; (2) *temporal dynamics*—whether the evolution of edema over the first ICU week matters more than its presence at one time point; and (3) *incremental value*—whether the sign adds measurable information beyond standard clinical variables.

Peripheral perfusion offers a complementary window. Capillary refill time (CRT) is a validated marker of tissue perfusion and mortality [11] whose normalization guided resuscitation in the ANDROMEDA-SHOCK trial [12]. Conceptually, peripheral edema indexes *congestion* (fluid leaving the vascular space) while CRT indexes *perfusion*; the two need not move together, and their combination may define clinically distinct phenotypes—congestion-dominant, hypoperfusion-dominant, mixed, or compensated [13].

We therefore conducted a retrospective cohort study in MIMIC-IV to test three hypotheses: (1) the day-3 landmark trajectory of peripheral edema (never, resolved, persistent, new onset) is independently associated with 28- and 90-day mortality; (2) the association is only partly explained by cumulative fluid balance and is modified by sepsis; and (3) combining peripheral edema with CRT into a congestion–perfusion dual-sign framework yields phenotypes with distinct prognoses. A plausibility analysis in eICU-CRD examined transportability and, critically, the recording practices that determine whether such a sign can be studied at all; the primary external-validation cohort was MIMIC-III CareVue.

Results

Cohort

Table 1. Baseline characteristics of the analysis cohort (MIMIC-IV, n = 18,098), by peripheral-edema trajectory group.

Characteristic	Overall (n = 18,098)	Never (n = 11,454)	Resolved (n = 1,437)	Persistent (n = 2,251)	New onset (n = 2,956)	Max SMD
Age, years	65.0 (16.5)	64.2 (16.6)	66.2 (16.1)	66.7 (16.3)	65.2 (15.7)	0.15
Male sex, %	57.0	57.0	55.5	57.1	57.5	0.03
Weight, kg	82.8 (24.4)	82.2 (24.2)	84.7 (26.1)	82.1 (24.4)	84.6 (25.8)	0.10
Day-1 SOFA score	7.3 (4.6)	6.8 (4.7)	8.7 (4.4)	8.6 (4.3)	8.7 (4.4)	0.42
Day-1 lactate, mmol/L, median (IQR)	2 (2–4)	2 (2–4)	2 (2–4)	2 (1–4)	2 (2–4)	0.11
Day-1 albumin, g/dL	3.0 (0.7)	3.0 (0.7)	2.9 (0.6)	2.9 (0.6)	2.9 (0.7)	0.36
Day-1 WBC, ×10⁹/L, median (IQR)	13 (9–18)	12 (9–17)	13 (9–18)	13 (10–18)	13 (10–18)	0.11
Day-1 creatinine, mg/dL, median (IQR)	1.0 (0.8–1.7)	1.0 (0.8–1.6)	1.0 (0.8–1.8)	1.0 (0.8–1.7)	1.0 (0.8–1.8)	0.16
Day-1 bilirubin, mg/dL, median (IQR)	1 (0–2)	1 (0–1)	1 (0–2)	1 (0–2)	1 (0–2)	0.06
Day-1 platelets, ×10⁹/L, median (IQR)	176 (120–238)	179 (124–241)	166 (111–233)	169 (114–236)	171 (116–237)	0.08
ICU length of stay, days, median (IQR)	6 (4–10)	5 (4–7)	6 (5–10)	8 (6–13)	9 (6–14)	0.62
Hospital length of stay, days, median (IQR)	12 (8–20)	10 (7–17)	14 (9–22)	16 (11–25)	16 (11–26)	0.45
Cumulative fluid balance, days 1–3, mL, median (IQR)	13,015 (3,374–25,680)	10,279 (2,501–21,780)	16,523 (6,401–28,906)	17,005 (7,064–29,482)	18,204 (7,025–31,950)	0.29
Congestive heart failure, %	27.8	26.5	36.5	37.6	31.3	0.24
Renal failure, %	19.2	18.2	24.4	25.1	21.5	0.17
Liver disease, %	15.2	13.6	20.3	20.6	20.0	0.19
Diabetes, %	29.1	27.8	32.1	29.2	32.0	0.09
Chronic pulmonary disease, %	25.2	23.8	28.0	29.1	26.8	0.12
Malignancy, %	14.1	14.4	13.8	14.8	13.0	0.04
Sepsis (ICD), %	22.5	18.2	29.2	34.6	32.7	0.38
Mechanical ventilation day 1, %	50.5	46.7	60.5	59.1	61.2	0.29
Renal replacement therapy day 1, %	4.0	3.6	4.3	5.2	5.2	0.08
Diuretic use day 1, %	28.7	28.5	31.2	31.4	26.9	0.06
Peripheral	39.0	20.6	100.0	100.0	34.4	2.78

edema within first 72 h, %						

Note: the resolved and persistent groups have peripheral edema within 72 h by definition (100%); the SMD for this row (2.78) is definitional and is not interpreted. The 34.4% in the new-onset group reflects stays with an early positive record that was negative at the day-3 landmark. The overall 39.0% corresponds to n = 7,067 exposed stays (rounding). Trajectory classification uses only the day-3 charted record and the day 5–7 window; days 1–2 and day 4 do not enter the grouping. The 20.6% in the never group therefore reflects edema recorded on days 1–2 that was absent at the day-3 landmark and throughout days 5–7; "never" denotes no edema at the landmark windows, not the absence of any edema documentation.

Of 94,458 ICU stays in MIMIC-IV, 20,696 had an ICU stay of at least 72 h (Figure S1). Peripheral edema was documented within 72 h in 7,067 of 18,098 analysis-cohort stays (39.0%; 9,064 of 20,587 landmark-eligible stays, 44.0%, including those later excluded for unclassifiable trajectory). The landmark population comprised 20,587 stays: 11,454 (55.6%) never, 1,437 (7.0%) resolved, 2,251 (10.9%) persistent, and 2,956 (14.4%) new onset; a further 2,489 (12.1%) were unclassifiable under the strict definition and excluded. The analysis cohort included 18,098 stays, with 3,325 deaths (18.4%) by day 28. Excluded stays had 28-day mortality of 18.8%, indicating exclusion did not preferentially remove low-risk patients.

Patients with any edema trajectory were sicker: day-1 SOFA 6.8 (never) versus 8.6–8.7 (exposed; maximum SMD 0.42), mechanical ventilation 46.7% versus 60.5%, sepsis 18.2% versus 34.6% (Table 1).

Landmark trajectory and mortality

Table 2. Association between peripheral-edema trajectory (day-3 landmark) and 28-/90-day mortality, and incremental prognostic value (MIMIC-IV).

Group	n	Crude 28-day mortality, %	Crude 90-day mortality, %	Adjusted OR (28-day)	Adjusted HR (28-day)	Adjusted HR (90-day)	Fine–Gray subHR (28-day)
Never	11,454	14.9	20.3	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Resolved	1,437	21.9	28.3	1.26 (1.09–1.46), P = 0.002	1.19 (1.06–1.35), P = 0.005	1.17 (1.05–1.30), P = 0.004	1.53 (1.35–1.72)
Persistent	2,251	27.5	36.3	1.64 (1.46–1.84), P = 4×10^{-17}	1.39 (1.27–1.53), P = 4×10^{-12}	1.42 (1.31–1.54), P = 3×10^{-17}	1.94 (1.78–2.13)
New onset	2,956	23.2	31.2	1.40 (1.25–1.56), P = 1×10^{-9}	1.27 (1.16–1.39), P = 3×10^{-7}	1.31 (1.21–1.42), P = 1×10^{-11}	1.60 (1.47–1.75)

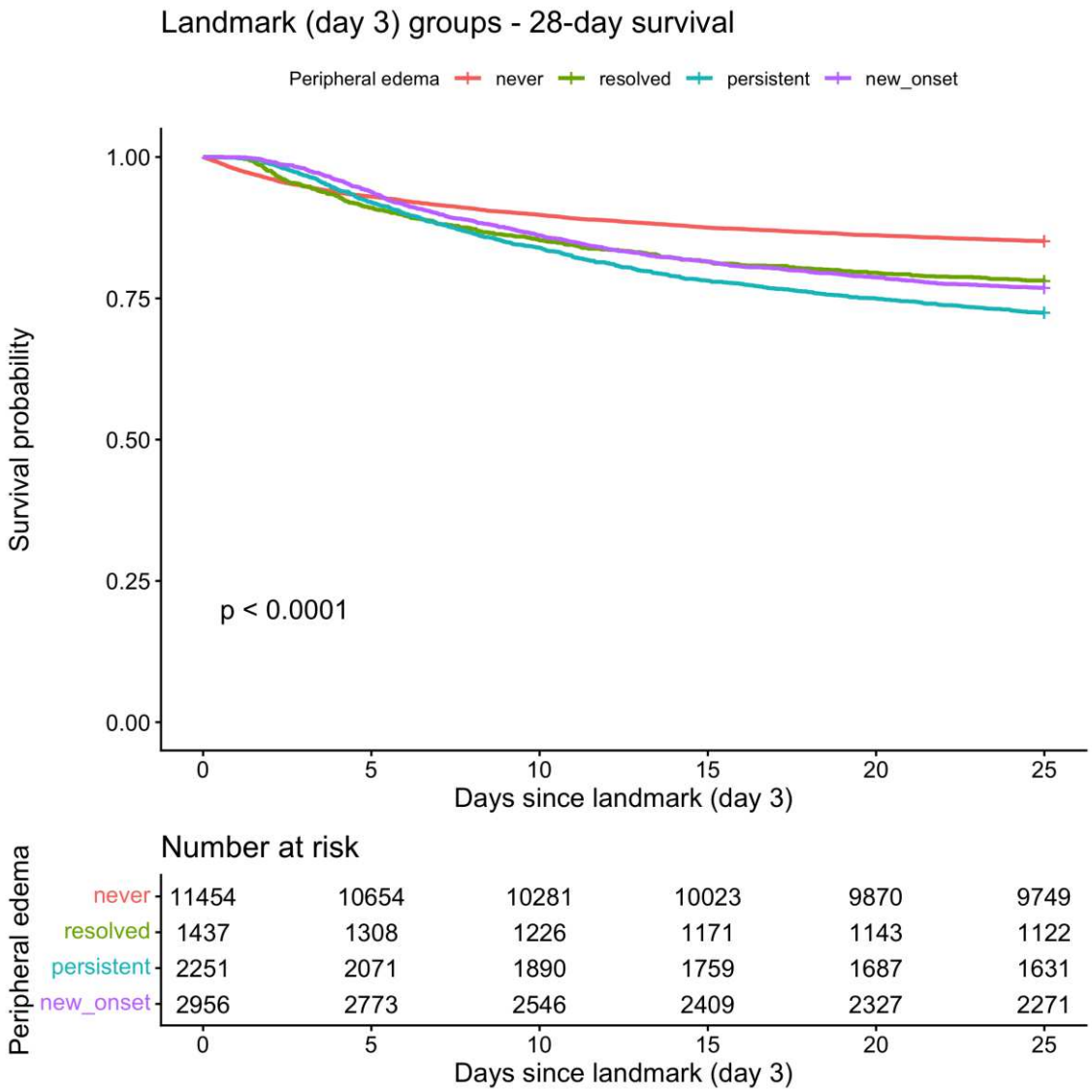

Figure 1. Landmark survival by peripheral-edema trajectory group (MIMIC-IV).

Crude 28-day mortality was 14.9% (never), 21.9% (resolved), 27.5% (persistent), and 23.2% (new onset); corresponding 90-day mortality was 20.3%, 28.3%, 36.3%, and 31.2% (Table 2; Figure 1). After adjustment, all three exposed trajectories remained associated with 28-day mortality: resolved OR 1.26 (95% CI 1.09–1.46, P = 0.002); persistent 1.64 (1.46–1.84, $P = 4 \times 10^{-17}$); new onset 1.40 (1.25–1.56, $P = 1 \times 10^{-9}$). Cox models were consistent (28-day HRs 1.19, 1.39, 1.27; 90-day 1.17, 1.42, 1.31). The adjusted 28-day logistic AUC was 0.749; the Cox concordance 0.722.

Incremental value and static versus trajectory exposure

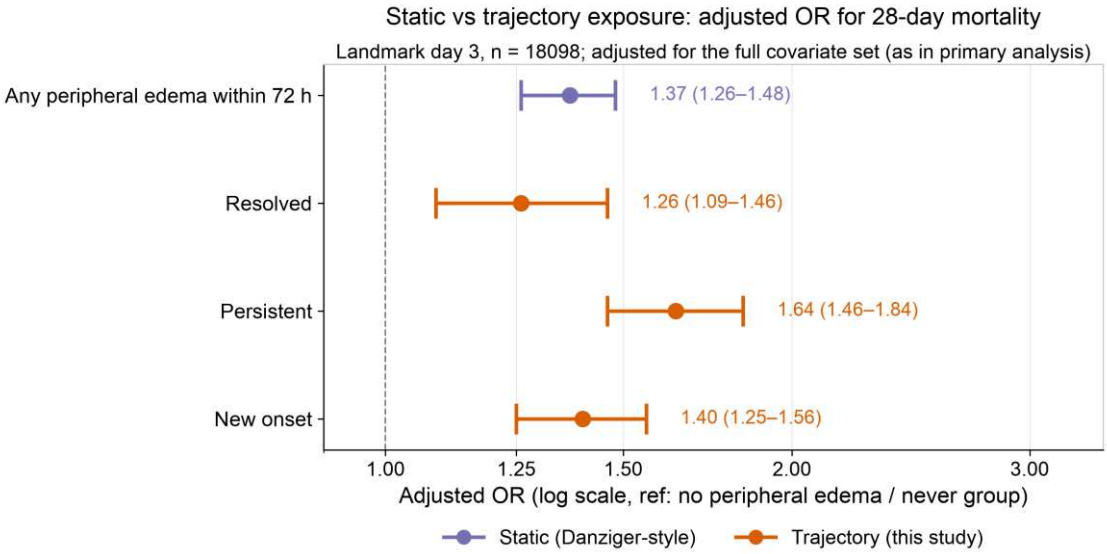

Figure 2. Adjusted associations: trajectory groups versus a Danziger-style static exposure.

Adding trajectory group to the baseline model increased AUC from 0.7426 to 0.7485 (DeLong P = 1.7×10^{-7}; Table 2). The category-free NRI was 0.281 ± 0.018 (P = 1.6×10^{-48}) and IDI 0.0045 ± 0.0011 (P = 5.4×10^{-5}). Models containing only edema variables discriminated poorly (AUC 0.573 for group), confirming the sign is an adjunct, not a standalone predictor.

The static exposure (any peripheral edema within 72 h) was present in 7,067 of 18,098 analysis-cohort stays (39.0%; crude 28-day mortality 23.7% versus 14.9%). It was independently associated (adjusted OR 1.37, 1.26–1.48, P = 1.5×10^{-13}; HR 1.27, 1.19–1.37, P = 1.4×10^{-11}), univariate AUC 0.570. Head-to-head, the static exposure raised baseline AUC only to 0.7459 (DeLong P = 2.6×10^{-4}), versus 0.7485 for trajectory; the trajectory model was significantly better (paired DeLong P = 0.011) and added information beyond static (LRT P = 5.1×10^{-10}), whereas the reverse was marginal (P = 1.7×10^{-4}; Figure 2). A static dose–response replication reproduced Danziger's qualitative pattern (adjusted ORs 1.24, 1.48, 2.01 for scores 1, 2, 4; trend OR per grade 1.21, P = 2.1×10^{-17}) but still discriminated worse than the trajectory model.

Effect modification, mediation, and dual-sign phenotypes

The edema–mortality association differed sharply by sepsis (interaction P = 3.9×10^{-7}). In sepsis (n = 4,255), adjusted HRs were near unity and non-significant (resolved 1.05, persistent 1.12, new onset 1.00). Without sepsis (n = 13,843), associations were stronger (resolved 1.26, persistent 1.64, new onset 1.50). Fine–Gray models gave slightly larger subdistribution HRs (resolved 1.53, persistent 1.94, new onset 1.60), indicating the association is not explained by differential discharge. Causal mediation through post-landmark fluid balance gave a proportion mediated of 16.4% (95% CI 11.7–24.1%; Baron–Kenny 17.7%, 12.8–24.6%); roughly five-sixths of the signal was not captured by fluid balance.

In the 2 × 2 congestion–perfusion cross-classification (n = 14,777 with both signs documented), 28-day mortality was 38.5% in the congestion-positive/perfusion-abnormal phenotype (n = 208), 24.6% congestion-positive/perfusion-normal (n = 2,766), 33.4% congestion-negative/perfusion-abnormal (n = 545), and 14.9% double-negative (n = 11,258). Adjusted HRs versus double-negative were 1.83, 1.34, and 1.60; 90-day estimates were concordant. Adding both signs gave the highest AUC (0.7542); the dual model outperformed CRT-alone (DeLong P = 9.3×10^{-8}) and edema-alone (LRT P = 5.1×10^{-7}), though the difference versus edema alone was not significant (DeLong P = 0.058).

Acute kidney injury

Table 3. Peripheral-edema trajectory and new-onset acute kidney injury (AKI) during days 4–10 (MIMIC-IV, n = 15,751).

Group	n	New-onset AKI, n (%)	Stage 1	Stage 2	Stage 3
Never	10,137	1,557 (15.4%)	1,097	251	209
Resolved	1,223	332 (27.1%)	215	62	55
Persistent	1,893	571 (30.2%)	381	100	90
New onset	2,498	826 (33.1%)	545	128	153

After excluding prevalent stage-3 AKI or early renal replacement therapy, 15,751 stays were analyzed; 3,286 (20.9%) developed new-onset AKI during days 4–10, rising across groups: 15.4% (never), 27.1% (resolved), 30.2% (persistent), 33.1% (new onset) (Table 3). All exposed trajectories were associated: resolved OR 1.59 (1.37–1.84), persistent 1.81 (1.61–2.04), new onset 2.19 (1.97–2.43). The static exposure was also associated (OR 1.29, 1.19–1.41), but the trajectory model outperformed it (AUC 0.7341 vs 0.7216; DeLong P = 6×10^{-11}). Renal recovery showed no trajectory gradient.

Site comparability and laterality

Persistent edema at every peripheral site carried nearly identical prognostic weight—adjusted HR 1.38 (hand), 1.34 (arm), 1.40 (leg), 1.35 (pedal), with overlapping CIs; new-onset showed the same pattern (HR 1.12–1.32). Generalized edema was distinct and stronger (new-onset HR 2.05). The static "any-edema-present" flag gave marginally protective point estimates (HR 0.66–0.85) and identical discrimination (C-index ≈ 0.693), confirming it is the weakest encoding; its ΔAUC (0.0033) was smaller than the trajectory classification's (0.0059). Hand edema was predominantly bilateral (83.1%); laterality carried no independent prognosis, arguing against a local mechanism and supporting a systemic, site-agnostic sign.

External validation in MIMIC-III CareVue

CareVue documentation was far sparser than MIMIC-IV: 163 of 6,176 landmark stays (2.6%) had peripheral edema within 72 h versus 44.0% of landmark-eligible MIMIC-IV stays (9,064 of 20,587; 39.0% of the analysis cohort, n = 18,098). Crude 28-day mortality was 33.7% (exposed) versus 21.9% (unexposed). After full-covariate adjustment, the static-exposure OR was 1.44 (95% CI 1.00–2.05; Firth 1.44, 1.01–2.06); with a reduced covariate set it was 1.52 (1.07–2.14). The corresponding MIMIC-IV estimate was 1.32 (1.22–1.42). The ratio of odds ratios was 0.92

(95% CI 0.63–1.32; P heterogeneity = 0.64). For 90-day mortality the CareVue OR was 1.99 (1.43–2.77, P = 4.1×10^{-5}). Transporting the MIMIC-IV model unchanged preserved discrimination (AUC 0.718 vs 0.747) with calibration slope 0.98 but intercept 0.44, indicating required recalibration of baseline risk rather than the exposure effect. The trajectory decomposition could not be validated: only 221 of 6,176 stays (3.6%) had both a day-3 and a days 5–7 record, and that subset was strongly selected (28-day mortality 35.7%). We therefore regard the trajectory decomposition as validated within MIMIC-IV only.

Temporal and subgroup robustness of external validation

Three pre-specified auxiliary analyses examined whether the static-exposure signal was stable across cohort halves and clinically meaningful subgroups. First, because MIMIC-IV dates are de-identified through anchor_year shifting (each patient offset independently to a future year spanning a full century), calendar-year era cannot be used; we therefore divided each cohort at the median admission time into earlier and later halves. In MIMIC-IV the adjusted OR for any peripheral edema was 1.38 (95% CI 1.24–1.53) in the earlier half (n = 10,293) and 1.29 (1.16–1.43) in the later half (n = 10,294). In CareVue the corresponding estimates were 1.34 (0.81–2.15) and 1.74 (1.06–2.83); the cross-half ratio of odds ratios was 1.07 (95% CI 1.04–1.10) in MIMIC-IV and 0.77 (95% CI 0.73–0.81) in CareVue. In both databases all four subgroup odds ratios remained positive (range 1.29–1.74) and their confidence intervals overlapped, indicating that the association was directionally robust across cohort halves. The small cross-half fluctuations are consistent with sampling variation—in MIMIC-IV the ratio, although statistically distinguishable from 1.0 by a z-test, corresponds to only a 7% difference in the odds ratio—rather than a systematic recording-era effect. Second, the sepsis × edema interaction in CareVue pointed in the same direction as in MIMIC-IV (subgroup OR 1.12 in sepsis versus 1.72 in non-sepsis; interaction P = 0.26), although underpowered; the same held for the age × edema pattern (≥65 years: 1.55; <65 years: 1.32). Together, these auxiliary analyses corroborate the static-exposure signal across cohort halves and clinically relevant strata, while confirming that external validation of the trajectory decomposition is intrinsically limited by how densely edema was documented.

Exploratory target-trial emulation

Among day-3 edema-positive, diuretic-naïve stays surviving to the day-5 landmark (n = 1,737; 751 started diuretics), crude 28-day mortality was 25.8% in both groups. After stabilized IPTW, diuretic initiation showed no mortality benefit (weighted HR 0.82, 95% CI 0.67–1.00, P = 0.052; E-value 1.73). A secondary resolution endpoint was not reliably estimable because of sparse post-day-3 documentation. Confounding by indication is the central threat; this analysis is strictly hypothesis-generating.

Discussion

Principal findings. In a large cohort of critically ill adults, the early trajectory of peripheral edema—a sign already charted during routine nursing care—carried independent prognostic information. Resolved, persistent, and new-onset trajectories were each associated with higher

28- and 90-day mortality after adjustment, with the largest estimates for persistent edema. The sign was an adjunct rather than a standalone predictor: the absolute gain in discrimination over a clinical baseline was small (ΔAUC 0.0059), although reclassification and decision-curve metrics indicated incremental value. The trajectory decomposition significantly outperformed a Danziger-style static exposure (DeLong P = 0.011), and the association was essentially absent in sepsis, mediated only partly by fluid balance, and concentrated in patients without sepsis and at low fluid overload.

Interpretation and relation to previous work. Our findings extend Danziger and colleagues' demonstration that edema on examination is a legitimate prognostic sign [8–10]. Using their static definition we replicated the core finding (adjusted OR 1.37), yet the trajectory decomposition was markedly stronger, and a static exposure pools patients whose edema will resolve with those in whom it persists or emerges—diluting precisely the trajectories that carry the sepsis-dependent signal, which may explain why Danziger et al. found no sepsis modification. The five-site comparison confirmed the signal is site-agnostic (persistent HR 1.34–1.40); "hand" is a convenient exemplar, not a privileged site, and standardized charting at any peripheral site—not site selection—determines utility. More broadly, the fluid-accumulation syndrome framing implies that the *trajectory*, not a single snapshot, encodes the relevant physiology, as group-based trajectory modelling of cumulative fluid balance has likewise shown [14]; this also reconciles acute heart failure trial data in which peripheral edema alone, without jugular venous distension, did not independently predict mortality [15].

The AKI analysis extends this to the organ most directly coupled to fluid handling: the trajectory formulation was stronger than the static exposure, and edema that persists or newly emerges may identify ongoing capillary leak and venous congestion raising renal interstitial pressure. That a focal bedside sign adds information beyond fluid balance is mechanistically plausible—most of the signal travels through channels other than net accumulation (capillary leak, glycocalyx degradation [5, 6], hypoalbuminemia, venous congestion)—consistent with fluid-overload phenotypes in which outcome is driven by pattern and context rather than net balance [16]. The sepsis interaction is our most interesting hypothesis-generating finding: in sepsis, pervasive capillary leak [6, 17, 18] makes a focal sign lose specificity, whereas outside sepsis it may flag active congestion or cardiac/renal fluid-handling failure [6]; attenuation at high FO% similarly suggests the sign is most informative when gross fluid loading does not dominate. The dual-sign framework operationalizes the congestion–perfusion distinction [11, 13, 19, 20]; the congestion-positive/perfusion-abnormal phenotype had the highest mortality and remained independent after adjustment, albeit on small numbers (n = 208), so these analyses are proof of concept given sparse CRT charting.

Clinical implications. Peripheral-edema charting is free, repeatable, and embedded in nursing workflow. Our results support three pragmatic uses: (1) as a risk flag—persistent or new-onset edema identifies patients without sepsis or massive overload whose trajectories merit review of fluid strategy and cardiac function; (2) as a component of structured bedside examination, pairing congestion with perfusion yields distinct phenotypes at no added cost [11, 21]; and (3) as a candidate dynamic covariate for de-resuscitation trials [4, 22, 23, 24, 25, 26].

Strengths and limitations. Strengths include a large, well-characterized cohort; a landmark design avoiding immortal-time bias; distinction between charted absence and missingness; and convergent evidence from multiple frameworks (competing-risk, mediation, dual-sign, external validation). Several limitations warrant emphasis. First, the exposure is a nursing-documented sign, not a standardized measurement; inter-rater reliability was not assessed, location chartings without paired depth were assigned depth 1, and results depend on documentation assumptions (strict vs missing-as-none). Because "never" required only absence of a peripheral-site label, patients with generalized edema were included in the reference group, which may have attenuated the contrast. Second, out-of-hospital deaths are incompletely captured in MIMIC-IV, so 90-day mortality is likely underestimated, though competing-risk models suggest this bias is conservative. Third, the persistent-trajectory and dual-positive groups were small, and the trajectory decomposition could not be validated externally because both comparison databases document edema too sparsely for classification. Standardized prospective charting—with inter-rater reliability, which no retrospective database can provide—is the prerequisite for clinical use and further validation.

Conclusions

The trajectory of peripheral edema—a zero-cost sign already recorded at the ICU bedside—is independently associated with 28- and 90-day mortality in critically ill adults. The signal is site-agnostic across peripheral sites (persistent-edema HR 1.34–1.40) and distinct from a stronger generalized-edema phenotype, although the absolute improvement in discrimination from a static flag is modest (ΔAUC 0.0059) and the association is confined to patients without sepsis and largely independent of cumulative fluid balance. Its practical value is in risk stratification and reclassification rather than standalone prediction, refined by concurrent perfusion assessment within a congestion–perfusion dual-sign framework. The static exposure was externally validated in an independent charting system; the trajectory decomposition remains validated within MIMIC-IV only, underscoring that standardized documentation of physical signs is a prerequisite for their study and use.

Methods

Study design and data sources

This retrospective cohort study used MIMIC-IV v3.1 (Beth Israel Deaconess Medical Center, Boston, MA, USA; ICU admissions 2008–2022) [27] as the derivation cohort and eICU-CRD v2.0 (208 hospitals across the USA, 2014–2015) [28] as a transportability cohort. Reporting follows the STROBE statement [29] and the RECORD extension for routinely collected health data [30]. Both databases are fully de-identified; the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved their creation and waived individual informed consent. The authors completed required human-subjects training and signed the PhysioNet data use agreement. No additional ethics approval was required. All analysis code and the aggregate result tables are openly available in the Zenodo

repository (see the Data availability statement at the end of the manuscript). During manuscript preparation, a large language model (Kimi, Moonshot AI) assisted with analysis-code development and drafting; all outputs were reviewed and verified by the authors.

Study population and exposure

We included the first ICU stay of adults (age ≥ 18 years) with an ICU length of stay of at least 72 h, because the exposure definition requires observation across the early trajectory window (landmark design). Peripheral edema was extracted from nursing flowsheet items recording edema location (itemid 224031) and amount/depth (itemid 224862, mapped to 0–4). The primary exposure was *any peripheral edema*—edema at a focal peripheral site (hand, arm, leg, or pedal)—with generalized edema explicitly excluded (analyzed separately). Location and amount were paired within the same event; unpaired locations were supplemented with the nearest amount within ± 4 h, otherwise assigned depth 1. A daily score (0–4) was the maximum paired amount per ICU day. Days with explicit "None" were distinguished from undocumented days; the primary analysis treats undocumented days as missing (strict), and a sensitivity treats them as no edema (missing-as-none).

Using a day-3 landmark, stays were classified from the *day-3 charted record* together with the *post-landmark window (days 5–7)*: *resolved* (positive on day 3, all charted days 5–7 negative), *persistent* (positive on day 3 and on at least one of days 5–7), *new onset* (negative on day 3, positive on at least one of days 5–7), and *never* (negative on day 3 and no positive record on days 5–7). Classification required a charted assessment on day 3 and at least one record in days 5–7; stays not meeting both were unclassifiable and excluded from group comparisons. Two consequences warrant emphasis. First, days 1–2 and day 4 do not enter classification, so labels describe the *landmark and post-landmark windows only*: 20.6% of "never" and 34.4% of "new onset" had a positive record somewhere in days 1–3. "Never" therefore means *no edema at the landmark windows*, not *no edema ever documented*. Second, because the static "any edema within 72 h" exposure includes days 1–2, the two definitions are not nested. The hand sub-site was used as an exemplar for the dual-sign and laterality analyses because it is the most granular, reliably charted focal site; the five-site comparison shows this choice does not affect the conclusion.

Outcomes and covariates

The primary outcome was 28-day all-cause mortality from the landmark; the secondary outcome was 90-day mortality. New-onset acute kidney injury (AKI) after the landmark was defined by KDIGO creatinine criteria [31] (increase to ≥ 1.5 × baseline, or ≥ 0.3 mg/dL within 48 h, during days 4–10; staging as specified). Baseline creatinine was the lowest value from 7 days before admission to ICU admission (available for 7,079 stays); the day-1 value was used when missing. Stays with prevalent stage-3 AKI before the landmark or renal replacement therapy within 48 h were excluded.

Covariates (identical across models): age, sex, weight, day-1 SOFA, comorbidities (heart failure, renal failure, liver disease, diabetes, COPD, malignancy, sepsis from ICD codes [32, 33]), cumulative fluid balance days 1–3, and days 1–3 exposures to diuretics, mechanical ventilation,

renal replacement therapy, maximum norepinephrine, maximum lactate, and minimum albumin. Missing norepinephrine was set to zero; missing weight, lactate, and albumin were median-imputed, giving complete covariate data for all eligible stays. The analysis cohort (n = 18,098) thus excluded only stays whose landmark trajectory could not be classified (n = 2,489); this reflects missing *exposure* documentation, not missing covariates. Fluid overload percentage (FO%) was cumulative fluid balance (L) over days 1–3 divided by admission weight (kg) × 100, stratified as < 5%, 5–10%, ≥ 10% [2, 4]. CRT was extracted from charted items (itemids 223951, 224308); values > 3 s or charted as abnormal were classified as abnormal.

Statistical analysis

Associations between trajectory group and mortality were estimated with multivariable logistic regression (28-day, odds ratios) and Cox models (28- and 90-day, hazard ratios), follow-up starting at the landmark. Discrimination is reported as AUC (logistic) and concordance (Cox). Incremental value beyond the baseline model was quantified with ΔAUC (DeLong test [34]), category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [35], likelihood-ratio tests, and decision curve analysis [36]. Competing risk of discharge alive was addressed with Fine–Gray subdistribution models [37]. Mediation through post-landmark cumulative fluid balance (days 4–7) was estimated with causal mediation analysis (1,000 bootstrap simulations) [38] and cross-checked with a Baron–Kenny decomposition. Effect modification by sepsis and FO% was pre-specified. For the dual-sign framework, stays were cross-classified by peripheral edema (congestion) and abnormal CRT (perfusion) in the early window and by their joint day-3-to-day-7 trajectories; adjusted Cox and model-comparison analyses were performed.

The eICU-CRD analysis replicated the cohort and landmark logic; structured peripheral-edema charting was so rare that only descriptive comparisons were possible. We therefore added MIMIC-III v1.4 (2001–2012) [39] restricted to the CareVue charting subsystem (28,391 stays) as a second, genuinely independent validation cohort (different vendor, own structured edema items, earlier period). Exposure was reconstructed from CareVue items *Edema #1/#2 [Location]* (163/164) and *[Amount]* (8383/8384), mapped to the identical 0–4 scale; the day-3 landmark and covariates were reproduced verbatim. The prespecified external-validation target was the static exposure (any peripheral edema within 72 h), because it does not require trajectory classification; transportability was assessed via the ratio of odds ratios, discrimination of the MIMIC-IV model applied unchanged to CareVue, and calibration of that transported model. Firth penalized likelihood was used given the small exposed group. Multiple imputation (MICE) [40] and gradient-boosted trees (XGBoost) [41] were used in supplementary sensitivity and machine-learning analyses. Analyses used PostgreSQL 18 and R 4.5.2. Two-sided $P < 0.05$ was significant; no multiplicity adjustment was applied.

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Author contributions

Authors' contributions: Yilong Hao: conceptualization, data curation, formal analysis, writing–original draft. Qin Long: investigation, data curation. Zhang Qian: investigation, data curation. Song Chen: methodology. Li Peiwu: validation. Wan Jian: resources, funding acquisition. Ye Hui: supervision, project administration, writing–review & editing. All authors read and approved the final manuscript.

Data availability

Raw MIMIC-IV v3.1, MIMIC-III CareVue v1.4 and eICU-CRD v2.0 data are available from PhysioNet to users who complete the required human-subjects training and sign the data use agreement; no participant-level data are redistributed by the authors. The analysis code and the aggregate result tables generated in this study (Zenodo release 1.2.1) are openly available in the Zenodo repository at https://doi.org/10.5281/zenodo.22674523

Additional Information

Ethics approval and consent to participate: MIMIC-IV and eICU-CRD are de-identified public databases; their creation was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, with waiver of individual informed consent. This study used de-identified public data and therefore did not require review by the authors' institutional ethics committee.

Consent for publication: Not applicable.

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Abbreviations

ACME: average causal mediation effect; ADE: average direct effect; AUC: area under the receiver operating characteristic curve; BIC: Bayesian information criterion; CI: confidence interval; CRT: capillary refill time; DCA: decision curve analysis; FO%: fluid overload percentage; HR: hazard ratio; ICD: International Classification of Diseases; ICU: intensive care unit; IDI: integrated discrimination improvement; IPTW: inverse probability of treatment weighting; LRT: likelihood-ratio test; MICE: multiple imputation by chained equations; MIMIC-IV: Medical Information Mart for Intensive Care IV; NRI: net reclassification improvement; OR: odds ratio; RECORD: REporting of studies Conducted using Observational Routinely-collected health Data; RRT: renal replacement therapy; SD: standard deviation; SHAP: SHapley Additive exPlanations; SMD: standardized mean difference; SOFA: Sequential Organ Failure Assessment; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

Supplementary Material

The following analyses are provided as Supplementary Information submitted with this manuscript and are not counted toward the main manuscript limits.

Supplementary Methods. MICE multiple imputation (m = 20) [40] of albumin, lactate, and weight; parametric g-formula for standardized risks; prognostic enrichment across five partitioning variables; XGBoost [41] and two-stage joint model; latent within-patient trajectory classes (lcmm); time-dependent Cox over the full eligible cohort; biochemical correlates of capillary leak (albumin, van der Heijden capillary leak index).

Supplementary Results. (i) Time-dependent Cox: HR 1.22 per point of daily edema score ($P = 2.2 \times 10^{-31}$); four-class latent trajectory (BIC 62,835); persistent class not significant after adjustment (HR 1.46, 0.93–2.30), underpowered. (ii) Incremental value: continuous daily score AUC 0.7451 ($P = 2.6 \times 10^{-4}$); DCA positive net benefit at 5–37.5% thresholds. (iii) FO% strata: persistent-edema HR strongest at FO% < 5% (1.77) and 5–10% (1.57), attenuated at ≥ 10% (1.24; interaction LRT $P = 7.9 \times 10^{-5}$). (iv) Sensitivities: missing-as-none attenuated but preserved associations (persistent HR 1.37); upper-extremity definition similar (1.39); diuretic-driven vs spontaneous resolution did not differ; charting-intensity stratification argued against informative-presence bias (lowest-stratum persistent HR 1.51). (v) Biochemical: albumin lower in exposed groups (Kruskal–Wallis $P < 1 \times 10^{-16}$); capillary leak index higher in persistent/new-onset in the sparse subset (n = 699). (vi) MICE: estimates virtually identical to median imputation (Δ ≤ 0.3%). (vii) G-computation: standardized risks 15.1% (never), 18.2% (resolved), 21.8% (persistent), 19.7% (new onset); RDs +3.1, +6.7, +4.6 pp. (viii) Enrichment: strongest in FO% < 5% (HR 1.77), no sepsis (1.64), SOFA above median (1.76); weakest in sepsis (1.12) and FO% ≥ 10% (1.24). (ix) ML/joint model: XGBoost ΔAUC 0.005–0.006, edema indicators bottom-third by SHAP; two-stage joint model random-slope HR 3.65 per point/day (1.21 per SD), random-intercept HR 1.39 (1.23 per SD), AIC 97,506 vs 97,529. (x) eICU-CRD: 124 stays with structured peripheral-site edema (>100-fold sparser than MIMIC-IV); trajectory gradient consistent for persistent (30.0% vs 16.0%) but uninterpretable for new onset; adjusted comparison infeasible.

Supplementary Tables and Figures. Table S1 (MICE), S2 (CareVue full validation), S3 (dual-sign), S4 (incremental value), S5 (static vs trajectory), S6 (site comparability), S7 (laterality); Figure S1 (flow diagram), S2 (KM curves), S3 (dual-sign phenotypes), S4 (eICU descriptive), S5 (latent trajectories), S6 (albumin), S7 (g-computation), S8 (enrichment), S9 (ML/joint), S10 (LMM profiles), S11 (lcmm KM), S12 (CareVue forest), S13 (CareVue calibration).

Supplementary Files

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