

Supplementary Materials
**Mapper-based topological subtyping of early diuretic
response in ICU patients with acute heart failure:
a retrospective study with external validation in
eICU-CRD**

(Author information as in the main manuscript)

Overview

This Supplementary Materials file provides additional methodological details and complete aggregated tables/figures for the isomorphic pipeline applied to the MIMIC-IV (main cohort) and eICU-CRD (external validation) ICU datasets. To comply with data use agreements, no individual-level patient records are disclosed.

Contents

S1 Supplementary Methods	5
S1.1 Data sources and ethics	5
S1.2 Time anchoring and analysis windows	5
S1.3 Mapper feature set and preprocessing	5
S1.4 Cross-database variable harmonization (MIMIC-IV ↔ eICU-CRD)	7
S1.5 Missingness and monitoring density (quality control)	9
S1.6 Mapper modeling and stability assessment	10
S1.7 Outcomes, dynamic patterns, and sensitivity analyses	10
S2 Supplementary Results: Main cohort	11
S2.1 Mapper network and branch annotation	11
S2.2 Clinical profile (Stage 1 Table 1)	11
S2.3 In-hospital mortality	16
S2.4 AKI within 48 hours (AKI48h; KDIGO creatinine proxy)	18
S2.5 Dynamic response phenotypes	19
S2.6 Robustness and sensitivity analyses	20
S3 Supplementary Results: External validation	22
S3.1 Cohort construction counts	22
S3.2 Mapper network and branch annotation	22
S3.3 Clinical profile (Stage 1 Table 1)	22
S3.4 In-hospital mortality	28
S3.5 AKI within 48 hours (AKI48h; KDIGO creatinine proxy)	30
S3.6 Dynamic response phenotypes	31
S3.7 Robustness and sensitivity analyses	32
S4 Model Diagnostics	33
S4.1 Cox proportional-hazards assumption	33
S4.2 Logistic calibration	35
S5 Full model outputs	39
S5.1 Main cohort (MIMIC-IV)	39
S5.2 External validation (eICU-CRD)	42
S6 Supplementary Appendix: Reference Lists (MIMIC-IV)	45
S6.1 Itemid reference list	45
S6.2 ICD-9 code reference list	46

List of Figures

S1	Mapper network for the main cohort (MIMIC-IV) with major branch annotations. . .	11
S2	Kaplan–Meier survival curves by major branch in the main cohort (MIMIC-IV). . .	17
S3	Forest plot for branch effects in the multivariable Cox model (MIMIC-IV).	18
S4	Dynamic response trajectories by major branch in the main cohort (MIMIC-IV). . .	20

S5	Observed-mode vs. zero-filled-mode sensitivity comparison (MIMIC-IV).	21
S6	Mapper network for the external validation cohort (eICU-CRD) with major branch annotations.	22
S7	Kaplan–Meier survival curves by major branch in external validation (eICU-CRD).	29
S8	Forest plot for branch effects in the multivariable Cox model (eICU-CRD external validation).	30
S9	Dynamic response trajectories by major branch in external validation (eICU-CRD).	32
S10	Stability metrics across prespecified sensitivity scenarios in external validation (eICU-CRD).	32
S11	Cox proportional-hazards assumption test summary for the main cohort (MIMIC-IV).	35
S12	Cox proportional-hazards assumption test summary for external validation (eICU-CRD).	35
S13	Logistic calibration for in-hospital mortality in the main cohort (MIMIC-IV; out-of-fold predictions).	37
S14	Logistic calibration for in-hospital mortality in external validation (eICU-CRD; out-of-fold predictions).	38

List of Tables

S1	Time anchoring and key analysis windows (both cohorts).	5
S2	Core Mapper feature set (16 features): definitions, units, and preprocessing.	5
S3	Harmonized variable mapping between MIMIC-IV and eICU-CRD for the 16 core Mapper features.	7
S4	Missingness and measurement-density quality-control summary for monitored domains used in Mapper features.	9
S5	Optimal Mapper parameters and graph statistics for the main cohort (MIMIC-IV).	10
S6	Main cohort (MIMIC-IV): Stage 1 Table 1a (clinical profile; field-level display).	12
S7	Main cohort (MIMIC-IV): Stage 1 Table 1b (pairwise standardized mean differences).	14
S8	Kaplan–Meier summary by branch (MIMIC-IV).	16
S9	AKI48h (creatinine-only KDIGO proxy) by branch (MIMIC-IV).	18
S10	Dynamic response pattern rates by branch (MIMIC-IV).	19
S11	Sensitivity scenarios for DEI denominator stabilization and CVP strategy (MIMIC-IV).	20
S12	External validation cohort construction counts (eICU-CRD v2.0).	22
S13	External validation (eICU-CRD): Stage 1 Table 1a (clinical profile; field-level display).	23
S14	External validation (eICU-CRD): Stage 1 Table 1b (pairwise standardized mean differences).	26
S15	Kaplan–Meier summary by branch (eICU-CRD).	28
S16	AKI48h (creatinine-only KDIGO proxy) by branch (eICU-CRD).	30
S17	Dynamic response pattern rates by branch (eICU-CRD).	31
S18	Cox proportional-hazards assumption test (Schoenfeld residuals; MIMIC-IV).	33
S19	Cox proportional-hazards assumption test (Schoenfeld residuals; eICU-CRD).	34
S20	Logistic calibration metrics (out-of-fold predictions; MIMIC-IV).	35
S21	Logistic calibration metrics (out-of-fold predictions; eICU-CRD).	36
S22	Multivariable Cox model coefficients for in-hospital mortality (MIMIC-IV).	39
S23	Logistic regression odds ratios for in-hospital mortality (MIMIC-IV).	40

S24	Adjusted odds ratios for AKI48h (MIMIC-IV).	41
S25	Multivariable Cox model coefficients for in-hospital mortality (eICU-CRD).	42
S26	Logistic regression odds ratios for in-hospital mortality (eICU-CRD).	43
S27	Adjusted odds ratios for AKI48h (eICU-CRD).	44
S28	MIMIC-IV itemid reference list used in feature extraction.	45
S29	MIMIC-IV ICD code reference list used in cohort construction.	46

S1 Supplementary Methods

S1.1 Data sources and ethics

The main cohort was derived from MIMIC-IV v3.1; the external validation cohort was derived from eICU-CRD v2.0. Both databases are de-identified and accessed under the corresponding data use agreements.

S1.2 Time anchoring and analysis windows

The analysis is anchored at t_0 , defined as the first eligible intravenous loop diuretic dose administered within 24 hours after ICU admission. Relative to t_0 , we defined early urine-output response windows (0–2h, 0–6h, 0–12h), baseline vital-sign windows (t_0 -6h to t_0 +2h), baseline laboratory windows (t_0 -24h to t_0 +6h), and AKI follow-up (t_0 to t_0 +48h).

Table S1: Time anchoring and key analysis windows (both cohorts).

Component	Definition
Anchor time (t_0)	First eligible IV loop diuretic dose within 24h after ICU admission
Urine-output / DEI windows	0–2h, 0–6h, 0–12h after t_0
Vital-sign baseline	t_0 -6h to t_0 +2h (closest value; window median when applicable)
Laboratory baseline	t_0 -24h to t_0 +6h (closest value)
AKI48h follow-up	t_0 to t_0 +48h (max creatinine; creatinine-only KDIGO proxy)

S1.3 Mapper feature set and preprocessing

The core Mapper model uses the same 16 features in both cohorts. Skewed non-negative variables are transformed by $\log(1 + x)$; missing values are handled via prespecified imputation strategies (main protocol: MICE); features are scaled with `RobustScaler`. The complete feature dictionary is provided in Table S2.

Table S2: Core Mapper feature set (16 features): definitions, units, and preprocessing.

Feature (column name)	Definition (brief)	Unit	Transform / imputation	Note
dei_2h_zero_filled_ml_per_mg	DEI in 0–2h after t_0 (urine output / first-dose loop diuretic; zero-filled)	mL/mg	log1p; MICE/median/KNN; RobustScaler	Observed-mode DEI used in sensitivity checks
dei_6h_zero_filled_ml_per_mg	DEI in 0–6h after t_0 (zero-filled)	mL/mg	log1p; impute; scale	Also used in some 2D lenses
dei_12h_zero_filled_ml_per_mg	DEI in 0–12h after t_0 (zero-filled)	mL/mg	log1p; impute; scale	Net urine output with irrigation adjustment (MIMIC-IV)
uo_2h_ml_zero_filled	Cumulative urine output in 0–2h after t_0 (zero-filled)	mL	log1p; impute; scale	
uo_6h_ml_zero_filled	Cumulative urine output in 0–6h after t_0 (zero-filled)	mL	log1p; impute; scale	
uo_12h_ml_zero_filled	Cumulative urine output in 0–12h after t_0 (zero-filled)	mL	log1p; impute; scale	

(continued)

Feature (column name)	Definition (brief)	Unit	Transform / imputation	Note
first_dose_furosemide_eq_mg	First intravenous loop diuretic dose at t_0 (furosemide-equivalent)	mg	log1p; impute; scale	Bumetanide converted by factor 40
furosemide_eq_total_24h_mg	Total loop diuretic dose in first 24h after ICU admission (furosemide-equivalent)	mg	log1p; impute; scale	eICU additionally includes torsemide (factor 2)
minutes_icu_to_first_diuretic	Time from ICU admission to first eligible diuretic administration	min	log1p; impute; scale	
map_nearest_mmhg	Mean arterial pressure (closest value around t_0)	mmHg	impute; scale	Window defined relative to t_0
cvp_nearest_mmhg	Central venous pressure (closest value around t_0)	mmHg	impute; scale	Highly missing; included with missingness indicator
creatinine_baseline_mgdl	Baseline creatinine (closest value around t_0)	mg/dL	impute; scale	Used for AKI48h definition (creatinine-only KDIGO proxy)
bun_baseline_mgdl	Baseline blood urea nitrogen (closest value around t_0)	mg/dL	log1p; impute; scale	
sodium_baseline_meql	Baseline sodium (closest value around t_0)	mEq/L	impute; scale	
age_at_admit	Age at ICU admission	years	impute; scale	
cvp_missing	Missingness indicator for CVP (0/1)	-	no log; impute; scale	Derived from whether cvp_nearest_mmhg is missing

S1.4 Cross-database variable harmonization (MIMIC-IV ↔ eICU-CRD)

Table S3 summarizes the harmonized feature definitions and source mappings used to implement an isomorphic 16-feature pipeline across MIMIC-IV and eICU-CRD.

Table S3: Harmonized variable mapping between MIMIC-IV and eICU-CRD for the 16 core Mapper features.

Feature	MIMIC-IV extraction	eICU-CRD extraction	Harmonization notes
dei_2h_zero_filled_ml_per_mg	DEI = urine output in 0–2h after t_0 divided by first-dose furosemide-equivalent (mg). Urine from <code>icu.outputevents</code> (mL; 0–5000) using urine itemids; GU irrigant-in is subtracted when present.	DEI defined analogously using <code>intakeOutput</code> urine entries (cell-label contains <code>urine/foley</code> ; exclude 0); count/occurrence; 0–5000 mL) within 0–2h after t_0 . First dose from <code>medication/infusionDrug</code> .	Zero-filled numerator: <code>COALESCE(uo_2h_ml, 0)</code> ; denominator is first-dose loop diuretic.
dei_6h_zero_filled_ml_per_mg	Same as above, using 0–6h urine aggregation (0–360 min) after t_0 .	Same as above, using 0–6h urine aggregation after t_0 .	Window definitions are isomorphic across cohorts.
dei_12h_zero_filled_ml_per_mg	Same as above, using 0–12h urine aggregation (0–720 min) after t_0 .	Same as above, using 0–12h urine aggregation after t_0 .	Sensitivity analyses evaluate alternative DEI denominators (dose flooring / 24h total dose).
uo_2h_ml_zero_filled	Cumulative urine output in 0–2h after t_0 from <code>icu.outputevents</code> (mL; 0–5000), with irrigation adjustment via negative contribution of GU irrigant-in itemid.	Cumulative urine output in 0–2h after t_0 from <code>intakeOutput</code> numeric urine entries (mL; 0–5000); no explicit irrigant subtraction in eICU.	Stored as zero-filled output for modeling; raw <code>uo_2h_ml</code> remains missing when no events.
uo_6h_ml_zero_filled	Same as above for 0–6h after t_0 .	Same as above for 0–6h after t_0 .	Urine monitoring density summarized in QC Table S4.
uo_12h_ml_zero_filled	Same as above for 0–12h after t_0 .	Same as above for 0–12h after t_0 .	Urine counts are captured by <code>urine_measurements_12h_n</code> .
first_dose_furosemide_eq_mg	First eligible IV loop diuretic dose within 24h after ICU admission from <code>icu.inpotevents</code> , 221794/228340 (furosemide) and 229639 (bumetanide). Furosemide-equivalent: bumetanide $\times 40$.	First eligible IV loop diuretic dose within 0–1440 min after ICU admission from <code>medication</code> (IV routes) and <code>infusionDrug</code> . Drugname patterns: <code>furosemide/lasix/bumetanide/bumex/torseamide</code> . Furosemide-equivalent: bumetanide $\times 40$, torseamide $\times 2$.	Dose QC: positive mg and ≤ 5000 when parsed; harmonized to mg furosemide-equivalent.
furosemide_eq_total_24h_mg	Sum of furosemide-equivalent loop diuretic doses in the first 24h after ICU admission from <code>icu.inpotevents</code> .	Sum of furosemide-equivalent loop diuretic doses in the first 24h after ICU admission from <code>medication/infusionDrug</code> .	Used as a baseline adjustment covariate and as an alternative DEI denominator in sensitivity analyses.
minutes_icu_to_first_diuretic	<code>DATE_DIFF('minute', icustays.intime, first_diuretic_time)</code> .	Minutes since ICU admission to first eligible diuretic; operationally equals <code>first_diuretic_offset_min</code> .	Both cohorts enforce t_0 within the first 24h after ICU admission.
map_nearest_mmhg	Nearest mean arterial pressure around t_0 from <code>icu.charthevents</code> , itemids 220052/220181; window t_0 -6h to t_0 +2h; QC range 20–200.	Nearest mean arterial pressure around t_0 from <code>vitalPeriodic.systemicmean</code> and <code>vitalAperiodic.noninvasivemean</code> ; window t_0 -360 to t_0 +120 min; QC range 20–200.	Monitoring density stored as <code>map_measurements_n</code> ; nearest selection minimizes <code> time - \tzero </code> .
cvp_nearest_mmhg	Nearest central venous pressure around t_0 from <code>icu.charthevents</code> , itemid 220074; window t_0 -6h to t_0 +2h; QC range -5–35.	Nearest CVP around t_0 from <code>vitalPeriodic.cvp</code> ; window t_0 -360 to t_0 +120 min; QC range -5–35.	CVP is sparse; missingness handled via indicator feature <code>cvp_missing</code> .
creatinine_baseline_mgdl	Nearest creatinine around t_0 from <code>hosp.labevents</code> , itemids 50912/52546; window t_0 -24h to t_0 +6h; QC range 0.1–20.	Nearest creatinine around t_0 from <code>lab</code> where <code>labname='creatinine'</code> ; window t_0 -1440 to t_0 +360 min; QC range 0.1–20.	Baseline creatinine is used for AKI48h definition (creatinine-only KDIGO proxy).

(continued)

Feature	MIMIC-IV extraction	eICU-CRD extraction	Harmonization notes
<code>bun_baseline_mgdl</code>	Nearest BUN around t_0 from <code>hosp.labevents</code> , 51006/52647; window t_0-24h to t_0+6h ; QC range 1-300.	Nearest BUN around t_0 from <code>lab</code> items where <code>labname='bun'</code> or contains <code>urea nitrogen</code> ; window t_0-1440 to t_0+360 min; QC range 1-300.	Both cohorts use the closest value to t_0 within the prespecified window.
<code>sodium_baseline_meql</code>	Nearest sodium around t_0 from <code>hosp.labevents</code> , 50983/52623; window t_0-24h to t_0+6h ; QC range 90-200.	Nearest sodium around t_0 from <code>lab</code> items where <code>labname='sodium'</code> ; window t_0-1440 to t_0+360 min; QC range 90-200.	Units are harmonized as mEq/L by source conventions; extreme values are filtered by QC rules.
<code>age_at_admit</code>	Age at ICU admission derived from <code>patients.anchor_age</code> , <code>patient.age</code> , <code>patients.anchor_year</code> , and <code>admissions.admittime</code> .	Age at ICU admission from <code>patients.anchor_age</code> ; <code>>89</code> is treated as 90.	Restricted to adults (≥ 18 years).
<code>cvp_missing</code>	Derived as indicator of missing <code>cvp_nearest_mmhg</code> (computed down-stream for modeling).	Computed during extraction as 1 if <code>cvp_nearest_mmhg</code> is NULL, else 0.	Used to stabilize inclusion of sparse monitoring (CVP) in clustering and sensitivity analyses.

S1.5 Missingness and monitoring density (quality control)

Table S4 summarizes missingness of the domain-specific baseline values and the measurement density of key monitoring streams (urine output, MAP, CVP, and baseline laboratories) for both cohorts.

Table S4: Missingness and measurement-density quality-control summary for monitored domains used in Mapper features.

Domain	MIMIC-IV			median	eICU-CRD		
	Missing (%)	No measurement (%)	Count [IQR]		Missing (%)	No measurement (%)	Count [IQR]
Urine output monitoring (0–12h after t_0)	1.0	1.0	9 [7, 11]		37.4	37.4	4 [2, 7]
MAP monitoring (t_0 -6h to t_0 +2h)	0.6	0.6	8 [5, 9]		3.2	3.2	12 [8, 22]
CVP monitoring (t_0 -6h to t_0 +2h)	80.7	80.7	8 [4, 9]		91.4	91.4	50 [22, 92]
Creatinine monitoring (t_0 -24h to t_0 +6h)	5.5	5.5	2 [1, 2]		7.4	7.4	6 [3, 8]
BUN monitoring (t_0 -24h to t_0 +6h)	5.6	5.6	2 [1, 2]		7.6	7.6	6 [3, 8]
Sodium monitoring (t_0 -24h to t_0 +6h)	4.8	4.8	2 [1, 3]		7.1	7.1	6 [3, 8]

S1.6 Mapper modeling and stability assessment

Mapper networks were built using Giotto-TDA, with a two-stage parameter search (coarse grid followed by local refinement) and bootstrap co-membership stability assessment (200 iterations; 80% subsampling without replacement). Table S5 summarizes the optimal parameters and graph statistics for the main cohort.

Table S5: Optimal Mapper parameters and graph statistics for the main cohort (MIMIC-IV).

Metric	Value
Lens	pca2d
n_intervals	8
overlap_frac	0.55
DBSCAN ϵ (eps)	0.7
DBSCAN min_samples	8
Nodes / edges	58 / 393
Coverage	1.000
Largest component fraction	1.000
Connected components	1
Modularity	0.399
Bootstrap Jaccard (mean \pm SD)	0.924 \pm 0.038
Stability score	0.944
Final score	0.859

S1.7 Outcomes, dynamic patterns, and sensitivity analyses

The primary outcome was in-hospital mortality. The mechanistic endpoint was AKI within 48 hours after t_0 using creatinine-only KDIGO criteria (AKI48h proxy). Dynamic response patterns were defined using segmented DEI trajectories (0–2h, 2–6h, 6–12h). Sensitivity analyses targeted (i) potential denominator artifacts in DEI caused by extremely small first doses and (ii) potential structural bias induced by highly missing monitoring variables (e.g., CVP), as well as observed vs. zero-filled response representations.

S2 Supplementary Results: Main Cohort (MIMIC-IV)

S2.1 Mapper network and branch annotation

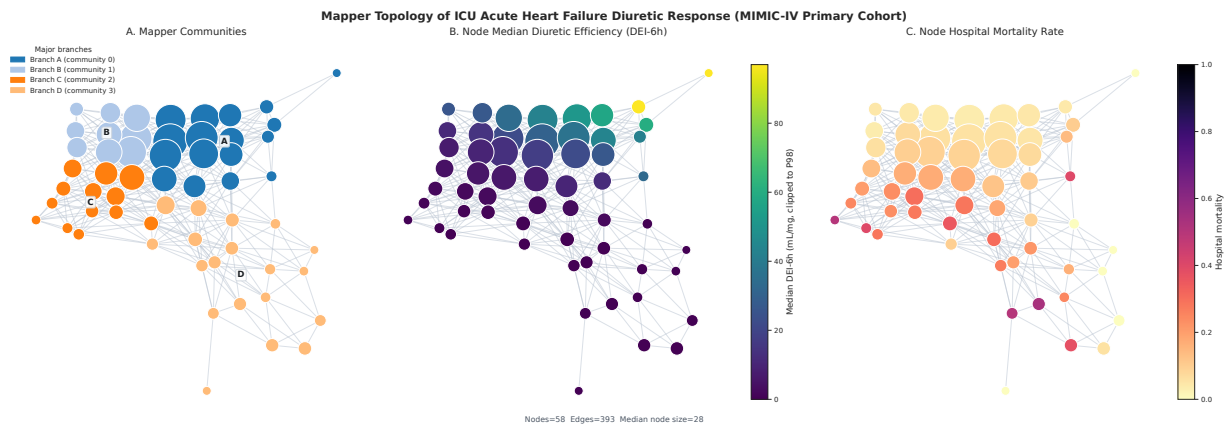


Fig. S1: Mapper network for the main cohort (MIMIC-IV) with major branch annotations.

S2.2 Clinical profile (Stage 1 Table 1)

For readability, Stage 1 Table 1 is presented in two parts: a clinical profile table (Table S6) and a pairwise standardized mean difference summary (Table S7).

Table S6: Main cohort (MIMIC-IV): Stage 1 Table 1a (clinical profile; field-level display).

Variable	Level	Overall	A	B	C	D	P Test	q(FDR-BH)
n		2373	1747	461	105	60		
age_at_admit, mean (SD)		73.2 (13.5)	74.1 (13.5)	70.3 (13.2)	72.5 (13.5)	73.4 (13.6)	< 0.001 One-way ANOVA	
first_dose_furosemide_eq_mg, mean (SD)		46.1 (42.4)	31.2 (19.5)	90.2 (56.6)	97.3 (67.3)	52.6 (39.3)	< 0.001 One-way ANOVA	
furosemide_eq_total_24h_mg, mean (SD)		130.1 (163.0)	75.7 (90.7)	288.1 (204.2)	353.2 (252.6)	110.4 (124.8)	< 0.001 One-way ANOVA	
minutes_icu_to_first_diuretic, mean (SD)		474.6 (416.1)	542.5 (430.2)	254.7 (271.4)	282.8 (297.0)	521.3 (415.5)	< 0.001 One-way ANOVA	
map_nearest_mmhg, mean (SD)		77.6 (15.5)	77.6 (15.2)	79.1 (16.0)	72.6 (15.9)	75.8 (18.4)	0.001 One-way ANOVA	0.005
cvp_nearest_mmhg, mean (SD)		14.1 (6.0)	13.0 (5.4)	17.6 (6.6)	18.9 (5.6)	21.9 (5.7)	< 0.001 One-way ANOVA	
creatinine_baseline_mgdl, mean (SD)		1.6 (0.9)	1.3 (0.6)	2.2 (1.0)	3.3 (1.5)	2.0 (1.2)	< 0.001 One-way ANOVA	
bun_baseline_mgdl, mean (SD)		36.8 (23.3)	29.5 (16.5)	56.1 (26.9)	69.6 (26.2)	42.4 (19.7)	< 0.001 One-way ANOVA	
sodium_baseline_meql, mean (SD)		137.8 (5.2)	138.1 (4.9)	137.2 (5.5)	135.6 (6.0)	137.5 (6.3)	< 0.001 One-way ANOVA	
uo_2h_ml_zero_filled, mean (SD)		390.6 (352.1)	406.3 (346.6)	460.3 (360.7)	43.5 (47.5)	3.1 (9.3)	< 0.001 One-way ANOVA	
uo_6h_ml_zero_filled, mean (SD)		881.6 (643.1)	882.1 (570.2)	1147.4 (786.6)	204.0 (151.7)	10.7 (25.0)	< 0.001 One-way ANOVA	
uo_12h_ml_zero_filled, mean (SD)		1422.5 (925.1)	1377.2 (784.5)	1972.2 (1143.2)	490.2 (399.2)	148.7 (317.2)	< 0.001 One-way ANOVA	
dei_2h_zero_filled_ml_per_mg, mean (SD)		17.9 (92.8)	22.5 (107.7)	6.7 (6.7)	0.6 (0.7)	0.1 (0.3)	< 0.001 One-way ANOVA	
dei_6h_zero_filled_ml_per_mg, mean (SD)		50.9 (579.8)	64.4 (675.2)	17.2 (18.2)	2.7 (2.3)	0.4 (0.9)	0.297 One-way ANOVA	0.430
dei_12h_zero_filled_ml_per_mg, mean (SD)		87.8 (1068.3)	110.6 (1244.2)	30.2 (31.4)	6.4 (5.2)	9.7 (46.5)	0.382 One-way ANOVA	0.430
gender, n (%)	F	1161 (48.9)	912 (52.2)	166 (36.0)	47 (44.8)	36 (60.0)	< 0.001 Chi-squared	
	M	1212 (51.1)	835 (47.8)	295 (64.0)	58 (55.2)	24 (40.0)		
insurance, n (%)	Medicaid	198 (8.3)	139 (8.0)	42 (9.1)	10 (9.5)	7 (11.7)	0.430 Chi-squared (warning: expected count < 5)	0.430
	Medicare	1782 (75.1)	1330 (76.1)	328 (71.1)	79 (75.2)	45 (75.0)		
	None	19 (0.8)	15 (0.9)	3 (0.7)	0 (0.0)	1 (1.7)		
	Other	40 (1.7)	32 (1.8)	7 (1.5)	0 (0.0)	1 (1.7)		
	Private	334 (14.1)	231 (13.2)	81 (17.6)	16 (15.2)	6 (10.0)		
admission_type, n (%)	DIRECT EMER.	118 (5.0)	76 (4.4)	33 (7.2)	7 (6.7)	2 (3.3)	0.034 Chi-squared (warning: expected count < 5)	0.085
	DIRECT OBSERVATION	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)		
	ELECTIVE	63 (2.7)	58 (3.3)	4 (0.9)	1 (1.0)	0 (0.0)		
	EU OBSERVATION	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)		
	EW EMER.	1554 (65.5)	1147 (65.7)	299 (64.9)	68 (64.8)	40 (66.7)		
	OBSERVATION ADMIT	3 (0.1)	1 (0.1)	2 (0.4)	0 (0.0)	0 (0.0)		

(continued)

Variable	Level	Overall	A	B	C	D	P Test	q(FDR-BH)
first_careunit, n (%)	SURGICAL SAME DAY ADMISSION	55 (2.3)	48 (2.7)	6 (1.3)	1 (1.0)	0 (0.0)	< 0.001 Chi-squared (warning: expected count < 5)	
	URGENT	577 (24.3)	415 (23.8)	116 (25.2)	28 (26.7)	18 (30.0)		
	Cardiac Vascular Intensive Care Unit (CVICU)	358 (15.1)	319 (18.3)	26 (5.6)	8 (7.6)	5 (8.3)		
	Coronary Care Unit (CCU)	1098 (46.3)	696 (39.8)	315 (68.3)	64 (61.0)	23 (38.3)		
	Medical Intensive Care Unit (MICU)	517 (21.8)	397 (22.7)	75 (16.3)	22 (21.0)	23 (38.3)		
	Medical/Surgical Intensive Care Unit (MICU/SICU)	260 (11.0)	216 (12.4)	31 (6.7)	7 (6.7)	6 (10.0)		
	Surgical Intensive Care Unit (SICU)	94 (4.0)	79 (4.5)	9 (2.0)	3 (2.9)	3 (5.0)		
	Trauma SICU (TSICU)	46 (1.9)	40 (2.3)	5 (1.1)	1 (1.0)	0 (0.0)		

Table S7: Main cohort (MIMIC-IV): Stage 1 Table 1b (pairwise standardized mean differences).

Variable	Level	SMD(A,B)	SMD(A,C)	SMD(A,D)	SMD(B,C)	SMD(B,D)	SMD(C,D)	P	q(FDR-BH)
n									
age_at_admit, mean (SD)		-0.284	-0.115	-0.049	0.168	0.233	0.065	< 0.001	
first_dose_furosemide_eq_mg, mean (SD)		1.392	1.334	0.689	0.114	-0.772	-0.812	< 0.001	
furosemide_eq_total_24h_mg, mean (SD)		1.344	1.462	0.318	0.283	-1.050	-1.218	< 0.001	
minutes_icu_to_first_diuretic, mean (SD)		-0.800	-0.703	-0.050	0.099	0.760	0.660	< 0.001	
map_nearest_mmhg, mean (SD)		0.096	-0.320	-0.103	-0.406	-0.188	0.189	0.001	0.005
cvp_nearest_mmhg, mean (SD)		0.765	1.077	1.593	0.218	0.692	0.515	< 0.001	
creatinine_baseline_mgdl, mean (SD)		1.202	1.802	0.816	0.850	-0.179	-0.936	< 0.001	
bun_baseline_mgdl, mean (SD)		1.190	1.830	0.707	0.510	-0.582	-1.175	< 0.001	
sodium_baseline_meql, mean (SD)		-0.160	-0.457	-0.107	-0.290	0.039	0.309	< 0.001	
uo_2h_ml_zero_filled, mean (SD)		0.153	-1.467	-1.645	-1.621	-1.792	-1.179	< 0.001	
uo_6h_ml_zero_filled, mean (SD)		0.386	-1.625	-2.159	-1.665	-2.043	-1.777	< 0.001	
uo_12h_ml_zero_filled, mean (SD)		0.607	-1.425	-2.053	-1.731	-2.174	-0.947	< 0.001	
dei_2h_zero_filled_ml_per_mg, mean (SD)		-0.206	-0.287	-0.294	-1.281	-1.396	-0.889	< 0.001	
dei_6h_zero_filled_ml_per_mg, mean (SD)		-0.099	-0.129	-0.134	-1.115	-1.304	-1.327	0.297	0.430
dei_12h_zero_filled_ml_per_mg, mean (SD)		-0.091	-0.118	-0.115	-1.059	-0.517	0.101	0.382	0.430
gender, n (%)	F	0.331	0.149	0.158	0.179	0.495	0.309	< 0.001	
	M								
insurance, n (%)	Medicaid	0.136	0.246	0.169	0.223	0.245	0.308	0.430	0.430
	Medicare								
	None								
	Other								
	Private								
admission_type, n (%)	DIRECT EMER.	0.259	-	-	-	-	-	0.034	0.085
	DIRECT OBSERVATION								
	ELECTIVE								
	EU OBSERVATION								
	EW EMER.								
	OBSERVATION ADMIT								
	SURGICAL SAME DAY								
	ADMISSION								
	URGENT								
first_careunit, n (%)	Cardiac Vascular Intensive Care Unit (CVICU)	0.636	0.494	0.466	0.173	0.684	0.516	< 0.001	
	Coronary Care Unit (CCU)								

(continued)

Variable	Level	SMD(A,B)	SMD(A,C)	SMD(A,D)	SMD(B,C)	SMD(B,D)	SMD(C,D)	P _q (FDR-BH)
	Medical Intensive Care Unit (MICU)							
	Medical/Surgical Intensive Care Unit (MICU/SICU)							
	Surgical Intensive Care Unit (SICU)							
	Trauma SICU (TSICU)							

S2.3 In-hospital mortality

Kaplan–Meier summaries are provided in Table S8. Survival curves and multivariable Cox model branch effects are shown in Fig. S2 and Fig. S3.

Table S8: Kaplan–Meier summary by branch (MIMIC-IV).

branch_label	n	events	median_survival_days	30d_survival	60d_survival
A	1747	123	127.378	0.748	0.562
B	461	41	inf	0.776	0.679
C	105	31	inf	0.575	0.575
D	60	17	inf	0.690	0.690

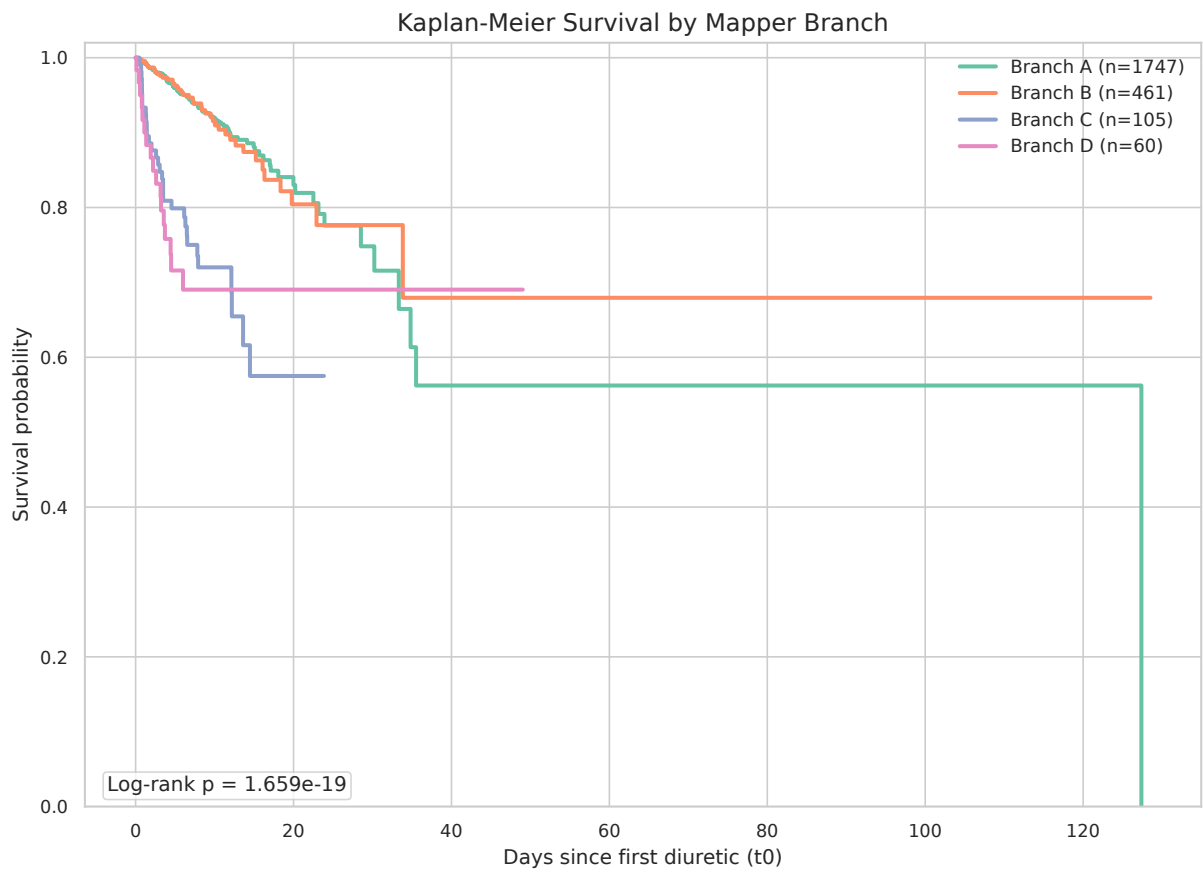


Fig. S2: Kaplan–Meier survival curves by major branch in the main cohort (MIMIC-IV).

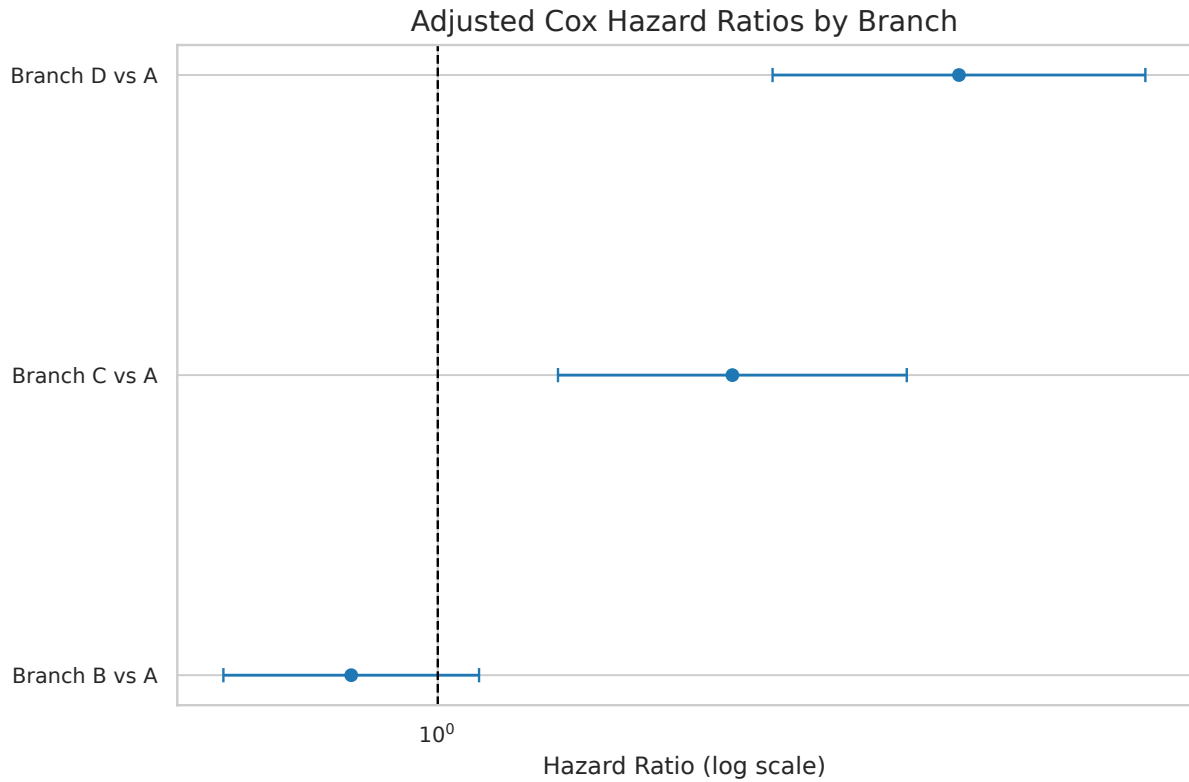


Fig. S3: Forest plot for branch effects in the multivariable Cox model (MIMIC-IV).

S2.4 AKI within 48 hours (AKI48h; KDIGO creatinine proxy)

Branch-level AKI48h rates are provided in Table S9. Full adjusted odds ratios are provided in Table S24.

Table S9: AKI48h (creatinine-only KDIGO proxy) by branch (MIMIC-IV).

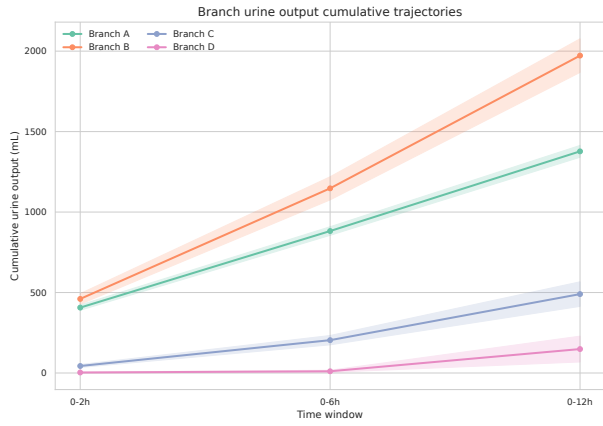
branch_label	n	followup_n	aki48_n	aki48_rate	stage2plus_n	stage2plus_rate
A	1747	1739	391	0.224	27	0.015
B	461	461	98	0.213	3	0.007
C	105	105	48	0.457	1	0.010
D	60	58	19	0.317	1	0.017

S2.5 Dynamic response phenotypes

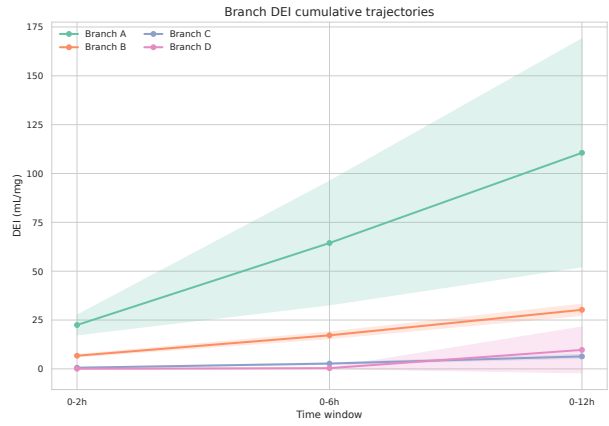
Dynamic response pattern rates and median segmented DEI increments are provided in Table S10. Cumulative urine output and DEI trajectories are shown in Fig. S4.

Table S10: Dynamic response pattern rates by branch (MIMIC-IV).

branch_label	n	primary_nonresponse_rate	tachyphylaxis_rate	dei_0_2_median	dei_2_6_median	dei_6_12_median
A	1747	0.232	0.079	12.500	14.500	14.400
B	461	0.534	0.017	4.600	6.900	8.500
C	105	1.000	0.000	0.375	1.375	2.625
D	60	1.000	0.000	0.000	0.000	0.000



(a) Cumulative urine output



(b) Cumulative DEI

Fig. S4: Dynamic response trajectories by major branch in the main cohort (MIMIC-IV).

S2.6 Robustness and sensitivity analyses

Table S11 summarizes prespecified sensitivity scenarios that stabilize DEI denominators and vary CVP inclusion. Fig. S5 visualizes the comparison between observed-mode and zero-filled response representations.

Table S11: Sensitivity scenarios for DEI denominator stabilization and CVP strategy (MIMIC-IV).

Scenario	n	CVP	DEI denominator	P99	Max	Robustness
S0 (raw first-dose DEI + CVP)	2373	Yes	raw (first dose)	258.99	27600.00	0.854
S1 (dose floor 10 mg + no CVP)	2373	No	first dose ≥ 10 mg	149.42	307.50	0.858
S2 (floor 10 mg + exclude < 5 mg + no CVP)	2325	No	floor + exclude < 5 mg	145.38	307.50	0.899
S3 (floor 10 mg + 24h total dose + no CVP)	2373	No	24h total dose denominator	110.64	221.00	0.902
S4 (floor 10 mg + CVP retained)	2373	Yes	first dose ≥ 10 mg	149.42	307.50	0.857

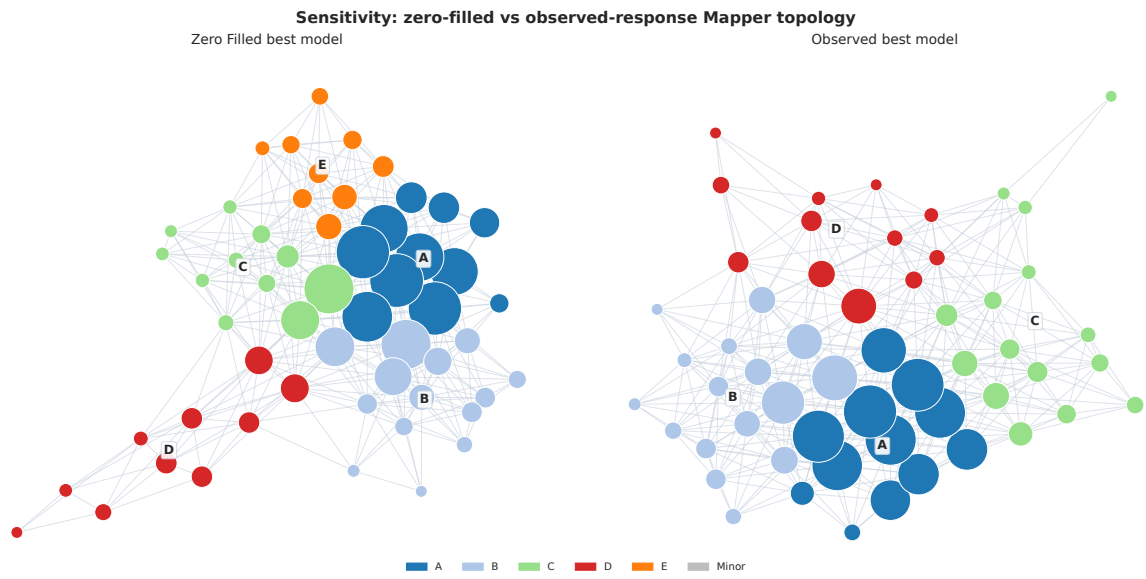


Fig. S5: Observed-mode vs. zero-filled-mode sensitivity comparison (MIMIC-IV).

S3 Supplementary Results: External Validation (eICU-CRD)

S3.1 Cohort construction counts

External validation uses ICU stays (`patientunitstayid`) as the analysis unit. The final cohort size after inclusion/exclusion criteria is $n = 4438$ ICU stays. Among these, $n = 16$ stays were assigned to a Minor branch and are excluded from major-branch summaries (A–C), yielding a major-branch analysis set of $n = 4422$.

Table S12: External validation cohort construction counts (eICU-CRD v2.0).

Step	n
All ICU stays	200,859
Adult ICU stays	200,234
Heart failure stays (broad)	17,128
Acute HF text-only subset	892
HF + IV loop diuretic within 24h	5,121
After excluding ESRD/dialysis	5,056
After excluding sepsis (final)	4,438

S3.2 Mapper network and branch annotation

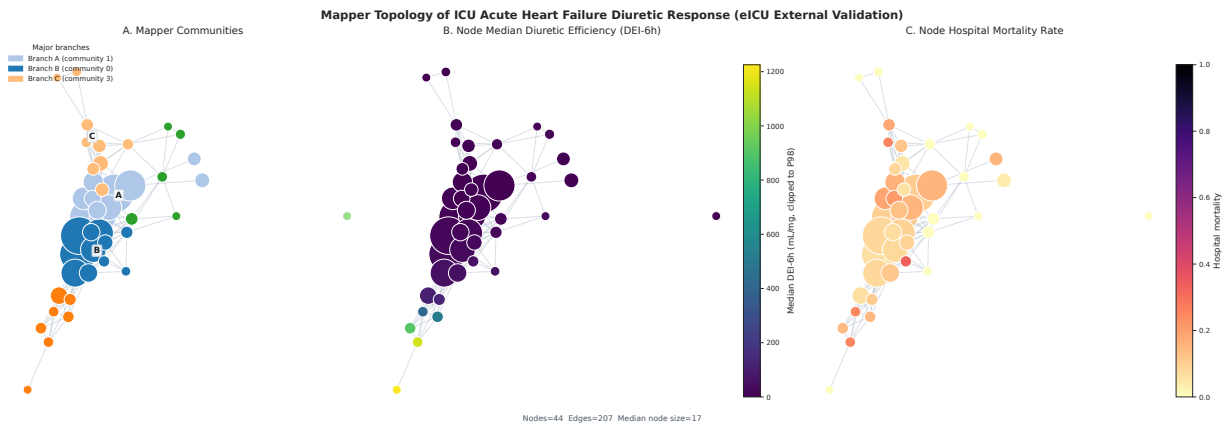


Fig. S6: Mapper network for the external validation cohort (eICU-CRD) with major branch annotations.

S3.3 Clinical profile (Stage 1 Table 1)

Stage 1 Table 1 summarizes the major branches (A–C) only ($n = 4422$), excluding the Minor branch ($n = 16$) from the full external validation cohort ($n = 4438$). For readability, Stage 1 Table 1 is presented in two parts: a clinical profile table (Table S13) and a pairwise standardized mean difference summary (Table S14).

Table S13: External validation (eICU-CRD): Stage 1 Table 1a (clinical profile; field-level display).

Variable	Level	Overall	A	B	C	P Test	q(FDR-BH)
n		4422	2395	2006	21		
age_at_admit, mean (SD)		70.7 (14.0)	71.2 (13.6)	70.1 (14.3)	60.5 (16.2)	< 0.001 One-way ANOVA	
first_dose_furosemide_eq_mg, mean (SD)		45.3 (34.5)	49.1 (41.9)	40.3 (20.8)	78.9 (43.1)	< 0.001 One-way ANOVA	
furosemide_eq_total_24h_mg, mean (SD)		68.4 (76.2)	74.8 (88.7)	60.4 (56.4)	93.6 (46.9)	< 0.001 One-way ANOVA	
minutes_icu_to_first_diuretic, mean (SD)		410.6 (390.9)	423.7 (399.6)	395.1 (379.7)	392.6 (394.2)	0.052 One-way ANOVA	0.121
map_nearest_mmhg, mean (SD)		85.1 (19.0)	84.3 (18.9)	86.0 (18.9)	93.2 (20.9)	0.002 One-way ANOVA	0.014
cvp_nearest_mmhg, mean (SD)		13.6 (7.5)	13.6 (7.5)	13.5 (7.5)	4.0 (2.8)	0.197 One-way ANOVA	0.345
creatinine_baseline_mgdl, mean (SD)		1.6 (1.1)	1.7 (1.0)	1.4 (0.8)	8.9 (1.3)	< 0.001 One-way ANOVA	
bun_baseline_mgdl, mean (SD)		33.4 (21.4)	35.1 (22.6)	30.9 (19.0)	79.7 (26.0)	< 0.001 One-way ANOVA	
sodium_baseline_meql, mean (SD)		137.7 (5.1)	137.5 (5.1)	137.9 (5.1)	136.8 (7.0)	0.035 One-way ANOVA	0.121
uo_2h_ml_zero_filled, mean (SD)		184.9 (347.9)	15.7 (62.8)	388.5 (431.5)	27.9 (80.6)	< 0.001 One-way ANOVA	
uo_6h_ml_zero_filled, mean (SD)		520.5 (713.1)	43.2 (123.1)	1095.2 (705.7)	46.7 (115.2)	< 0.001 One-way ANOVA	
uo_12h_ml_zero_filled, mean (SD)		892.4 (1065.8)	265.2 (610.1)	1648.6 (1005.6)	174.5 (384.4)	< 0.001 One-way ANOVA	
dei_2h_zero_filled_ml_per_mg, mean (SD)		5.1 (10.4)	0.3 (1.0)	11.1 (13.3)	0.4 (1.2)	< 0.001 One-way ANOVA	
dei_6h_zero_filled_ml_per_mg, mean (SD)		14.1 (20.8)	0.8 (1.9)	30.6 (21.7)	0.7 (1.5)	< 0.001 One-way ANOVA	
dei_12h_zero_filled_ml_per_mg, mean (SD)		24.9 (57.6)	8.4 (68.2)	45.4 (30.8)	2.0 (4.1)	< 0.001 One-way ANOVA	
icu_los_minutes, mean (SD)		4969.8 (5681.9)	4945.3 (5616.5)	5000.7 (5784.8)	4806.1 (2337.3)	0.941 One-way ANOVA	0.941
hosp_los_minutes, mean (SD)		11505.6 (15614.2)	11736.1 (18306.1)	11226.1 (11671.7)	11924.2 (10386.6)	0.555 One-way ANOVA	0.648
gender, n (%)	Female	2107 (47.6)	1226 (51.2)	874 (43.6)	7 (33.3)	< 0.001 Chi-squared	
	Male	2315 (52.4)	1169 (48.8)	1132 (56.4)	14 (66.7)		
race, n (%)	African American	626 (14.2)	353 (14.7)	265 (13.2)	8 (38.1)	< 0.001 Chi-squared (warning: expected count < 5)	
	Asian	56 (1.3)	35 (1.5)	20 (1.0)	1 (4.8)		
	Caucasian	3226 (73.0)	1749 (73.0)	1467 (73.1)	10 (47.6)		
	Hispanic	265 (6.0)	93 (3.9)	172 (8.6)	0 (0.0)		
	Native American	17 (0.4)	10 (0.4)	7 (0.3)	0 (0.0)		
	None	17 (0.4)	10 (0.4)	7 (0.3)	0 (0.0)		
	Other/Unknown	215 (4.9)	145 (6.1)	68 (3.4)	2 (9.5)		
first_careunit, n (%)	CCU-CTICU	531 (12.0)	243 (10.1)	286 (14.3)	2 (9.5)	< 0.001 Chi-squared (warning: expected count < 5)	
	CSICU	164 (3.7)	101 (4.2)	62 (3.1)	1 (4.8)		

(continued)

Variable	Level	Overall	A	B	C	P Test	q(FDR-BH)
admission_location, n (%)	CTICU	119 (2.7)	75 (3.1)	44 (2.2)	0 (0.0)	0.418 Chi-squared (warning: expected count < 5)	0.585
	Cardiac ICU	620 (14.0)	333 (13.9)	286 (14.3)	1 (4.8)		
	MICU	383 (8.7)	236 (9.9)	142 (7.1)	5 (23.8)		
	Med-Surg ICU	2290 (51.8)	1223 (51.1)	1057 (52.7)	10 (47.6)		
	Neuro ICU	95 (2.1)	44 (1.8)	50 (2.5)	1 (4.8)		
	SICU	220 (5.0)	140 (5.8)	79 (3.9)	1 (4.8)		
	Acute Care/Floor	175 (4.0)	100 (4.2)	75 (3.7)	0 (0.0)		
	Chest Pain Center	10 (0.2)	1 (0.0)	9 (0.4)	0 (0.0)		
	Direct Admit	375 (8.5)	207 (8.6)	166 (8.3)	2 (9.5)		
	Emergency Department	2502 (56.6)	1320 (55.1)	1168 (58.2)	14 (66.7)		
discharge_location, n (%)	Floor	731 (16.5)	415 (17.3)	314 (15.7)	2 (9.5)	< 0.001 Chi-squared (warning: expected count < 5)	
	ICU	25 (0.6)	15 (0.6)	10 (0.5)	0 (0.0)		
	ICU to SDU	36 (0.8)	19 (0.8)	17 (0.8)	0 (0.0)		
	None	5 (0.1)	1 (0.0)	4 (0.2)	0 (0.0)		
	Operating Room	202 (4.6)	120 (5.0)	81 (4.0)	1 (4.8)		
	Other	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)		
	Other Hospital	114 (2.6)	70 (2.9)	43 (2.1)	1 (4.8)		
	Other ICU	62 (1.4)	31 (1.3)	30 (1.5)	1 (4.8)		
	PACU	3 (0.1)	2 (0.1)	1 (0.0)	0 (0.0)		
	Recovery Room	36 (0.8)	22 (0.9)	14 (0.7)	0 (0.0)		
	Step-Down Unit (SDU)	145 (3.3)	72 (3.0)	73 (3.6)	0 (0.0)		
	Acute Care/Floor	449 (10.2)	209 (8.7)	235 (11.7)	5 (23.8)		
	Death	226 (5.1)	156 (6.5)	69 (3.4)	1 (4.8)		
	Floor	2236 (50.6)	1260 (52.6)	972 (48.5)	4 (19.0)		
	Home	247 (5.6)	103 (4.3)	141 (7.0)	3 (14.3)		
	ICU	28 (0.6)	20 (0.8)	8 (0.4)	0 (0.0)		
	None	6 (0.1)	5 (0.2)	0 (0.0)	1 (4.8)		
Nursing Home	8 (0.2)	5 (0.2)	3 (0.1)	0 (0.0)			
Other	19 (0.4)	14 (0.6)	5 (0.2)	0 (0.0)			
Other External	63 (1.4)	44 (1.8)	19 (0.9)	0 (0.0)			
Other Hospital	101 (2.3)	64 (2.7)	37 (1.8)	0 (0.0)			
Other ICU	141 (3.2)	76 (3.2)	63 (3.1)	2 (9.5)			
Other Internal	14 (0.3)	8 (0.3)	6 (0.3)	0 (0.0)			
Rehabilitation	17 (0.4)	3 (0.1)	14 (0.7)	0 (0.0)			
Skilled Nursing Facility	56 (1.3)	27 (1.1)	29 (1.4)	0 (0.0)			
Step-Down Unit (SDU)	499 (11.3)	267 (11.1)	229 (11.4)	3 (14.3)			
Telemetry	312 (7.1)	134 (5.6)	176 (8.8)	2 (9.5)			

(continued)

Variable	Level	Overall	A	B	C	P Test	q(FDR-BH)
unitdischargestatus, n (%)	Alive	4195 (94.9)	2239 (93.5)	1937 (96.6)	19 (90.5)	< 0.001 Chi-squared (warning: expected count < 5)	
	Expired	226 (5.1)	156 (6.5)	69 (3.4)	1 (4.8)		
	None	1 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)		
hospitaldischargestatus, n (%)	Alive	3948 (89.3)	2080 (86.8)	1849 (92.2)	19 (90.5)	< 0.001 Chi-squared (warning: expected count < 5)	
	Expired	418 (9.5)	268 (11.2)	148 (7.4)	2 (9.5)		
	None	56 (1.3)	47 (2.0)	9 (0.4)	0 (0.0)		

Table S14: External validation (eICU-CRD): Stage 1 Table 1b (pairwise standardized mean differences).

Variable	Level	SMD(A,B)	SMD(A,C)	SMD(B,C)	P q(FDR-BH)	
n						
age_at_admit, mean (SD)		-0.078	-0.719	-0.631 < 0.001		
first_dose_furosemide_eq_mg, mean (SD)		-0.263	0.702	1.139 < 0.001		
furosemide_eq_total_24h_mg, mean (SD)		-0.194	0.265	0.640 < 0.001		
minutes_icu_to_first_diuretic, mean (SD)		-0.073	-0.078	-0.006	0.052	0.121
map_nearest_mmhg, mean (SD)		0.090	0.450	0.364	0.002	0.014
cvp_nearest_mmhg, mean (SD)		-0.014	-1.693	-1.684	0.197	0.345
creatinine_baseline_mgdl, mean (SD)		-0.267	6.296	7.030 < 0.001		
bun_baseline_mgdl, mean (SD)		-0.205	1.829	2.146 < 0.001		
sodium_baseline_meql, mean (SD)		0.078	-0.117	-0.182	0.035	0.121
uo_2h_ml_zero_filled, mean (SD)		1.209	0.169	-1.162 < 0.001		
uo_6h_ml_zero_filled, mean (SD)		2.077	0.029	-2.074 < 0.001		
uo_12h_ml_zero_filled, mean (SD)		1.663	-0.178	-1.937 < 0.001		
dei_2h_zero_filled_ml_per_mg, mean (SD)		1.153	0.136	-1.137 < 0.001		
dei_6h_zero_filled_ml_per_mg, mean (SD)		1.939	-0.066	-1.950 < 0.001		
dei_12h_zero_filled_ml_per_mg, mean (SD)		0.698	-0.134	-1.976 < 0.001		
icu_los_minutes, mean (SD)		0.010	-0.032	-0.044	0.941	0.941
hosp_los_minutes, mean (SD)		-0.033	0.013	0.063	0.555	0.648
gender, n (%)	Female	0.153	0.368	0.212 < 0.001		
	Male					
race, n (%)	African American	0.234	0.719	0.875 < 0.001		
	Asian					
	Caucasian					
	Hispanic					
	Native American					
	None					
	Other/Unknown					
first_careunit, n (%)	CCU-CTICU	0.200	0.569	0.635 < 0.001		
	CSICU					
	CTICU					
	Cardiac ICU					
	MICU					
	Med-Surg ICU					
	Neuro ICU					
	SICU					
admission_location, n (%)	Acute Care/Floor	0.145	–	0.571	0.418	0.585

(continued)

Variable	Level	SMD(A,B)	SMD(A,C)	SMD(B,C)	P q(FDR-BH)
discharge_location, n (%)	Chest Pain Center				
	Direct Admit				
	Emergency Department				
	Floor				
	ICU				
	ICU to SDU				
	None				
	Operating Room				
	Other				
	Other Hospital				
	Other ICU				
	PACU				
	Recovery Room				
	Step-Down Unit (SDU)				
	Acute Care/Floor	0.297	1.075	0.905	< 0.001
	Death				
	Floor				
Home					
ICU					
None					
Nursing Home					
Other					
Other External					
Other Hospital					
Other ICU					
Other Internal					
Rehabilitation					
Skilled Nursing Facility					
Step-Down Unit (SDU)					
Telemetry					
unitdischargestatus, n (%)	Alive	-	0.323	0.326	< 0.001
	Expired				
hospitaldischargestatus, n (%)	None				
	Alive	0.195	0.210	0.122	< 0.001
	Expired				
	None				

S3.4 In-hospital mortality

Kaplan–Meier summaries are provided in Table S15. Survival curves and multivariable Cox model branch effects are shown in Fig. S7 and Fig. S8.

Table S15: Kaplan–Meier summary by branch (eICU-CRD).

branch_label	n	events	median_survival_days	7d_survival	30d_survival
A	2395	272	366.759	0.904	0.700
B	2006	149	57.860	0.943	0.652
C	21	2	inf	0.871	0.871

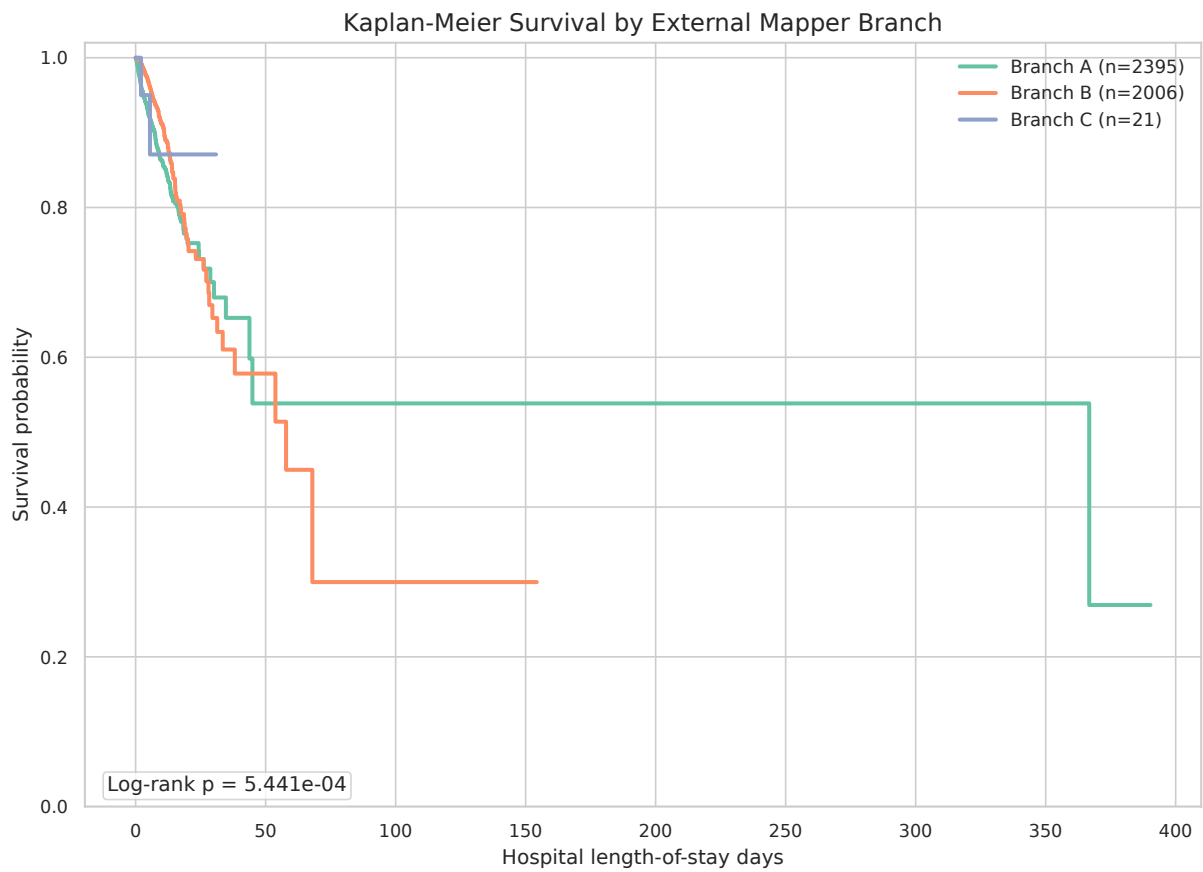


Fig. S7: Kaplan–Meier survival curves by major branch in external validation (eICU-CRD).

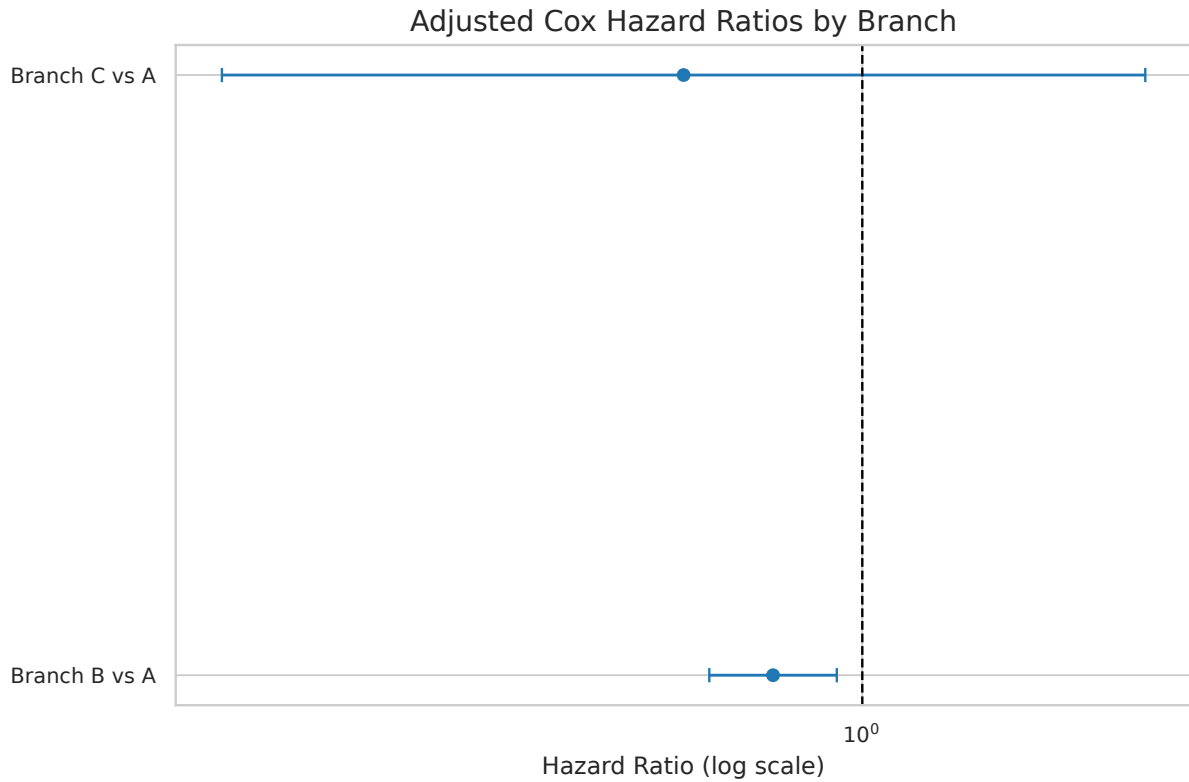


Fig. S8: Forest plot for branch effects in the multivariable Cox model (eICU-CRD external validation).

S3.5 AKI within 48 hours (AKI48h; KDIGO creatinine proxy)

Branch-level AKI48h rates are provided in Table S16. Full adjusted odds ratios are provided in Table S27.

Table S16: AKI48h (creatinine-only KDIGO proxy) by branch (eICU-CRD).

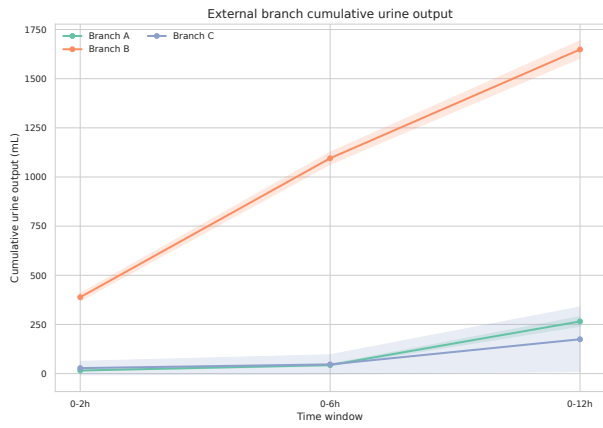
branch_label	n	followup_n	aki48_n	aki48_rate	stage2plus_n	stage2plus_rate	stage3_n	stage3_rate
A	2395	2219	518	0.216	105	0.044	78	0.033
B	2006	1921	325	0.162	33	0.016	23	0.011
C	21	20	6	0.286	6	0.286	6	0.286

S3.6 Dynamic response phenotypes

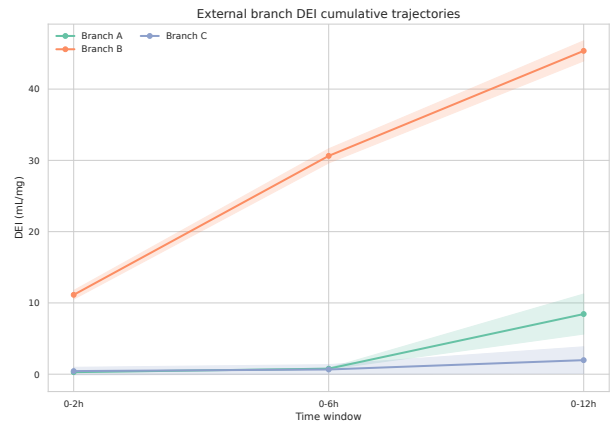
Dynamic response pattern rates and median segmented DEI increments are provided in Table S17. Cumulative urine output and DEI trajectories are shown in Fig. S9.

Table S17: Dynamic response pattern rates by branch (eICU-CRD).

branch_label	n	primary_nonresponse_rate	tachyphylaxis_rate	dei_0_2_median	dei_2_6_median	dei_6_12_median
A	2395	0.927	0.000	0.000	0.000	0.000
B	2006	0.330	0.082	7.500	14.688	10.000
C	21	0.857	0.000	0.000	0.000	0.000



(a) Cumulative urine output



(b) Cumulative DEI

Fig. S9: Dynamic response trajectories by major branch in external validation (eICU-CRD).

S3.7 Robustness and sensitivity analyses

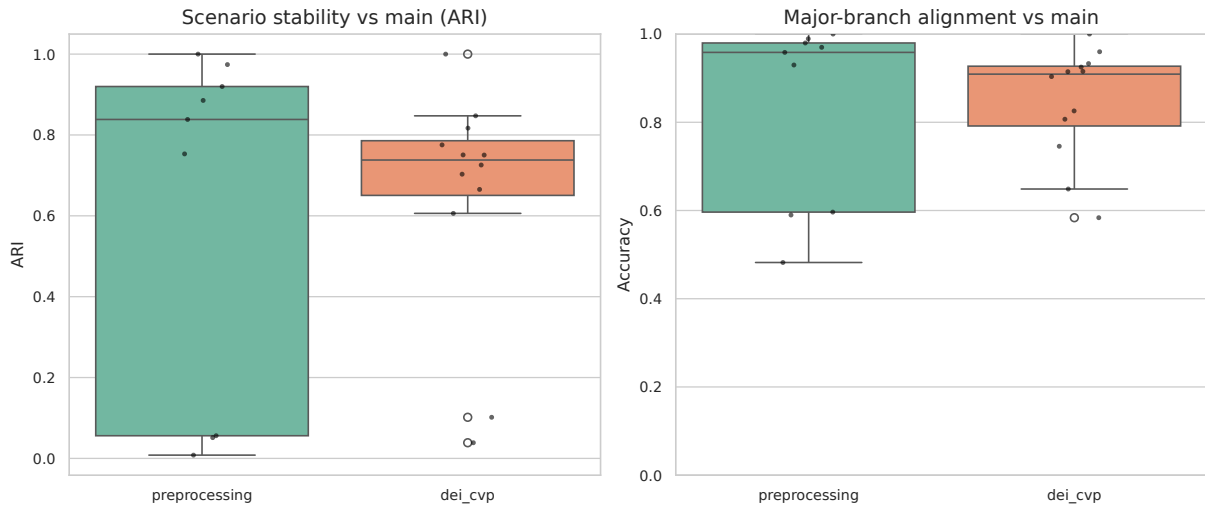


Fig. S10: Stability metrics across prespecified sensitivity scenarios in external validation (eICU-CRD).

S4 Model Diagnostics

S4.1 Cox proportional-hazards assumption

Schoenfeld residual-based proportional-hazards tests for the multivariable Cox models are summarized in Table S18 (MIMIC-IV) and Table S19 (eICU-CRD). The corresponding $-\log_{10}(p)$ visual summaries are shown in Fig. S11 and Fig. S12. In the main cohort, the Schoenfeld test did not indicate a departure from the PH assumption for branch B ($p = 0.104$); in external validation, the test indicated strong evidence against PH for branch B ($p = 3.3 \times 10^{-7}$), consistent with a time-varying branch effect in eICU-CRD. Accordingly, Cox branch hazard ratios in external validation are interpreted as time-averaged associations over follow-up.

Table S18: Cox proportional-hazards assumption test (Schoenfeld residuals; MIMIC-IV).

variable	test_statistic	p	$-\log_2(p)$
age_at_admit	4.536	0.033	4.913
branch_B	2.649	0.104	3.271
branch_C	0.294	0.588	0.767
branch_D	6.878	0.009	6.840
creatinine_baseline_mgdl	0.043	0.835	0.260
log_dose24	8.748	0.003	8.334
male	0.382	0.536	0.899
map_nearest_mmhg	3.923	0.048	4.392

Table S19: Cox proportional-hazards assumption test (Schoenfeld residuals; eICU-CRD).

variable	test_statistic	p	-log2(p)
age_at_admit	0.002	0.964	0.053
branch_B	26.045	3.335e-07	21.516
branch_C	0.852	0.356	1.490
creatinine_baseline_mgdl	8.857	0.003	8.420
log_dose24	0.019	0.890	0.168
male	0.317	0.574	0.802
map_nearest_mmhg	0.011	0.915	0.129

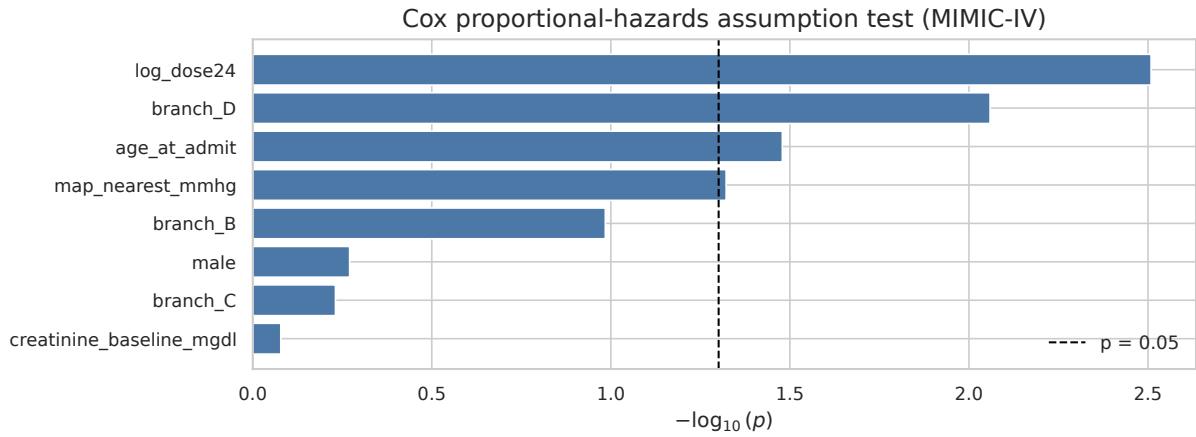


Fig. S11: Cox proportional-hazards assumption test summary for the main cohort (MIMIC-IV).

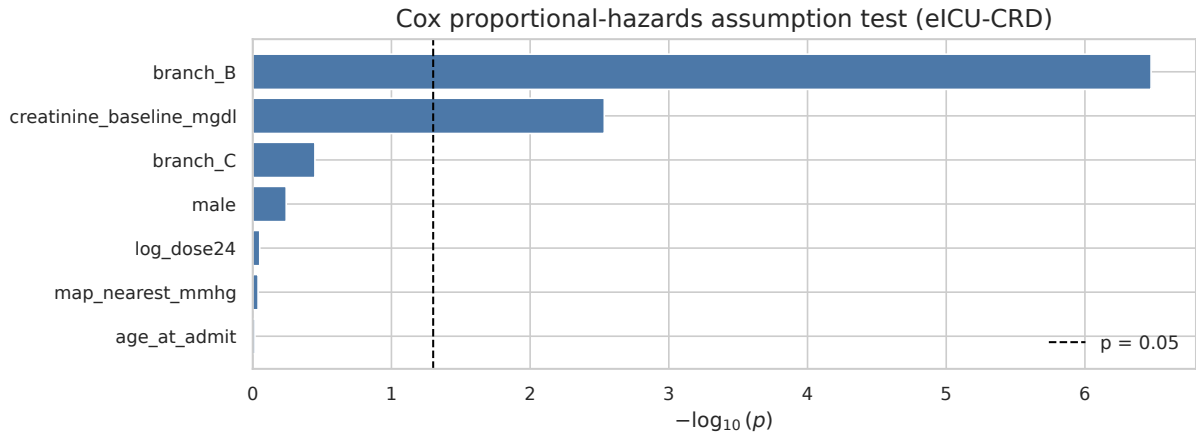


Fig. S12: Cox proportional-hazards assumption test summary for external validation (eICU-CRD).

S4.2 Logistic calibration

Calibration metrics based on 5-fold out-of-fold predictions are reported in Table S20 (MIMIC-IV) and Table S21 (eICU-CRD). Decile-based calibration curves are shown in Fig. S13 and Fig. S14.

Table S20: Logistic calibration metrics (out-of-fold predictions; MIMIC-IV).

Model	AUC	Brier	CITL	Calibration slope	Branch levels (incl. ref.)	CV folds
Base	0.708	0.077	-4.538e-05	0.961	1	5
Base + Branch	0.731	0.075	0.002	0.956	4	5

Table S21: Logistic calibration metrics (out-of-fold predictions; eICU-CRD).

Model	AUC	Brier	CITL	Calibration slope	Branch levels (incl. ref.)	CV folds
Base	0.627	0.085	-8.345e-04	0.875	1	5
Base + Branch	0.637	0.085	0.001	0.882	3	5

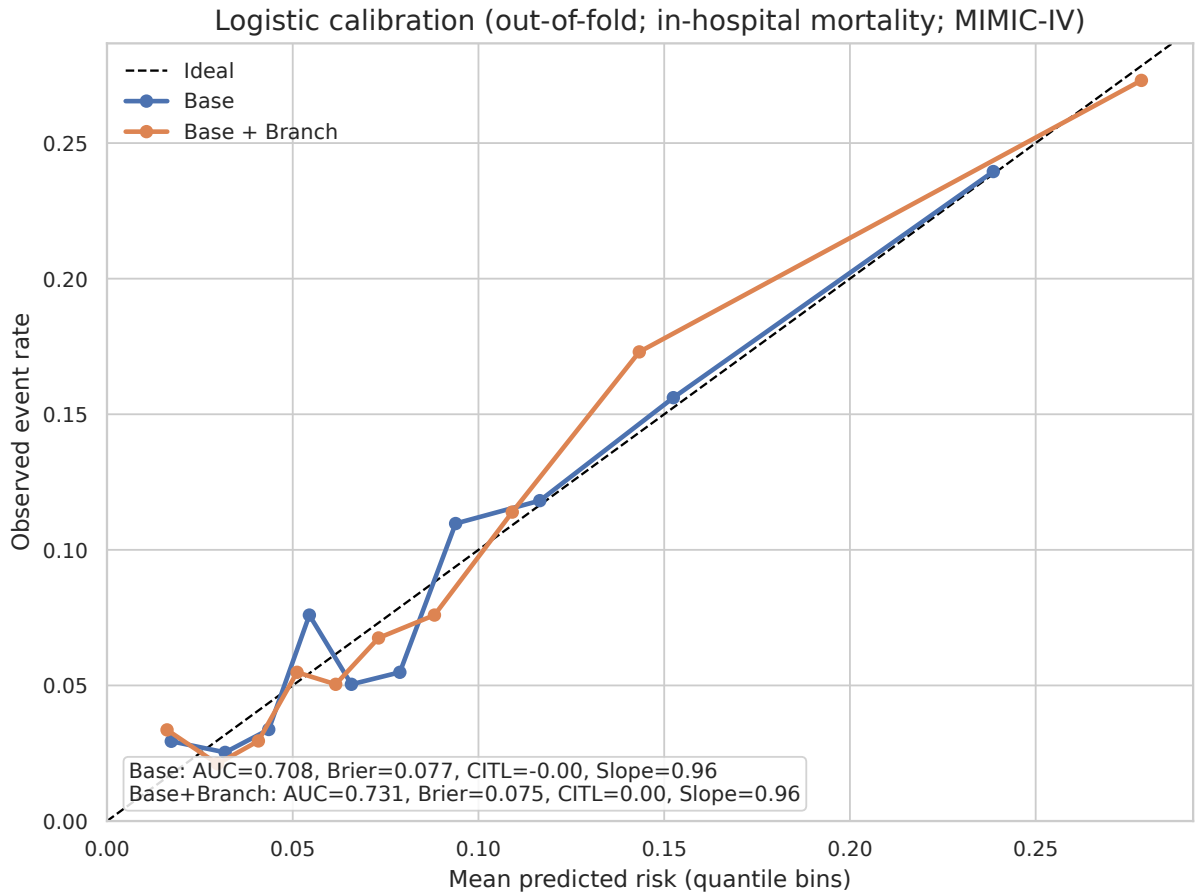


Fig. S13: Logistic calibration for in-hospital mortality in the main cohort (MIMIC-IV; out-of-fold predictions).

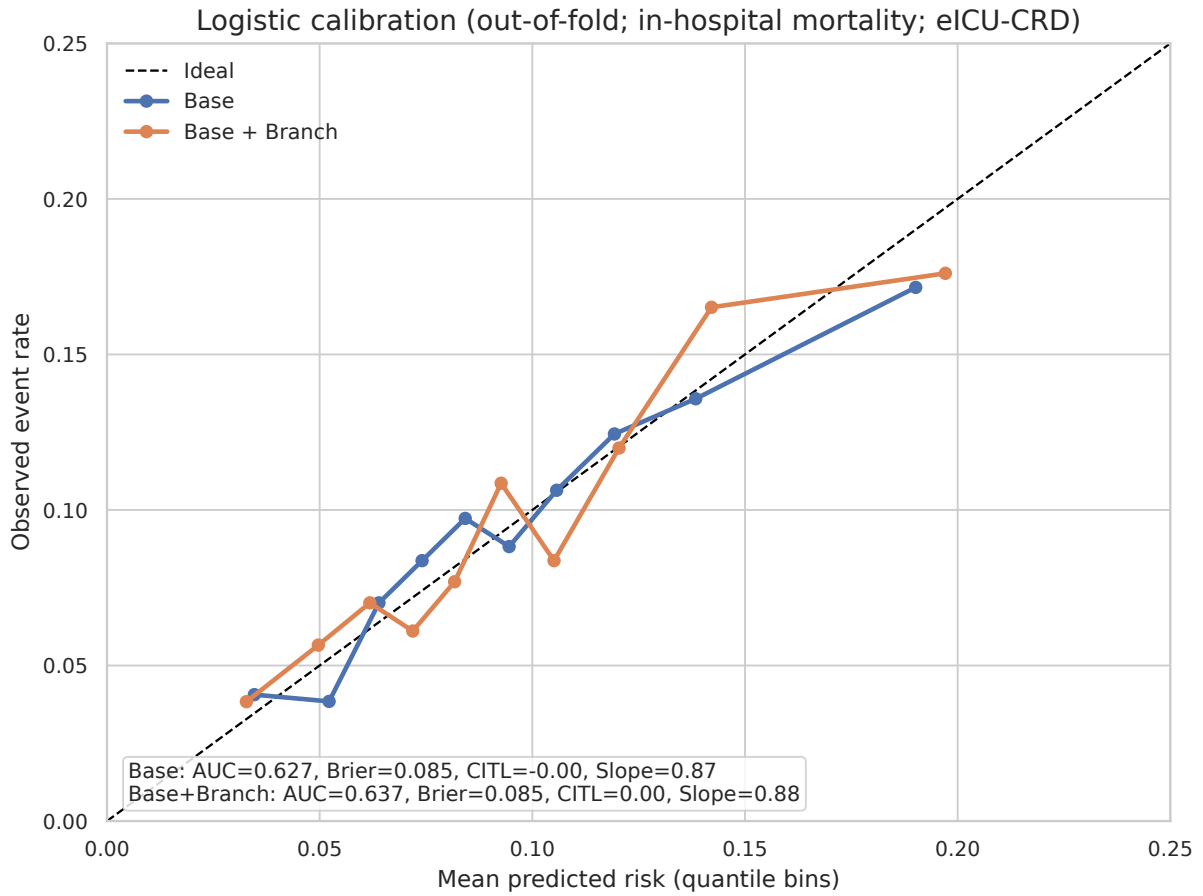


Fig. S14: Logistic calibration for in-hospital mortality in external validation (eICU-CRD; out-of-fold predictions).

S5 Supplementary Tables: Full Model Outputs

S5.1 Main cohort (MIMIC-IV)

Table S22: Multivariable Cox model coefficients for in-hospital mortality (MIMIC-IV).

Variable	Coef	SE	HR	HR L95	HR U95	z	P
age_at_admit	0.036	0.005	1.036	1.026	1.047	6.712	1.918e-11
male	0.030	0.127	1.031	0.804	1.321	0.240	0.810
creatinine_baseline_mgdl	0.081	0.068	1.085	0.950	1.238	1.200	0.230
map_nearest_mmhg	-0.010	0.004	0.990	0.981	0.998	-2.440	0.015
log_dose24	0.248	0.066	1.281	1.125	1.459	3.729	1.926e-04
branch_B	-0.241	0.182	0.786	0.550	1.122	-1.327	0.184
branch_C	0.821	0.248	2.272	1.398	3.692	3.311	9.292e-04
branch_D	1.452	0.265	4.270	2.541	7.176	5.481	4.241e-08

Table S23: Logistic regression odds ratios for in-hospital mortality (MIMIC-IV).

Variable	Model	OR	OR L95	OR U95	P
const	base	0.002	3.460e-04	0.008	5.977e-15
age_at_admit	base	1.042	1.028	1.056	1.320e-09
male	base	0.988	0.734	1.329	0.934
creatinine_baseline_mgdl	base	1.273	1.100	1.473	0.001
map_nearest_mmhg	base	0.985	0.974	0.995	0.003
log_dose24	base	1.451	1.257	1.674	3.558e-07
const	base_plus_branch	0.001	2.316e-04	0.006	2.418e-15
age_at_admit	base_plus_branch	1.044	1.030	1.058	5.246e-10
male	base_plus_branch	1.087	0.803	1.470	0.590
creatinine_baseline_mgdl	base_plus_branch	1.102	0.926	1.311	0.273
map_nearest_mmhg	base_plus_branch	0.987	0.977	0.997	0.012
log_dose24	base_plus_branch	1.500	1.267	1.777	2.619e-06
branch_B	base_plus_branch	0.772	0.485	1.229	0.276
branch_C	base_plus_branch	2.607	1.402	4.848	0.002
branch_D	base_plus_branch	4.831	2.551	9.149	1.331e-06

Table S24: Adjusted odds ratios for AKI48h (MIMIC-IV).

Variable	OR	OR L95	OR U95	P
const	0.075	0.029	0.195	1.082e-07
age_at_admit	1.002	0.995	1.010	0.523
male	0.913	0.748	1.114	0.370
creatinine_baseline_mgdl	1.403	1.233	1.596	2.635e-07
map_nearest_mmhg	1.000	0.994	1.007	0.925
log_dose24	1.206	1.078	1.349	0.001
branch_B	0.525	0.379	0.726	9.924e-05
branch_C	1.137	0.688	1.879	0.616
branch_D	1.227	0.684	2.201	0.493

S5.2 External validation (eICU-CRD)

Table S25: Multivariable Cox model coefficients for in-hospital mortality (eICU-CRD).

Variable	Coef	SE	HR	HR L95	HR U95	z	P
age_at_admit	0.020	0.004	1.021	1.014	1.028	5.854	4.787e-09
male	-0.006	0.090	0.994	0.833	1.186	-0.065	0.948
creatinine_baseline_mgdl	0.100	0.045	1.106	1.013	1.207	2.247	0.025
map_nearest_mmhg	-0.012	0.003	0.988	0.983	0.993	-4.494	6.985e-06
log_dose24	0.080	0.065	1.084	0.954	1.230	1.239	0.216
branch_B	-0.254	0.093	0.775	0.647	0.930	-2.743	0.006
branch_C	-0.509	0.671	0.601	0.161	2.240	-0.759	0.448

Table S26: Logistic regression odds ratios for in-hospital mortality (eICU-CRD).

Variable	Model	OR	OR L95	OR U95	P
const	base	0.050	0.018	0.140	1.277e-08
age_at_admit	base	1.019	1.011	1.027	6.234e-06
male	base	0.975	0.793	1.199	0.812
creatinine_baseline_mgdl	base	1.175	1.076	1.283	3.376e-04
map_nearest_mmhg	base	0.980	0.974	0.986	6.041e-11
log_dose24	base	1.227	1.054	1.429	0.008
const	base_plus_branch	0.063	0.022	0.178	1.817e-07
age_at_admit	base_plus_branch	1.018	1.010	1.027	1.304e-05
male	base_plus_branch	0.992	0.805	1.222	0.938
creatinine_baseline_mgdl	base_plus_branch	1.202	1.082	1.336	6.318e-04
map_nearest_mmhg	base_plus_branch	0.980	0.974	0.986	1.741e-10
log_dose24	base_plus_branch	1.189	1.022	1.385	0.025
branch_B	base_plus_branch	0.700	0.565	0.868	0.001
branch_C	base_plus_branch	0.294	0.056	1.553	0.149

Table S27: Adjusted odds ratios for AKI48h (eICU-CRD).

Variable	OR	OR L95	OR U95	P
const	0.075	0.035	0.159	1.343e-11
age_at_admit	1.003	0.997	1.008	0.335
male	0.899	0.768	1.052	0.183
creatinine_baseline_mgdl	1.414	1.306	1.530	1.331e-17
map_nearest_mmhg	1.002	0.998	1.006	0.380
log_dose24	1.133	1.008	1.274	0.037
branch_B	0.743	0.634	0.871	2.440e-04
branch_C	0.118	0.038	0.367	2.190e-04

S6 Supplementary Appendix: Reference Lists (MIMIC-IV)

S6.1 Itemid reference list

Table S28: MIMIC-IV itemid reference list used in feature extraction.

source_table	variable_group	itemid label	linksto	category	unitname
icu_d_items	iv_loop_diuretic_ inputevents	221794 Furosemide (Lasix)	inputevents	Medications	mg
icu_d_items	iv_loop_diuretic_ inputevents	228340 Furosemide (Lasix) 250/50	inputevents	Medications	mg
icu_d_items	iv_loop_diuretic_ inputevents	229639 Bumetanide (Bumex)	inputevents	Medications	mg
icu_d_items	urine_output_ outputevents	226557 R Ureteral Stent	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226558 L Ureteral Stent	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226559 Foley	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226560 Void	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226561 Condom Cath	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226563 Suprapubic	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226564 R Nephrostomy	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226565 L Nephrostomy	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226566 Urine and GU Irrigant Out	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226567 Straight Cath	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226584 Ileoconduit	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226627 OR Urine	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	226631 PACU Urine	outputevents	Output	mL
icu_d_items	urine_output_ outputevents	227489 GU Irrigant/Urine Volume Out	outputevents	Output	mL
icu_d_items	gu_irrigant_in_ outputevents	227488 GU Irrigant Volume In	outputevents	Output	mL
icu_d_items	map_chartevents	220052 Arterial Blood Pressure mean	chartevents	Routine Vital Signs	mmHg
icu_d_items	map_chartevents	220181 Non Invasive Blood Pressure mean	chartevents	Routine Vital Signs	mmHg
icu_d_items	cvp_chartevents	220074 Central Venous Pressure	chartevents	Hemodynamics	mmHg
hosp_d_labitems	creatinine_labevents	50912 Creatinine		Chemistry	
hosp_d_labitems	creatinine_labevents	52546 Creatinine		Chemistry	
hosp_d_labitems	bun_labevents	51006 Urea Nitrogen		Chemistry	
hosp_d_labitems	bun_labevents	52647 Urea Nitrogen		Chemistry	
hosp_d_labitems	sodium_labevents	50983 Sodium		Chemistry	
hosp_d_labitems	sodium_labevents	52623 Sodium		Chemistry	
hosp_d_labitems	ntprobnp_labevents	50963 NTproBNP		Chemistry	

S6.2 ICD-9 code reference list

Table S29: MIMIC-IV ICD code reference list used in cohort construction.

code_group	icd_code	long_title
acute_hf_icd9	42821	Acute systolic heart failure
acute_hf_icd9	42831	Acute diastolic heart failure
acute_hf_icd9	42843	Acute on chronic combined systolic and diastolic heart failure
acute_hf_icd9	42833	Acute on chronic diastolic heart failure
acute_hf_icd9	42823	Acute on chronic systolic heart failure
acute_hf_icd9	42841	Acute combined systolic and diastolic heart failure
sepsis_icd9_exclusion	0382	Pneumococcal septicemia [Streptococcus pneumoniae septicemia]
sepsis_icd9_exclusion	03843	Septicemia due to pseudomonas
sepsis_icd9_exclusion	03842	Septicemia due to escherichia coli [E. coli]
sepsis_icd9_exclusion	03849	Other septicemia due to gram-negative organisms
sepsis_icd9_exclusion	67022	Puerperal sepsis, delivered, with mention of postpartum complication
sepsis_icd9_exclusion	77181	Septicemia [sepsis] of newborn
sepsis_icd9_exclusion	0223	Anthrax septicemia
sepsis_icd9_exclusion	03841	Septicemia due to hemophilus influenzae [H. influenzae]
sepsis_icd9_exclusion	0389	Unspecified septicemia
sepsis_icd9_exclusion	0545	Herpetic septicemia
sepsis_icd9_exclusion	78552	Septic shock
sepsis_icd9_exclusion	99591	Sepsis
sepsis_icd9_exclusion	03812	Methicillin resistant Staphylococcus aureus septicemia
sepsis_icd9_exclusion	03810	Staphylococcal septicemia, unspecified
sepsis_icd9_exclusion	67024	Puerperal sepsis, postpartum condition or complication
sepsis_icd9_exclusion	03819	Other staphylococcal septicemia
sepsis_icd9_exclusion	0383	Septicemia due to anaerobes
sepsis_icd9_exclusion	0388	Other specified septicemias
sepsis_icd9_exclusion	67020	Puerperal sepsis, unspecified as to episode of care or not applicable
sepsis_icd9_exclusion	0031	Salmonella septicemia
sepsis_icd9_exclusion	0380	Streptococcal septicemia
sepsis_icd9_exclusion	03811	Methicillin susceptible Staphylococcus aureus septicemia
sepsis_icd9_exclusion	03840	Septicemia due to gram-negative organism, unspecified
sepsis_icd9_exclusion	03844	Septicemia due to serratia
sepsis_icd9_exclusion	99592	Severe sepsis
esrd_dialysis_icd9_exclusion	40413	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	40311	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	40391	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	V4511	Renal dialysis status
esrd_dialysis_icd9_exclusion	V4512	Noncompliance with renal dialysis
esrd_dialysis_icd9_exclusion	V568	Encounter for other dialysis
esrd_dialysis_icd9_exclusion	40492	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	V451	Renal dialysis status
esrd_dialysis_icd9_exclusion	40402	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	40403	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	40412	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	40493	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
esrd_dialysis_icd9_exclusion	5856	End stage renal disease
esrd_dialysis_icd9_exclusion	V560	Encounter for extracorporeal dialysis

(continued)

code_group	icd_code	long_title
esrd_dialysis_icd9_exclusion	V5631	Encounter for adequacy testing for hemodialysis
esrd_dialysis_icd9_exclusion	V5632	Encounter for adequacy testing for peritoneal dialysis
esrd_dialysis_icd9_exclusion	40301	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease
