Supplementary Information

Early physiologic trajectory classes show concordant mortality associations among critically ill adults with operational stage 4 cardiovascular–kidney–metabolic syndrome

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Supplementary Methods

Reporting boundary and frozen analytical sequence

The study population was an algorithm-defined operational stage 4 cardiovascular–kidney–metabolic (CKM) syndrome electronic health record cohort rather than a clinically adjudicated disease cohort. No independent clinical reference-standard validation was performed; sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were therefore not estimated. MIMIC-IV version 3.1 was the derivation database and eICU Collaborative Research Database version 2.0 was the frozen transport database. The databases were analyzed separately.

Protocol version CKM_TRAJECTORY_PROTOCOL_V1.5 governed the analysis. Outcome-blind cohort construction, preprocessing, selection of the three-class k-means solution, and freezing of the MIMIC preprocessing parameters and centroids preceded outcome analysis. The V1.5 correction removed records with an unknown hospital outcome or hospital-discharge timing incompatible with the 24-hour landmark risk set; it did not retrain or reselect the class solution.

Operational CKM stage 4 definition and cohort assembly

Operational CKM stage 4 required a recorded cardiovascular disease component before the index ICU admission together with diabetes, hypertension, or chronic kidney disease/renal failure. In MIMIC-IV, qualifying diagnoses came only from hospitalizations ending before the index ICU admission. Diagnoses arising during the index hospitalization were not used to establish eligibility. In eICU-CRD, only prespecified structured `pastHistory` entries were used. Obesity, dyslipidemia, and metabolic syndrome were not used as common-core eligibility components because corresponding structured eICU paths were unavailable.

Construct	MIMIC-IV ICD-9-CM	MIMIC-IV ICD-10-CM	eICU-CRD structured pastHistory entries
Coronary disease or prior myocardial infarction	410–414	I20–I25	Myocardial Infarction; Angina; Procedural Coronary Intervention; Coronary Artery Bypass
Heart failure	428	I50	Congestive Heart Failure
Atrial fibrillation	42731	I48	Atrial Fibrillation
Stroke	430–438	I60–I69	Strokes
Peripheral arterial disease	440–444	I70; I738–I739	Peripheral Vascular Disease
Diabetes	250	E10–E14	Insulin Dependent Diabetes; Non-Insulin Dependent

Construct	MIMIC-IV ICD-9-CM	MIMIC-IV ICD-10-CM	eICU-CRD structured pastHistory entries
			Diabetes
Hypertension	401–405	I10–I16	Hypertension Requiring Treatment
Chronic kidney disease or renal failure	585	N18	Renal Failure
CKM stage 4b	5856; V4511	N186; Z992	Renal failure—hemodialysis; Renal failure—peritoneal dialysis

Each patient contributed one deterministic index ICU stay. MIMIC-IV used the chronologically earliest ICU stay. eICU-CRD first required `unitvisitnumber=1` and then applied a deterministic patient-level record rule; deidentified identifier order within the same year was not interpreted as clinical chronology. Adults younger than 18 years and records with invalid or zero ICU duration were excluded.

Time axis, trajectory variables, and deterministic aggregation

Time zero was ICU admission. The trajectory window comprised four fixed bins: [0,6), [6,12), [12,18), and [18,24) hours. Physiologically implausible values were set to missing before aggregation and were not truncated to the nearest boundary. Repeated valid measurements within a bin were summarized by the median. Within a MIMIC patient, timestamp, and variable, simultaneous valid source-item values were first averaged before bin-level aggregation. eICU MAP combined valid `vitalperiodic.systemicmean` and `vitalaperiodic.noninvasivemean` measurements without source priority.

Variable	MIMIC-IV source	eICU-CRD source	Unit	Valid range	Prespecified aggregation
Heart rate	chartevents	vitalperiodic.heartrate	beats/min	20–250	Median in each 6-hour bin
Mean arterial pressure	chartevents	vitalperiodic.systemicmean; vitalaperiodic.noninvasivemean	mmHg	20–200	Median in each 6-hour bin
Oxygen saturation	chartevents	vitalperiodic.sao2	%	40–100	Median in each 6-hour bin
Respiratory rate	chartevents	vitalperiodic.respiration	breaths/min	4–80	Median in each 6-hour bin
Creatinine	labevents.itemid=50912	lab.labname='creatinine'	mg/dL	0.1–30	First valid value in 0–24 hours; descriptor and common-core eligibility only
Glucose	labevents.itemid=50931; chartevents.itemid 225664, 220621, or 226537	lab.labname glucose or bedside glucose	mg/dL	20–1000	First valid value in 0–24 hours; descriptor and common-core eligibility only

For each vital sign, at least three bins had to be observed. A single internal missing bin was linearly interpolated; a single missing boundary bin was filled with the nearest observed bin. Patients with at least two missing bins for any vital sign or without an eligible creatinine or glucose value were excluded from the common-core sample. Creatinine and glucose were not used to form the final classes.

Frozen representation and transport

The 16-dimensional clustering vector contained four bins for each of MAP, heart rate, oxygen saturation, and respiratory rate, in that order. MIMIC-derived 0.5th and 99.5th percentile winsorization limits were applied first. Each dimension was then robustly standardized using its MIMIC median and interquartile

range. Every four-bin vital-sign vector was multiplied by 0.5 so that the four physiologic domains had equal nominal contributions to squared Euclidean distance.

Candidate K values from 2 to 6 were assessed using outcome-blind consensus k-means. Each K used 100 repetitions of an 80% patient subsample and at least 50 random starts. Candidate solutions were rejected if any class contained less than 5% of patients or bootstrap Jaccard stability was below 0.75. The smallest K was preferred when ambiguity was indistinguishable. Stability was quantified using 200 patient-level bootstrap samples.

An initial 18-dimensional model that also included first creatinine and glucose was rejected before outcome access because a single creatinine dimension contributed 99.875% of centroid separation. The final K=3 solution therefore used only the 16 repeated vital-sign features. For eICU-CRD, MIMIC winsorization limits, scaling parameters, domain weights, K, and centroids were applied unchanged. Each eICU patient was assigned to the nearest MIMIC centroid; no eICU reclustering or parameter refitting was performed.

Landmark outcome, covariates, and inference

The mortality association risk set required both the ICU record and hospital-discharge time to extend strictly beyond 24 hours, no recorded death at or before 24 hours, and an observed hospital outcome. MIMIC-IV admissions with `hospital_expire_flag=1` but a missing death time and eICU-CRD stays with missing or nonstandard hospital-discharge status were outcome-indeterminate rather than non-events. Records whose hospital-discharge time or offset was at or before 24 hours despite an ICU record extending beyond 24 hours were treated as time-axis conflicts and excluded. The common outcome was observed in-hospital death strictly after the 24-hour landmark.

MIMIC-IV adjustment variables were age modeled with a centered four-degree-of-freedom natural cubic spline, sex, the prespecified cardiovascular and CKM components, CKM stage 4b status, admission source, first ICU type, and deidentified calendar-year group. eICU-CRD used the analogous clinical variables plus admission source, ICU type, discharge year, hospital size category, region, and teaching status. Variables arising during the trajectory window were not treated as baseline confounders.

Database-specific logistic regression models estimated marginal standardized post-landmark mortality risks by frozen class. MIMIC-IV used HC3 covariance and eICU-CRD used hospital-clustered HC1 covariance. Pairwise risk differences and risk ratios used class 1 as the prespecified reference; 95% confidence intervals were obtained from 10,000 multivariate-normal parameter draws. The overall class-term Wald test preceded the pairwise contrasts, whose coefficient P values were controlled using the Benjamini–Hochberg procedure. These estimates describe observational associations and not causal effects of class membership.

Prespecified MIMIC sensitivity analyses added obesity to the adjustment set, restricted the sample to complete four-bin trajectories, used linear rather than spline-modeled age, and assessed interaction by CKM stage 4a/4b. Versioned post-primary analyses evaluated no-imputation partial-distance assignment, alternative K values, a full-covariance three-component Gaussian mixture model, inclusion weighting within the observed-outcome landmark risk set, a vital-sign–eligible cohort that did not require creatinine or glucose measurements, and leave-one-hospital-out eICU estimates. None was eligible to replace the frozen primary K=3 common-core analysis.

Supplementary Table S1. Complete participant characteristics by frozen class

Values are median [interquartile range] or n (%). These data are descriptive; no between-class P values are reported.

Panel A. MIMIC-IV

Characteristic	Overall	Class 1	Class 2	Class 3
Age, years	75.0 [66.0, 83.0]	75.0 [67.0, 83.0]	76.0 [67.0, 84.0]	71.0 [62.0, 81.0]
Female sex	3,214 (41.7%)	1,646 (40.8%)	874 (44.4%)	694 (40.7%)
Coronary heart disease or myocardial infarction	4,753 (61.7%)	2,728 (67.6%)	1,091 (55.4%)	934 (54.7%)
Heart failure	3,485 (45.2%)	1,896 (47.0%)	934 (47.4%)	655 (38.4%)
Atrial fibrillation	2,866 (37.2%)	1,446 (35.9%)	820 (41.6%)	600 (35.2%)
Stroke	1,495 (19.4%)	742 (18.4%)	355 (18.0%)	398 (23.3%)
Peripheral arterial disease	1,757 (22.8%)	964 (23.9%)	445 (22.6%)	348 (20.4%)
Diabetes	3,671 (47.6%)	1,958 (48.5%)	929 (47.2%)	784 (46.0%)
Hypertension	7,324 (95.0%)	3,831 (95.0%)	1,852 (94.1%)	1,641 (96.2%)
Chronic kidney disease	2,977 (38.6%)	1,591 (39.4%)	734 (37.3%)	652 (38.2%)
Operational CKM stage 4b	548 (7.1%)	301 (7.5%)	119 (6.0%)	128 (7.5%)

Panel B. eICU-CRD

Characteristic	Overall	Class 1	Class 2	Class 3
Age, years	73.0 [63.0, 81.0]	74.0 [65.0, 82.0]	73.0 [64.0, 82.0]	70.0 [61.0, 79.0]
Female sex	9,303 (42.5%)	3,726 (42.4%)	2,626 (43.7%)	2,951 (41.7%)
Myocardial infarction	5,049 (23.1%)	2,136 (24.3%)	1,307 (21.8%)	1,606 (22.7%)
Heart failure	8,423 (38.5%)	3,489 (39.7%)	2,559 (42.6%)	2,375 (33.6%)
Atrial fibrillation	6,721 (30.7%)	2,669 (30.4%)	2,048 (34.1%)	2,004 (28.3%)
Coronary artery bypass	3,546 (16.2%)	1,531 (17.4%)	948 (15.8%)	1,067 (15.1%)
Percutaneous coronary intervention	4,132 (18.9%)	1,773 (20.2%)	965 (16.1%)	1,394 (19.7%)
Angina	1,654 (7.6%)	778 (8.9%)	366 (6.1%)	510 (7.2%)
Stroke	4,807 (22.0%)	1,787 (20.3%)	1,234 (20.5%)	1,786 (25.3%)
Peripheral vascular disease	2,878 (13.2%)	1,254 (14.3%)	759 (12.6%)	865 (12.2%)
Diabetes	10,410 (47.6%)	4,316 (49.1%)	2,838 (47.2%)	3,256 (46.1%)
Hypertension	19,024 (87.0%)	7,543 (85.8%)	5,161 (85.9%)	6,320 (89.4%)
Renal failure	2,218 (10.1%)	1,015 (11.5%)	562 (9.4%)	641 (9.1%)
Operational CKM stage 4b	1,422 (6.5%)	671 (7.6%)	344 (5.7%)	407 (5.8%)

Supplementary Table S2. Measurement coverage by database and frozen class

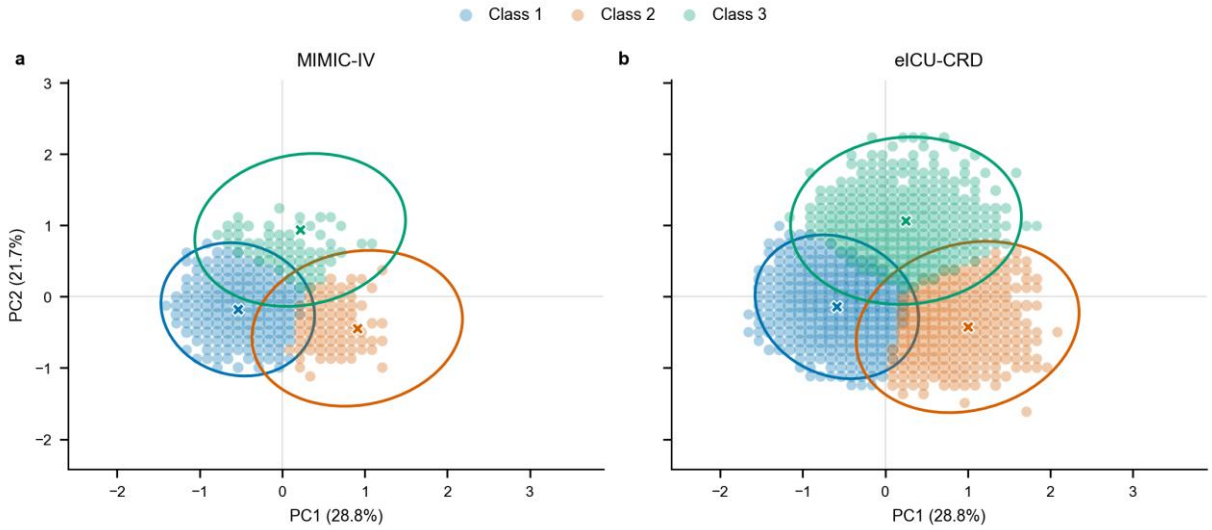
Coverage is shown for the outcome-blind structural samples used to define or receive the frozen class assignment.

Database	Group	Variable	Coverage definition	n	Denominator	Proportion
MIMIC-IV	Overall	MAP	3 of 4 observed bins	7,738	7,738	100.0%
MIMIC-IV	Overall	MAP	4 of 4 observed bins	7,550	7,738	97.6%
MIMIC-IV	Overall	Heart rate	3 of 4 observed bins	7,738	7,738	100.0%
MIMIC-IV	Overall	Heart rate	4 of 4 observed bins	7,574	7,738	97.9%
MIMIC-IV	Overall	SpO2	3 of 4 observed bins	7,738	7,738	100.0%
MIMIC-IV	Overall	SpO2	4 of 4 observed bins	7,538	7,738	97.4%
MIMIC-IV	Overall	Respiratory rate	3 of 4 observed bins	7,738	7,738	100.0%
MIMIC-IV	Overall	Respiratory rate	4 of 4 observed bins	7,554	7,738	97.6%
MIMIC-IV	Class 1	MAP	3 of 4 observed bins	4,043	4,043	100.0%
MIMIC-IV	Class 1	MAP	4 of 4 observed bins	3,914	4,043	96.8%
MIMIC-IV	Class 1	Heart rate	3 of 4 observed bins	4,043	4,043	100.0%
MIMIC-IV	Class 1	Heart rate	4 of 4 observed bins	3,923	4,043	97.0%
MIMIC-IV	Class 1	SpO2	3 of 4 observed bins	4,043	4,043	100.0%
MIMIC-IV	Class 1	SpO2	4 of 4 observed bins	3,907	4,043	96.6%
MIMIC-IV	Class 1	Respiratory rate	3 of 4 observed bins	4,043	4,043	100.0%
MIMIC-IV	Class 1	Respiratory rate	4 of 4 observed bins	3,916	4,043	96.9%
MIMIC-IV	Class 2	MAP	3 of 4 observed bins	1,985	1,985	100.0%
MIMIC-IV	Class 2	MAP	4 of 4 observed bins	1,951	1,985	98.3%
MIMIC-IV	Class 2	Heart rate	3 of 4 observed bins	1,985	1,985	100.0%
MIMIC-IV	Class 2	Heart rate	4 of 4 observed bins	1,960	1,985	98.7%
MIMIC-IV	Class 2	SpO2	3 of 4 observed bins	1,985	1,985	100.0%
MIMIC-IV	Class 2	SpO2	4 of 4 observed bins	1,945	1,985	98.0%
MIMIC-IV	Class 2	Respiratory rate	3 of 4 observed bins	1,985	1,985	100.0%
MIMIC-IV	Class 2	Respiratory rate	4 of 4 observed bins	1,955	1,985	98.5%
MIMIC-IV	Class 3	MAP	3 of 4 observed bins	1,710	1,710	100.0%
MIMIC-IV	Class 3	MAP	4 of 4 observed bins	1,685	1,710	98.5%
MIMIC-IV	Class 3	Heart rate	3 of 4 observed bins	1,710	1,710	100.0%
MIMIC-IV	Class 3	Heart rate	4 of 4 observed bins	1,691	1,710	98.9%
MIMIC-IV	Class 3	SpO2	3 of 4 observed bins	1,710	1,710	100.0%
MIMIC-IV	Class 3	SpO2	4 of 4 observed bins	1,686	1,710	98.6%
MIMIC-IV	Class 3	Respiratory rate	3 of 4 observed bins	1,710	1,710	100.0%
MIMIC-IV	Class 3	Respiratory rate	4 of 4 observed bins	1,683	1,710	98.4%
eICU-CRD	Overall	MAP	3 of 4 observed bins	22,118	22,118	100.0%
eICU-CRD	Overall	MAP	4 of 4 observed bins	21,791	22,118	98.5%
eICU-CRD	Overall	Heart rate	3 of 4 observed bins	22,118	22,118	100.0%
eICU-CRD	Overall	Heart rate	4 of 4 observed bins	21,862	22,118	98.8%
eICU-CRD	Overall	SpO2	3 of 4 observed	22,118	22,118	100.0%

Database	Group	Variable	Coverage definition	n	Denominator	Proportion
			bins			
eICU-CRD	Overall	SpO2	4 of 4 observed bins	21,566	22,118	97.5%
eICU-CRD	Overall	Respiratory rate	3 of 4 observed bins	22,118	22,118	100.0%
eICU-CRD	Overall	Respiratory rate	4 of 4 observed bins	21,478	22,118	97.1%
eICU-CRD	Class 1	MAP	3 of 4 observed bins	8,887	8,887	100.0%
eICU-CRD	Class 1	MAP	4 of 4 observed bins	8,764	8,887	98.6%
eICU-CRD	Class 1	Heart rate	3 of 4 observed bins	8,887	8,887	100.0%
eICU-CRD	Class 1	Heart rate	4 of 4 observed bins	8,779	8,887	98.8%
eICU-CRD	Class 1	SpO2	3 of 4 observed bins	8,887	8,887	100.0%
eICU-CRD	Class 1	SpO2	4 of 4 observed bins	8,681	8,887	97.7%
eICU-CRD	Class 1	Respiratory rate	3 of 4 observed bins	8,887	8,887	100.0%
eICU-CRD	Class 1	Respiratory rate	4 of 4 observed bins	8,630	8,887	97.1%
eICU-CRD	Class 2	MAP	3 of 4 observed bins	6,095	6,095	100.0%
eICU-CRD	Class 2	MAP	4 of 4 observed bins	6,010	6,095	98.6%
eICU-CRD	Class 2	Heart rate	3 of 4 observed bins	6,095	6,095	100.0%
eICU-CRD	Class 2	Heart rate	4 of 4 observed bins	6,037	6,095	99.0%
eICU-CRD	Class 2	SpO2	3 of 4 observed bins	6,095	6,095	100.0%
eICU-CRD	Class 2	SpO2	4 of 4 observed bins	5,971	6,095	98.0%
eICU-CRD	Class 2	Respiratory rate	3 of 4 observed bins	6,095	6,095	100.0%
eICU-CRD	Class 2	Respiratory rate	4 of 4 observed bins	5,926	6,095	97.2%
eICU-CRD	Class 3	MAP	3 of 4 observed bins	7,136	7,136	100.0%
eICU-CRD	Class 3	MAP	4 of 4 observed bins	7,017	7,136	98.3%
eICU-CRD	Class 3	Heart rate	3 of 4 observed bins	7,136	7,136	100.0%
eICU-CRD	Class 3	Heart rate	4 of 4 observed bins	7,046	7,136	98.7%
eICU-CRD	Class 3	SpO2	3 of 4 observed bins	7,136	7,136	100.0%
eICU-CRD	Class 3	SpO2	4 of 4 observed bins	6,914	7,136	96.9%
eICU-CRD	Class 3	Respiratory rate	3 of 4 observed bins	7,136	7,136	100.0%
eICU-CRD	Class 3	Respiratory rate	4 of 4 observed bins	6,922	7,136	97.0%

Supplementary Figure S1. Two-dimensional projection of the frozen 16-feature representation

a, MIMIC-IV projection from a principal-component analysis fitted in the frozen MIMIC feature space. **b,** eICU-CRD projected with the unchanged MIMIC loadings. PC1 and PC2 explain 28.8% and 21.7% of MIMIC variance. Bubbles are fixed-grid aggregate cells with at least 10 patients; crosses mark class means and outlines show descriptive 90% Gaussian reference ellipses. Substantial overlap is visible. The projection was not used for clustering, validation, or outcome analysis.


Class 1
Class 2
Class 3
a
MIMIC-IV
b
eICU-CRD
PC2 (21.7%)
PC1 (28.8%)
PC1 (28.8%)