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Association Between the Endothelial Activation and Stress Index and All-Cause Mortality in Critically Ill Patients with Stage 4 Cardiovascular-Kidney-Metabolic Syndrome: A Retrospective Cohort Study Based on MIMIC-IV and External Validation in eICU-CRD

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Abstract

Objective

To investigate the association between the endothelial activation and stress index (EASIX) measured within 24 hours of admission to the intensive care unit (ICU) and 30-, 90- and 365-day all-cause mortality in patients with stage 4 cardiovascular-kidney-metabolic (CKM) syndrome, and to characterize the shape of this association as it changes with time since admission.

Methods

Retrospective cohort study; data were obtained from MIMIC-IV. Adults who met stage 4 CKM criteria at ICU admission, survived to 24 hours after admission, and had EASIX measurable within 24 hours were included. The first EASIX value within 0–24 hours was taken, and $\log_2$(EASIX) was used as a continuous exposure. The primary outcome was 30-day all-cause mortality, and the secondary outcomes were 90-day and 365-day all-cause mortality. Cox proportional hazards models were used, with adjustment from M1 (unadjusted) to M4 (fully adjusted); the proportional hazards assumption was tested with scaled Schoenfeld residuals, categorical covariates violating the assumption were changed to stratification factors, continuous covariates were entered with a time-varying coefficient ($\gamma \times \ln t$), and hazard ratios (HRs) were reported at different time points. Restricted cubic splines, quartile analysis and directly standardized survival curves were also fitted, and subgroup analysis and E-value analysis were performed. Patients with stage 4 CKM were identified in eICU-CRD by an approximate definition for external validation; the endpoint in that database was all-cause mortality during hospitalization.

Results

A total of 9,766 patients with stage 4 CKM were finally included. Median age was 71 (61–81) years, 5,694 patients (58.3%) were male, and median EASIX was 2.1 (1.0–5.0). All-cause deaths at 30, 90 and 365 days were 2,278 (23.3%), 2,938 (30.1%) and 3,802 (38.9%), respectively. In the fully adjusted model, for each doubling of EASIX, the HR for 30-day mortality was 1.243 (95%CI 1.182–1.306) at 1 day after admission and 1.131 (1.079–1.185) at 30 days, and decreased with longer time since admission (γ = −0.0277, P = 0.026); for the 365-day outcome, the HR at the 365-day time point was 1.038 (0.993–1.086). For each 1-standard-deviation increase in $\log_2$(EASIX) (1.861), the HR for 30-day mortality was 1.257 (1.152–1.372). Compared with Q1, the HR for 30-day mortality in Q4 was 1.660 (1.273–2.164), and the differences of Q2 and Q3 from Q1 were not statistically significant. The P values of the non-linearity test were 0.002 to < 0.001. Among the 9 subgroups, at the 30-day time point the interaction was statistically significant for heart failure, SOFA-4 and malignancy (P = 0.003, < 0.001, 0.039), and CKM stage 4a/4b did not reach significance (0.079). In the type 2 diabetes subgroup (n = 3,459), comparing the highest with the lowest quartile, the HR for 30-day mortality was 1.704 (1.061–2.735). The E value estimated at the 30-day time point was 1.40 (1.29). External validation included 1,103 patients, 173 of whom died during

hospitalization (15.7%); after full adjustment, the HR of each doubling of EASIX for in-hospital death was 1.121 (1.045–1.203).

Conclusions

In ICU patients with stage 4 CKM, a higher EASIX calculated within 24 hours of admission was associated with a higher risk of all-cause mortality; the association was strongest early after admission and decreased over time, and was more evident in the higher EASIX range. In eICU-CRD the direction of this association was consistent, but the endpoint in that database was in-hospital mortality, which does not constitute a replication on the 30-day endpoint. The above findings should be interpreted as a descriptive association rather than a validated risk stratification tool; prospective validation on a consistent endpoint is still required before clinical implementation.

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome refers to a continuum in which obesity and abnormal glucose metabolism, chronic kidney disease (CKD) and cardiovascular disease drive each other and progress stepwise; in 2023 the American Heart Association formally defined it as an independent syndrome, and divided it into stages 0–4 according to the presence or absence of subclinical or clinical cardiovascular disease and the presence or absence of kidney failure [1]. Stage 4 refers to those who already have clinical cardiovascular disease (coronary heart disease, heart failure, stroke, atrial fibrillation, peripheral artery disease) and also have metabolic risk factors or CKD, and is further divided into stage 4a without kidney failure and stage 4b with kidney failure; the mortality risk of this stage is the highest among all stages, and the damage involves the vasculature, heart, kidney and metabolic regulation simultaneously [1].

Endothelial dysfunction is considered one of the common pathways linking the above components. In CKD, decreased nitric oxide bioavailability, enhanced oxidative stress, and accumulation of advanced glycation end products and uremic toxins together lead to endothelial activation, increased permeability and a switch to a procoagulant phenotype [2]; under acute insults, endothelial activation further causes microcirculatory disturbance, leukocyte adhesion and microthrombus formation, and is one of the core components of sepsis-related organ dysfunction [3]. EASIX (endothelial activation and stress index) was constructed from this: LDH × creatinine / platelets, all three taken from routine tests at admission, reflecting cell injury and turnover, glomerular filtration, and coagulation and inflammatory consumption, respectively; it was initially used to describe the mortality risk of acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation [4]. Since then EASIX has been progressively applied to other settings with endothelial disturbance: in septic ICU patients it was associated with 28-day and 90-day mortality [5], in ICU patients with coronary heart disease with 30-day and 365-day mortality [6], in patients with acute kidney injury with 1-year and ICU mortality [7], and in severe COVID-19, after age adjustment, with ICU mortality [8]. These studies covered a single disease or a single organ injury, and

mostly summarized the association with a single hazard ratio within a certain follow-up period; whereas in critically ill patients the relation between exposure and outcome often changes over time, the proportional hazards assumption does not hold, and a single hazard ratio is only the average over the whole period, which underestimates the association early and overestimates it late [9]; the length of follow-up itself is also sufficient to produce apparent differences in conclusions. In the dimension of CKM staging, the current report comes from a community population with stages 0–3 (National Health and Nutrition Examination Survey, n = 10,885): for each 1-unit increase in EASIX, the HR was 1.41 (95%CI 1.24–1.61) for all-cause mortality and 1.30 (1.13–1.49) for cardiovascular mortality, and no non-linearity was seen for all-cause mortality [10]. That population had not yet developed clinical cardiovascular disease, the median follow-up was 97 months, and what was reported was the average effect over a long follow-up; the stage 4 population, which already has clinical cardiovascular disease and is admitted to the ICU for acute problems, is not included, and the mortality risk of this group is the highest among all CKM stages, with its endothelial burden superimposed on chronic metabolic and kidney damage plus acute insults, and the early distribution of risk also differs from that of stages 0–3.

On this basis, the present study used MIMIC-IV and eICU-CRD to investigate whether EASIX within 24 hours of admission is associated with 30-, 90- and 365-day all-cause mortality in critically ill patients with stage 4 cardiovascular-kidney-metabolic syndrome, and what shape this association takes at different time points.

Methods

Data Source and Study Population

Data were obtained from the MIMIC-IV database [11], and only the first ICU admission record of each patient was used. Stage 4 CKM was operationalized as: the presence of clinical cardiovascular disease (one of myocardial infarction, coronary heart disease, heart failure, stroke, atrial fibrillation, peripheral artery disease) together with at least one metabolic or kidney condition (hypertension, BMI ≥ 25 kg/m², metabolic syndrome with ≥ 3 components, type 2 diabetes, estimated glomerular filtration rate < 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, urinary albumin/creatinine ratio ≥ 30 mg/g). The study population comprised adult patients who already met the above definition at ICU admission, survived to 24 hours after admission, and had all three tests of LDH, creatinine and platelet count completed within 0–24 hours of admission. Those with a negative survival time were excluded.

Time zero was the time of ICU admission. Era information used the era grouping variable provided by the database (2008–2010, 2011–2013, 2014–2016, 2017–2019, 2020–2022). Reporting followed the STROBE statement [12]. The screening flow of the study population is shown in Fig. 1.

Study Variables

Exposure: EASIX = LDH (U/L) × creatinine (mg/dL) / platelet count (×10^9/L), with all three taken as the first measured value within 0–24 hours of admission. For analysis, EASIX was log-transformed to base 2 (log_2 EASIX). Results were reported on two scales: per doubling (each 1-unit increase in log_2) and per 1 standard deviation.

Outcomes: the primary outcome was 30-day all-cause mortality, and the secondary outcomes were 90-day and 365-day all-cause mortality. Survival time was counted from the time of ICU admission; the time of death was taken from the hospital death time field, and when this field was missing it fell back to the date of death field (counted as 00:00 of that day); ties in event times were handled with the Efron approximation.

Covariates: there were 13 covariates: age, sex, admission era, heart failure, coronary heart disease or myocardial infarction, atrial fibrillation, stroke, peripheral artery disease, type 2 diabetes, chronic liver disease, malignancy, CKM stage 4a/4b, and SOFA-4. The severity score used was SOFA-4 [13], that is, retaining 4 components — respiratory (PaO_2/FiO_2), hepatic (bilirubin), circulatory (mean arterial pressure/vasoactive drugs) and central nervous (Glasgow Coma Scale) — and removing the two components of coagulation (platelets) and renal (creatinine), with a total score range of 0–16 and each component taken as the worst value within 0–24 hours. Stage 4b CKM was determined on the basis of diagnostic codes (ICD-9 5856, V4511, V56 series; ICD-10 N186, Z992, Z4901, Z4902) or an eGFR < 15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ estimated from the last creatinine before ICU admission using the CKD-EPI 2021 equation [14]; those not meeting this were stage 4a; dialysis procedure codes were not used.

Missing values were not imputed: diagnostic variables without the corresponding code were recorded as absence of the disease, test-based criteria with missing measurement were recorded as not meeting the condition, and missing items of the SOFA-4 components were scored 0 according to the convention of that scoring system. In the respiratory component of SOFA-4, when there was no FiO_2 record and no record of any oxygen administration within 24 hours (oxygen therapy device or oxygen flow), FiO_2 was taken as 0.21; those with a record of oxygen administration but without an FiO_2 value were treated as missing.

Statistical Analysis

Cox proportional hazards models were used, with stepwise adjustment by M1 (unadjusted), M2 (+ age, sex, admission era), M3 (+ comorbidities) and M4 (+ SOFA-4), and the main results were taken from M4. The proportional hazards assumption was tested with scaled Schoenfeld residuals (**Supplementary Fig. 1**); categorical covariates violating the assumption were changed to stratification factors, continuous covariates were entered with a time-varying coefficient $\gamma \times \ln t$ ($HR(t) = \exp(\beta + \gamma \ln t)$), and the adequacy of log-linearity was judged by the likelihood ratio test of the $(\ln t)^2$ term. The stratification and tvc variables were fixed as the union across the three endpoints: log_2(EASIX) and SOFA-4 were given tvc; heart failure, coronary heart disease or myocardial infarction, atrial fibrillation, chronic liver disease, malignancy, type 2 diabetes, CKM 4b and admission era were changed to strata; stroke and peripheral

artery disease were retained as covariates. Results were reported at 1, 7, 30, 90 and 365 days after admission.

EASIX was additionally grouped by quartile (Q1 as reference) with a trend test; the dose-response relation was modeled with restricted cubic splines [15], with 4 knots placed at the 5th, 35th, 65th and 95th percentiles of $\log_2$(EASIX), the reference point at its median, and tvc added to all spline terms. Survival curves used direct standardization (g-formula): based on the M4 model of the 365-day outcome, retaining the observed values of individual covariates, setting EASIX to the median of each quartile, predicting the survival function for each individual and then averaging, with only point estimates reported. Nine subgroups were prespecified: age (< 65/≥ 65 years), sex, type 2 diabetes, heart failure, CKM 4a/4b, malignancy, chronic liver disease, SOFA-4 (≤ 3/> 3), and admission era (2008–2010, 2011–2017, 2018–2022); interaction was judged by the joint likelihood ratio test (2 degrees of freedom for each dummy variable, 4 degrees of freedom for admission era), and each subgroup was exploratory. Unmeasured confounding was measured with the E value [16], anchored to the 30-day time point of the primary outcome. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was completed using Python 3.13.14 (Python Software Foundation, Wilmington, DE, USA) and Stata 19.0 (StataCorp, College Station, TX, USA).

External Validation

External validation was performed independently in the eICU-CRD 2.0 database [17]. Stage 4 CKM was identified by an approximate definition: the presence of clinical cardiovascular disease (diagnostic codes or structured past history) together with at least one metabolic or kidney condition (type 2 diabetes, chronic kidney disease, BMI ≥ 25 kg/m²); the two pathways of eGFR and urinary albumin/creatinine ratio were not included, and stages 4a and 4b were not distinguished.

Patients with a first ICU admission and a hospital stay ≥ 24 hours were included. The exposure was calculated by the same formula, taking the first value within 0–24 hours. Covariates were age, sex, Glasgow Coma Scale (GCS), the lowest mean arterial pressure recalculated within 0–24 hours, and mechanical ventilation; severity was represented by the above three items, and SOFA-4 was not constructed; missing GCS and mean arterial pressure were scored 0 according to the convention of that scoring system (GCS 15 points, mean arterial pressure 70 mmHg), and no individual was excluded because of missing covariates.

The endpoint was all-cause mortality during hospitalization, and survival to discharge was censored. The model was a Cox proportional hazards model (Efron approximation): M1 unadjusted, M2 with age and sex added, M3 with GCS, lowest mean arterial pressure and mechanical ventilation added (main model); no strata and no time-varying coefficients were set, and a single HR was reported. All tests were two-sided.

Results

Study Population

Among the 9,766 patients, median age was 71 (61–81) years, 5,694 patients (58.3%) were male, median SOFA-4 was 4 (1–7) points, and median EASIX was 2.1 (1.0–5.0) (**Supplementary Fig. 2**). There were 877 patients (9.0%) with stage 4b CKM and 8,889 (91.0%) with stage 4a. During follow-up, all-cause deaths at 30, 90 and 365 days were 2,278 (23.3%), 2,938 (30.1%) and 3,802 (38.9%), respectively.

After grouping by EASIX quartile, Q1 to Q4 comprised 2,442, 2,441, 2,441 and 2,442 patients, respectively, and median EASIX was 0.7 (0.5–0.8), 1.4 (1.2–1.7), 3.0 (2.5–3.9) and 10.6 (6.8–23.3), respectively. For Q1 and Q4, respectively: heart failure 32.3% and 54.2%, chronic liver disease 6.2% and 31.9%, malignancy 14.5% and 21.5%, CKM 4b 0.1% and 27.6%, stroke 34.9% and 17.1%; median SOFA-4 from Q1 to Q4 was 2, 3, 4 and 5. The proportion of 30-day deaths in Q1 and Q4 was 13.9% and 38.3%, respectively, and the 365-day proportions were 27.6% and 55.7%. The distribution of admission era did not differ statistically significantly among the four groups (P = 0.267). Baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics of the study population, by EASIX quartile

Characteristic	Overall (*n* = 9,766)	Q1 (*n* = 2,442)	Q2 (*n* = 2,441)	Q3 (*n* = 2,441)	Q4 (*n* = 2,442)	*P* value
Age, years	71.0 (61.0–81.0)	70.0 (60.0–80.0)	73.0 (63.0–82.0)	72.0 (63.0–82.0)	69.0 (59.0–79.0)	< 0.001
Male sex	5,694 (58.3)	1,138 (46.6)	1,431 (58.6)	1,544 (63.3)	1,581 (64.7)	< 0.001
EASIX	**2.1 (1.0–5.0)**	**0.7 (0.5–0.8)**	**1.4 (1.2–1.7)**	**3.0 (2.5–3.9)**	**10.6 (6.8–23.3)**	**< 0.001**
SOFA-4 score	4.0 (1.0–7.0)	2.0 (1.0–5.0)	3.0 (1.0–6.0)	4.0 (2.0–8.0)	5.0 (2.0–9.0)	< 0.001
Heart failure	4,571 (46.8)	788 (32.3)	1,116 (45.7)	1,344 (55.1)	1,323 (54.2)	< 0.001
Coronary artery disease or myocardial infarction	5,096 (52.2)	1,035 (42.4)	1,289 (52.8)	1,379 (56.5)	1,393 (57.0)	< 0.001
Stroke	2,335 (23.9)	853 (34.9)	590 (24.2)	475 (19.5)	417 (17.1)	< 0.001
Atrial fibrillation	4,634 (47.5)	1,057 (43.3)	1,164 (47.7)	1,222 (50.1)	1,191 (48.8)	< 0.001
Peripheral artery disease	1,609 (16.5)	382 (15.6)	395 (16.2)	416 (17.0)	416 (17.0)	0.474
Type 2 diabetes	3,459 (35.4)	726 (29.7)	853 (34.9)	927 (38.0)	953 (39.0)	< 0.001
Admission glucose, mg/dL	131 (105–174)	122 (102–152)	132 (108–174)	136 (107–182)	139 (107–193)	< 0.001
HbA1c measured	1,909 (19.5)	725 (29.7)	522 (21.4)	412 (16.9)	250 (10.2)	< 0.001
HbA1c, % (measured subgroup)	5.8 (5.4–6.6)	5.8 (5.4–6.4)	5.8 (5.5–6.6)	5.9 (5.5–7.1)	5.9 (5.3–6.9)	0.121
Insulin (during hospitalisation)	6,252 (64.0)	1,448 (59.3)	1,507 (61.7)	1,589 (65.1)	1,708 (69.9)	< 0.001
Oral glucose-lowering drugs (during hospitalisation)	473 (4.8)	150 (6.1)	148 (6.1)	116 (4.8)	59 (2.4)	< 0.001
Chronic liver disease	1,625 (16.6)	152 (6.2)	249 (10.2)	446 (18.3)	778 (31.9)	< 0.001

Characteristic	Overall (*n* = 9,766)	Q1 (*n* = 2,442)	Q2 (*n* = 2,441)	Q3 (*n* = 2,441)	Q4 (*n* = 2,442)	*P* value
Malignancy	1,576 (16.1)	354 (14.5)	322 (13.2)	376 (15.4)	524 (21.5)	< 0.001
CKM stage 4b (kidney failure)	877 (9.0)	2 (0.1)	27 (1.1)	175 (7.2)	673 (27.6)	< 0.001
Admission era						0.267
2008–2010	2,459 (25.2)	622 (25.5)	633 (25.9)	626 (25.6)	578 (23.7)	
2011–2013	1,683 (17.2)	435 (17.8)	422 (17.3)	428 (17.5)	398 (16.3)	
2014–2016	1,906 (19.5)	463 (19.0)	486 (19.9)	478 (19.6)	479 (19.6)	
2017–2019	2,146 (22.0)	551 (22.6)	530 (21.7)	506 (20.7)	559 (22.9)	
2020–2022	1,572 (16.1)	371 (15.2)	370 (15.2)	403 (16.5)	428 (17.5)	
30-day mortality	**2,278 (23.3)**	**339 (13.9)**	**419 (17.2)**	**584 (23.9)**	**936 (38.3)**	**< 0.001**
90-day mortality	2,938 (30.1)	470 (19.2)	570 (23.4)	762 (31.2)	1,136 (46.5)	< 0.001
365-day mortality	3,802 (38.9)	674 (27.6)	763 (31.3)	1,006 (41.2)	1,359 (55.7)	< 0.001

Values are median (IQR) for continuous variables and n (%) for categorical variables. P values were obtained with the Kruskal–Wallis test (continuous variables) or the χ^2 test (categorical variables). EASIX quartile cut-offs: Q1 ≤ 1.02; Q2 1.02–2.06; Q3 2.06–4.98; Q4 > 4.98. SOFA-4, Sequential Organ Failure Assessment score restricted to the respiratory, hepatic, cardiovascular and neurological components (range 0–16); the coagulation and renal components were not used. CKM, cardiovascular–kidney–metabolic; IQR, interquartile range; EASIX, Endothelial Activation and Stress Index. All 13 covariates were complete in the study population; no variable required imputation. Admission glucose was the first value recorded during the hospital stay. HbA1c was available within the first 24 h in 19.5% of patients (29.7% in Q1 and 10.2% in Q4; P < 0.001) and is described only among patients in whom it was measured. Insulin and oral glucose-lowering drugs refer to any in-hospital prescription; MIMIC-IV contains no pre-admission outpatient medication records.

Abbreviations. CKM, cardiovascular–kidney–metabolic; EASIX, Endothelial Activation and Stress Index; HbA1c, glycated haemoglobin; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

Survival Curves

In the unadjusted Kaplan–Meier estimates, 30-day survival from Q1 to Q4 was 86.1%, 82.8%, 76.1% and 61.7%, respectively, and 365-day survival was 72.4%, 68.7%, 58.8% and 44.3% (log-rank P < 0.001). After

direct standardization to the whole cohort with the M4 model, 30-day survival was 82.5%, 79.9%, 77.1% and 71.6%, respectively, and 365-day survival was 67.6%, 64.7%, 61.5% and 55.8% (Fig. 2, **Supplementary Table 1**).

Association Between EASIX and All-Cause Mortality and Its Variation over Time

In the fully adjusted model (M4), for each doubling of EASIX, the HR for 30-day mortality was 1.243 (1.182–1.306) at 1 day after admission, 1.177 (1.148–1.208) at 7 days, and 1.131 (1.079–1.185) at 30 days; γ = −0.0277 (P = 0.026). The point estimates at the 1-day time point from M1 to M4 were 1.334 (1.285–1.385), 1.374 (1.322–1.428), 1.417 (1.351–1.485) and 1.243 (1.182–1.306), respectively (Fig. 3, **Supplementary Table 2**).

For the 90-day outcome, the values were 1.237 (1.183–1.294) at 1 day, 1.136 (1.102–1.172) at 30 days and 1.106 (1.056–1.158) at 90 days, with γ = −0.0250 (P = 0.005). For the 365-day outcome, the values were 1.247 (1.199–1.297) at 1 day, 1.174 (1.148–1.201) at 7 days, 1.122 (1.097–1.147) at 30 days, 1.084 (1.052–1.118) at 90 days and 1.038 (0.993–1.086) at 365 days, with γ = −0.0311 (P < 0.001). After adding the $(\ln t)^2$ term to M4, the likelihood ratio test P values for the three endpoints were 0.145, 0.249 and 0.367, respectively (**Supplementary Table 3**).

When the unit was 1 standard deviation (1.861, equivalent to a 3.6-fold difference in EASIX), the HR for 30-day mortality was 1.498 (1.365–1.644) at 1 day, 1.355 (1.293–1.421) at 7 days and 1.257 (1.152–1.372) at 30 days (**Supplementary Table 2B**).

Quartiles and Dose-Response Relationship

With Q1 as reference, the HR for 30-day mortality in Q4 was 3.946 (2.815–5.530) at 1 day, 2.404 (2.077–2.783) at 7 days and 1.660 (1.273–2.164) at 30 days; the 30-day HR was 1.185 (0.913–1.539) for Q3 and 0.915 (0.699–1.197) for Q2, and neither differed statistically significantly from Q1. With quartile as an ordinal variable in the trend test, for each one-quartile increase, the HR for 30-day mortality was 1.397 (1.296–1.506) at 1 day and 1.161 (1.090–1.237) at 30 days, P < 0.001 (**Supplementary Table 4**).

In the restricted cubic splines, the overall association was statistically significant for all three endpoints (P < 0.001), and the non-linearity test P values were 0.002 (30 days), 0.002 (90 days) and < 0.001 (365 days), respectively (**Supplementary Table 5**). The curve rose more steeply above the median, and the curve for the 365-day outcome was flatter than that for 30 days (Fig. 4).

Subgroup Analysis

Among the 9 prespecified subgroups, at the 30-day time point the interaction was statistically significant for heart failure (P = 0.003; without 1.206 (1.136–1.279), with 1.026 (0.954–1.104)), SOFA-4 (P < 0.001; ≤ 3 points 1.213 (1.127–1.306), > 3 points 1.089 (1.029–1.152)) and malignancy (P = 0.039); the

interaction was not statistically significant for CKM 4a/4b (0.079; 4a 1.134 (1.080–1.191), 4b 1.047 (0.893–1.229)), admission era (0.061), chronic liver disease (0.132), type 2 diabetes (0.276), sex (0.698) or age (0.713) (**Supplementary Table 6**, Fig. 5).

Within the type 2 diabetes subgroup (n = 3,459, 791 30-day deaths), the model with the same structure was fitted using this population's own quartiles (cut-offs 1.16, 2.34, 5.49) (post hoc analysis): compared with Q1, the HR for 30-day mortality in Q4 was 4.061 (2.245–7.347) at 1 day, 2.471 (1.911–3.195) at 7 days and 1.704 (1.061–2.735) at 30 days; for the 365-day outcome, it was 1.760 (1.445–2.143) at the 30-day time point, 1.386 (1.074–1.789) at the 90-day time point and 1.023 (0.697–1.503) at the 365-day time point. The unadjusted proportion of 30-day deaths from Q1 to Q4 was 12.1%, 18.8%, 22.4% and 35.2%, respectively; in the trend test, for each one-quartile increase, the HR at the 30-day time point was 1.140 (1.017–1.278) (**Supplementary Table 7**).

Robustness to Unmeasured Confounding

With the primary outcome (30 days) as the anchor time point, the point-estimate E value was 1.40, and the E value corresponding to the lower confidence limit was 1.29 (**Supplementary Table 8**).

eICU-CRD Validation

In eICU-CRD, 1,342 patients met the approximate stage 4 CKM definition, and after the two restrictions of first ICU admission and survival to 24 hours the number was 1,103, accounting for 11.3% of the derivation population. Median age was 67 (56–77) years, 641 patients (58.1%) were male, median EASIX was 2.88 (1.33–8.44), and 339 patients (30.7%) received mechanical ventilation; 173 patients (15.7%) died during hospitalization, and median hospital days were 6.9 (3.9–12.3).

The unadjusted proportion of in-hospital deaths from Q1 to Q4 was 10.1%, 15.6%, 12.0% and 25.0%, respectively (log-rank P = 0.005). In the fully adjusted model (M3), for each doubling of EASIX, the HR for in-hospital death was 1.121 (95%CI 1.045–1.203, P = 0.002); it was 1.145 (1.072–1.223) in M1 and 1.159 (1.084–1.240) in M2. With the database's own standard deviation (2.133 on the $\log_2$ scale) as the unit, the HR corresponding to each 1-standard-deviation increase was 1.276 (1.098–1.482) (**Supplementary Table 9**).

In the quartile analysis, with Q1 as reference, the value was 1.333 (0.818–2.169) for Q2, 0.822 (0.493–1.369) for Q3 and 1.513 (0.964–2.374) for Q4, P = 0.072; the trend test with quartile as an ordinal variable gave 1.080 (0.989–1.179, P = 0.085) (Fig. 6, Fig. 7).

Discussion

In the present study, among 9,766 adult patients who already had stage 4 CKM at ICU admission, we examined the association of EASIX calculated within 24 hours of admission with 30-, 90- and 365-day all-cause mortality. Higher EASIX was associated with a higher risk of death; for the 30-day outcome after full adjustment, the HR per doubling was 1.243 (95%CI 1.182–1.306) at 1 day after admission and 1.131

(1.079–1.185) at 30 days. This association was not constant: the time coefficient was γ = −0.0277 (P = 0.026), and the HR decreased with longer time since admission, being 1.038 (0.993–1.086) at the 365-day time point for the 365-day outcome. The shape of the association was also not uniform: it was steeper in the high EASIX range and flatter in the low range, with non-linearity test P values from 0.002 to < 0.001, and in the quartile analysis only the difference between Q4 and Q1 was clear (30 days 1.660, 1.273–2.164). The decrease of the HR with time since admission also needs to be read in light of the composition of the risk set: those who died early after admission were mainly those with higher EASIX, and as time went on the proportion of high-EASIX patients among survivors decreased, so the risk set changed accordingly, and this decrease should not be directly interpreted as the injurious effect itself weakening over time.

Comparison with Previous Studies

Compared with previous studies, both the direction and the magnitude of the present study fall within the range of existing reports. In 7,504 septic ICU patients, for each 1-unit increase in $\log_2$(EASIX), the HR for 28-day mortality was 1.10 (1.07–1.13) [5]; in the 30-day outcome of the present study, the estimate on the same scale was 1.131 (1.079–1.185), and the two are close. In 2,468 ICU patients with coronary heart disease, the HR for 30-day mortality of the highest versus the lowest tertile was 2.24 (1.53–3.26) and that for 365 days was 2.20 (1.55–3.13) [6]; in the present study the 30-day HR of Q4 versus Q1 was 1.660 (1.273–2.164), a comparable magnitude. In 17,624 patients with acute kidney injury, the HR of $\log_2$(EASIX) for 1-year mortality was 1.41 (1.32–1.50) [7]. This value cannot be directly compared with the present study: that study took the 1-year cumulative risk as its object, whereas the present study, in the 365-day outcome, reports the instantaneous HR at the 365-day time point (1.038, 0.993–1.086), and the two mean different things; moreover, acute kidney injury in that population itself raises the numerator of EASIX, and the degree of collinearity between exposure and outcome is also higher than in the present study. The differences of the present study are mainly in the time dimension: previous reports mostly summarized with a single HR, and the sepsis study reported a linear relation [5], whereas in the present study the HRs of all three endpoints decreased with time and were non-linear. The two are not contradictory: when the follow-up period is short or the proportion of early deaths is high, a single HR will be closer to the early estimate of the present study; when the follow-up period is long it is pulled toward 1. As for non-linearity, the test P values of the three endpoints in the present study lay between 0.002 and < 0.001, and the shape was stable; the absence of a difference of Q2 and Q3 from Q1 at 30 days is also consistent with "a small slope in the low range". Mechanistically, the three components of EASIX correspond to cell injury, decreased renal clearance and platelet consumption [2][3]; in the stage 4 CKM population, these three pathways are more readily activated simultaneously because of the background of metabolic abnormality and CKD [1][2], so when EASIX enters the upper part of the distribution it often means that multiple systems are involved at the same time, and the risk rises accordingly.

In the dimension of CKM staging, the published community cohort with stages 0–3 (n = 10,885) reported that for each 1-unit increase in EASIX, the HR was 1.41 (1.24–1.61) for all-cause mortality and 1.30 (1.13–1.49) for cardiovascular mortality, and no non-linearity was seen for all-cause mortality [10]. The

scale of that study is the original unit of EASIX, which differs from the per-doubling and per-1-standard-deviation scales of the present study, so the two sets of values cannot be directly converted, nor can the magnitudes be judged to be consistent on that basis; what is comparable is the direction — in both CKM staging segments and in both types of population (community and ICU), those with higher EASIX had a higher risk of death. In shape the two differ: that study had no evidence of non-linearity for all-cause mortality (P = 0.466), whereas in the present study the non-linearity tests of all three endpoints were statistically significant, the curve became steeper above the median, and at the same time the HR decreased with time since admission. The difference in stage and setting can explain this difference: the endothelial burden in stages 0–3 is mainly chronic and of low amplitude, whereas in stage 4 patients admitted to the ICU an acute insult is superimposed on this, and the shape of the association at that point is closer to acute multi-system involvement rather than a slow change in a single pathway.

Independent External Validation and Potential Implications

The present study also performed independent validation in eICU-CRD. Among 1,103 patients with stage 4 CKM identified by the approximate definition, after full adjustment the HR of each doubling of EASIX for in-hospital death was 1.121 (1.045–1.203), with a confidence interval excluding 1, and the direction was consistent with the main study. It needs to be made clear that this point cannot be taken as a replication of the main study's results. The endpoints on the two sides do not have the same name: the endpoint of the validation cohort was all-cause mortality during hospitalization, with discharge as censoring, whereas the main study took 30-day all-cause mortality as the primary endpoint; the median hospital stay in that database was only 6.9 days and 96.8% of patients left hospital within 30 days, so deaths after discharge were unobservable and a 30-day endpoint could not be constructed structurally, and therefore there are no two time scales that can be checked against each other. The granularity of severity adjustment also differs: the validation cohort used only three proxies — GCS, lowest mean arterial pressure and mechanical ventilation — because that database lacks PaO_2/FiO_2 and vasoactive drug dose records consistent with the main study's definitions, and the respiratory and circulatory components of SOFA-4 could not be constructed; insufficient adjustment will leave part of the effect of severity in the exposure term, and the direction is usually to inflate rather than attenuate the association. The dispersion of $\log_2$(EASIX) also differs between the two databases (1.861 versus 2.133), and the per-1-standard-deviation estimates (1.276, 1.098–1.482 versus 1.257, 1.152–1.372), even if numerically close, are two estimates under two populations, two endpoints and two sets of covariates, and numerical closeness itself does not constitute evidence. What can be said is that the direction is consistent, and that at the quartile level the validation cohort did not reach significance (Q4 versus Q1 was 1.513, 0.964–2.374; trend test P = 0.085): that database had only 173 events, and the width of the interval for the quartile comparison is sufficient to cover the 1.660 of the main study, which is a matter of insufficient precision rather than an opposite direction. The value of the validation lies in the fact that the composition of medical institutions, the coding system and the routine of care in that database all differ from the derivation database; that a concordant association was still observed against this background indicates that the association is unlikely to arise solely from the coding habits of a single database or the practice pattern of a single center.

Beyond independent validation, the significance of the present study is not limited to the above association itself. Clinically, EASIX is composed of three routine tests at admission and requires no additional tests or equipment, and can be obtained within 24 hours of admission [4]; in the present study the association was strongest at 1 day after admission and then progressively weakened, suggesting that if EASIX is to be used for risk identification, its informational value is most likely to be reflected in the intensity of monitoring and in treatment decisions early after admission. Methodologically, the present study shows that the effect of an exposure in critically ill populations can change over time, and that reporting HR(t) together with fixed time points reflects the true shape better than reporting a single HR, and also makes comparison across studies easier [9]; this is particularly important for an index such as EASIX that contains a renal function component, because renal function itself changes during hospitalization.

In terms of research, the present study suggests that stage 4 CKM is a population with a high endothelial burden that can be characterized by routine tests, and provides a baseline description for subsequent endothelial-targeted research in this population. The boundaries need to be made clear at the same time: existing ICU severity scores (such as SOFA) are composed of physiological and biochemical indicators of organ dysfunction [13] and do not contain markers of endothelial activation, and what the two describe are different aspects; but the present study does not build a prediction model, does not evaluate discriminative ability, and does not set a threshold, and therefore cannot claim that EASIX is superior to or supplements any existing score. The association between EASIX and death is an observational association, and it cannot be inferred from it that lowering EASIX would improve prognosis.

Limitations

The present study is an observational design, and residual confounding cannot be excluded; the E-value analysis showed that the association for the 30-day outcome could be fully explained by an unmeasured confounder whose association with both the exposure and the outcome was 1.40. EASIX can be calculated only in patients with all three tests available within 24 hours of admission, and the conclusions apply only to this population. The exposure took only the first value within 0–24 hours of admission and does not reflect its dynamic change. The determination of stage 4 CKM relied on diagnostic codes and test values, underreporting exists in coding, and the 877 patients (9.0%) with stage 4b may be underestimated; the determination of metabolic syndrome lacked waist circumference data, and HDL and triglycerides were frequently missing. The quartile analysis within the type 2 diabetes subgroup was a post hoc analysis and was not corrected for multiple comparisons. Peripheral artery disease violated the proportional hazards assumption in the 365-day model and was still retained as a covariate. The endpoint of the external validation does not have the same name as that of the main study (in-hospital all-cause mortality versus 30-day all-cause mortality), the follow-up window is short, severity is represented by only three proxies, there were 173 events, and the quartile comparison did not reach significance.

Conclusions

In ICU patients with stage 4 CKM, a higher EASIX calculated within 24 hours of admission was associated with a higher risk of 30-, 90- and 365-day all-cause mortality; the association was strongest early after admission, weakened over time, and was more evident in the higher EASIX range. In the type 2 diabetes subgroup (n = 3,459) the association also held and was of comparable magnitude, with an HR for 30-day mortality of 1.704 (95%CI 1.061–2.735) for the highest versus the lowest quartile. Among 1,103 patients with approximate stage 4 CKM in eICU-CRD, the association of the same exposure with in-hospital mortality was in the same direction (per doubling 1.121, 95%CI 1.045–1.203), but the endpoint and the follow-up window differ, and it does not constitute a replication on the 30-day endpoint.

These findings should be interpreted as a descriptive association rather than a validated risk stratification tool: the present study did not build a prediction model, did not evaluate discriminative ability, and did not set a threshold; the specific value of EASIX is not used for individual risk judgment and does not constitute causal inference. The results support the potential value of describing risk status by endothelial burden in critically ill patients with stage 4 CKM; however, this association has not yet been validated on the 30-day endpoint with consistent definitions, and prospective studies are still needed for confirmation before clinical implementation.

Declarations

Acknowledgements

Not applicable

Author contributions

Study conception and design: Qilin Lu. Data extraction and data analysis: Junning Liu, Yuhang Luo. Writing the paper: Qilin Lu, Junning Liu, Yuhang Luo. Important revisions: Qilin Lu, Junning Liu, Juyi Wan, Bin Liao. Research Guidance: Juyi Wan, Bin Liao.

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Availability of data and materials

The data analysed in this study are publicly available and were not generated by the authors. MIMIC-IV and eICU-CRD 2.0 are distributed through PhysioNet (https://physionet.org/content/mimiciv/ and https://physionet.org/content/eicu-crd/). Access to either database requires completion of the CITI

"Data or Specimens Only Research" training course and signature of a data use agreement, under which the records may not be redistributed; the individual-level data are therefore not shared by the authors. The code used to define the study population, calculate EASIX, fit the models is available from the corresponding author on reasonable request..

Ethics Approval and Consent to Participate

This study is a retrospective analysis of two publicly available, de-identified critical care databases. No new data were collected, no intervention was performed, and no individual could be identified from the records analysed. The establishment and sharing of MIMIC-IV were approved by the institutional review boards of the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, and the establishment and sharing of eICU-CRD were approved by the institutional review board of the Beth Israel Deaconess Medical Center; both approvals included a waiver of the requirement for informed consent, because all records are de-identified. The present analysis was conducted under the data use agreements of the two databases and did not involve any additional ethical review.

Competing interests

The authors declare no competing interests.

Consent for publication

All the authors agree to publish.

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Figures

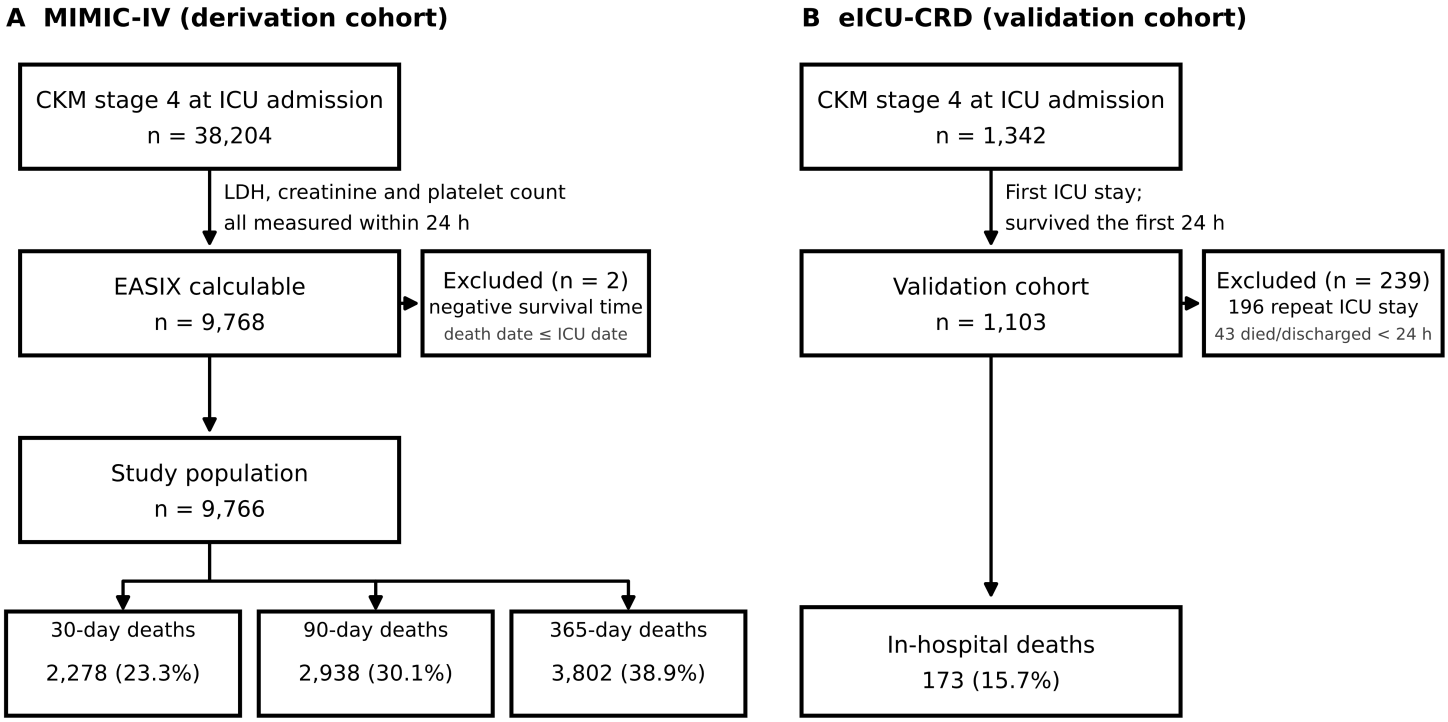


Figure 1

Selection of the study population. Selection of the study population in the derivation and validation cohorts. **(A)** Derivation cohort (MIMIC-IV): CKM stage 4 at ICU admission, survival beyond 24 h, and lactate dehydrogenase, creatinine and platelet count measured within 24 h; 9,768 patients met these criteria, two were excluded for a negative survival time, and the study population comprised 9,766 patients, with 2,278, 2,938 and 3,802 all-cause deaths at 30, 90 and 365 days. **(B)**Validation cohort (eICU-CRD): CKM stage 4 approximated by cardiovascular disease (diagnosis codes or structured past history) together with at least one metabolic risk factor (diabetes, chronic kidney disease or body-mass index ≥ 25 kg/m²) among patients in whom all three EASIX components were available; 1,342 patients met these criteria, 196 were excluded for a repeat ICU stay and 43 for death or discharge within 24 h, leaving 1,103 patients, of whom 173 (15.7%) died in hospital. The endpoint in (B) was in-hospital death. CKM, cardiovascular–kidney–metabolic; EASIX, Endothelial Activation and Stress Index; ICU, intensive care unit; LDH, lactate dehydrogenase.

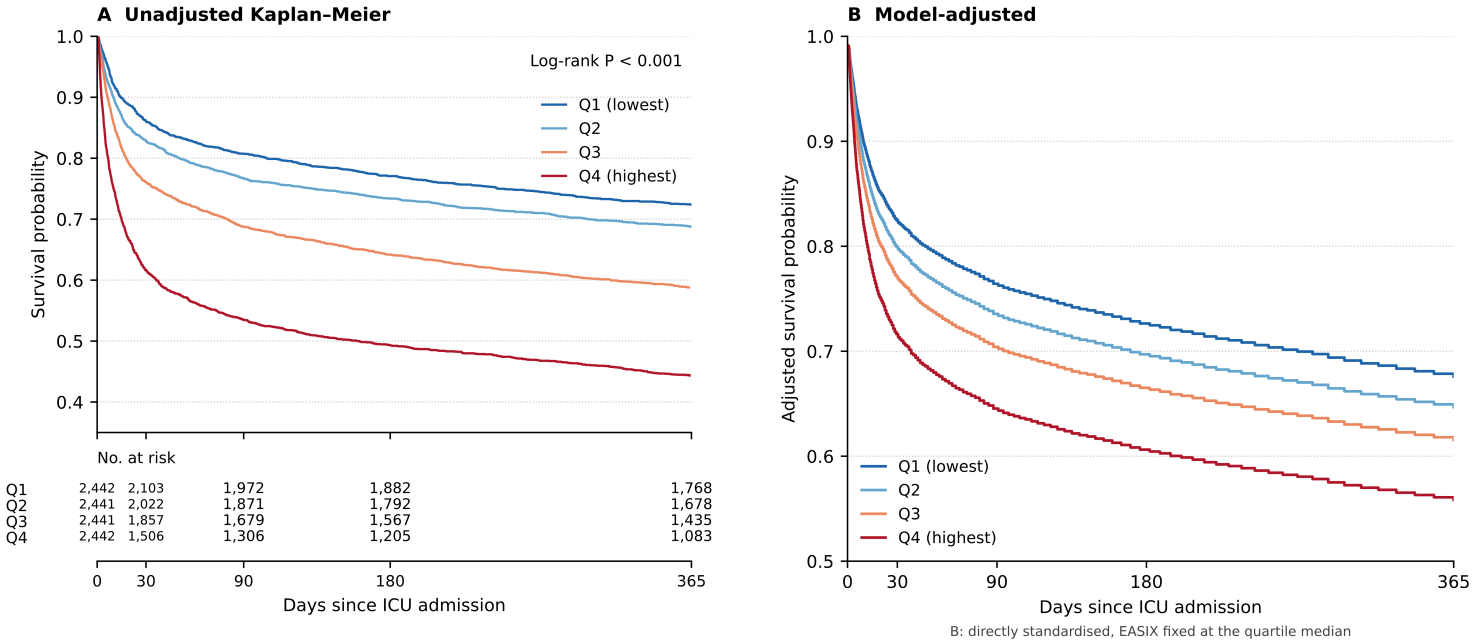


Figure 2

Survival by EASIX quartile. Survival by EASIX quartile over 365 days. **(A)**Unadjusted Kaplan–Meier curves for the four EASIX quartiles (Q1 lowest to Q4 highest), 365-day outcome; log-rank P < 0.001; the numbers of patients at risk are given below the panel. **(B)** Survival curves standardised to the whole cohort by direct standardisation from model M4 for the 365-day outcome, with covariates at their observed values and EASIX fixed at the median of each quartile; point estimates only. EASIX quartile cut-points were 1.02, 2.06 and 4.98. EASIX, Endothelial Activation and Stress Index; Q, quartile.

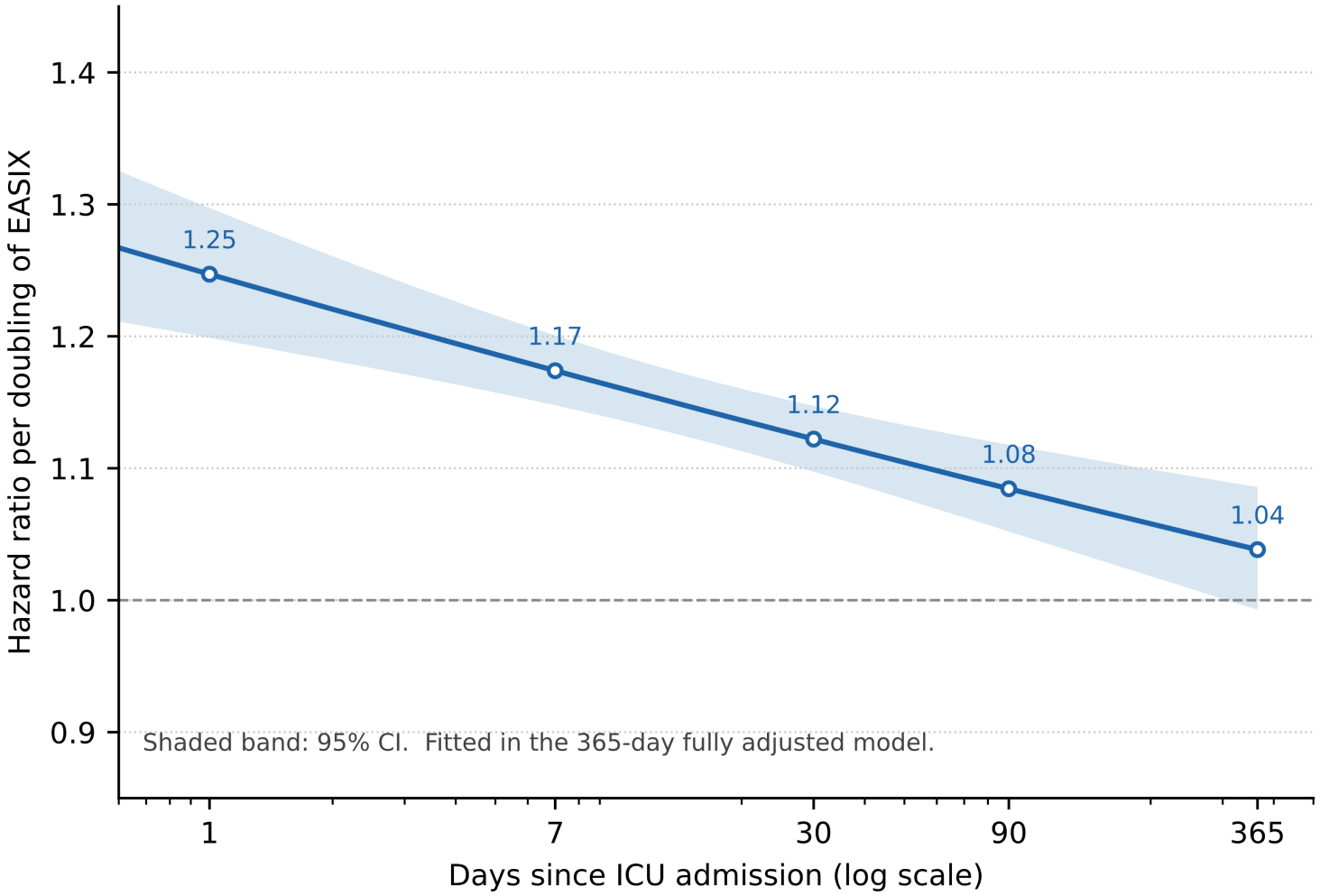


Figure 3

Hazard ratio for EASIX over time. Hazard ratio for EASIX over time. Hazard ratio for EASIX (per doubling) as a function of time since ICU admission, from model M4 for the 365-day outcome; log2(EASIX) carried a time-varying coefficient (γ × ln t), and the estimate at time t is exp(β + γ ln t). Solid line, point estimate; shaded band, 95% confidence interval; open circles, the pre-specified time points of 1, 7, 30, 90 and 365 days, annotated with the corresponding hazard ratio; horizontal dashed line, hazard ratio of 1. The time axis is on a logarithmic scale. CI, confidence interval; EASIX, Endothelial Activation and Stress Index; HR, hazard ratio

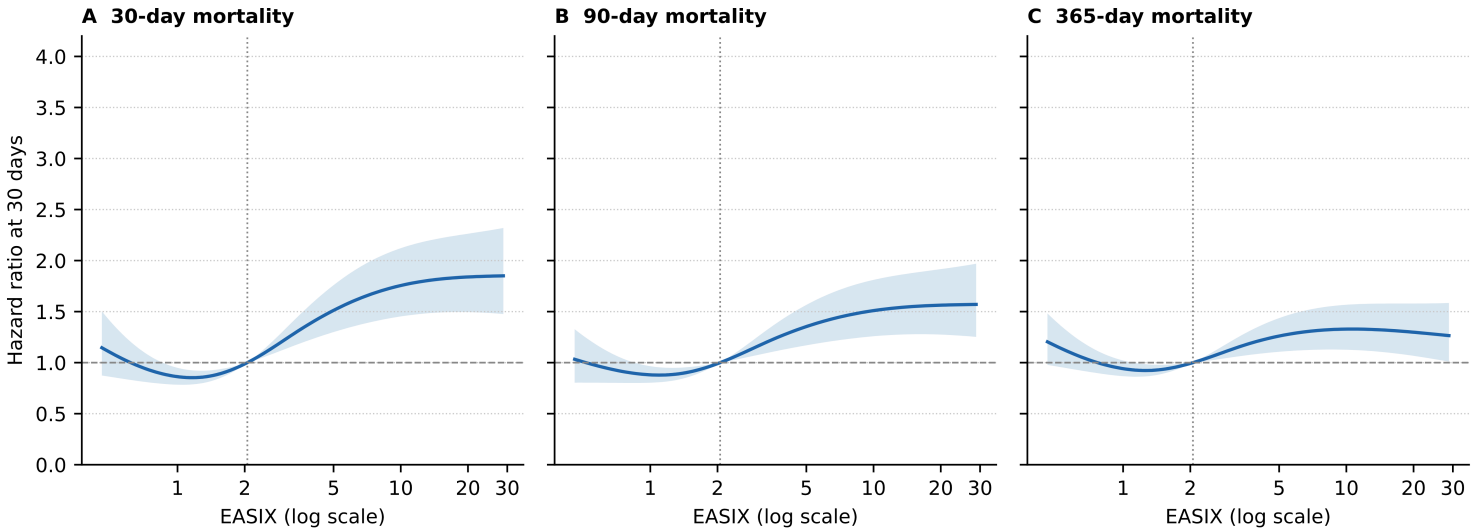


Figure 4

Dose–response relationship. Dose–response relationship between EASIX and all-cause mortality. Restricted cubic splines for (A) 30-day, (B) 90-day and (C) 365-day mortality. Four knots were placed at the 5th, 35th, 65th and 95th percentiles of log2(EASIX) — log2 = -1.125, 0.419, 1.734 and 4.848, corresponding to EASIX = 0.458, 1.337, 3.326 and 28.807. Reference (dotted vertical line): median log2(EASIX) = 1.039 (EASIX = 2.055), hazard ratio 1. Solid lines, point estimates; shaded bands, 95% confidence intervals. All three spline terms carried a time-varying coefficient (× ln t). The EASIX axis is on a logarithmic scale. The P value for the overall association was < 0.001 for all three outcomes; the P value for non-linearity was 0.002, 0.002 and <0.001, respectively. CI, confidence interval; EASIX, Endothelial Activation and Stress Index; HR, hazard ratio.

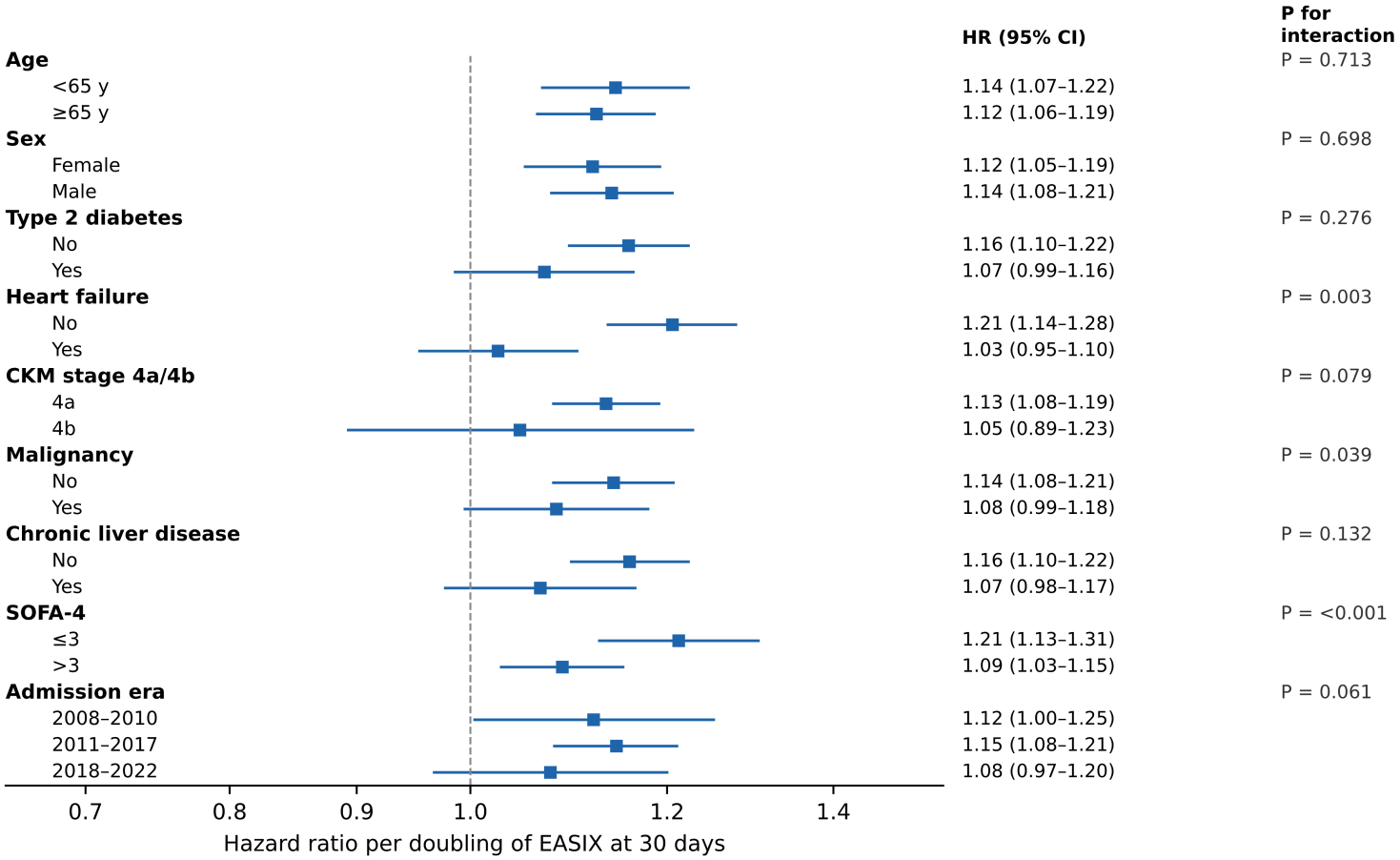
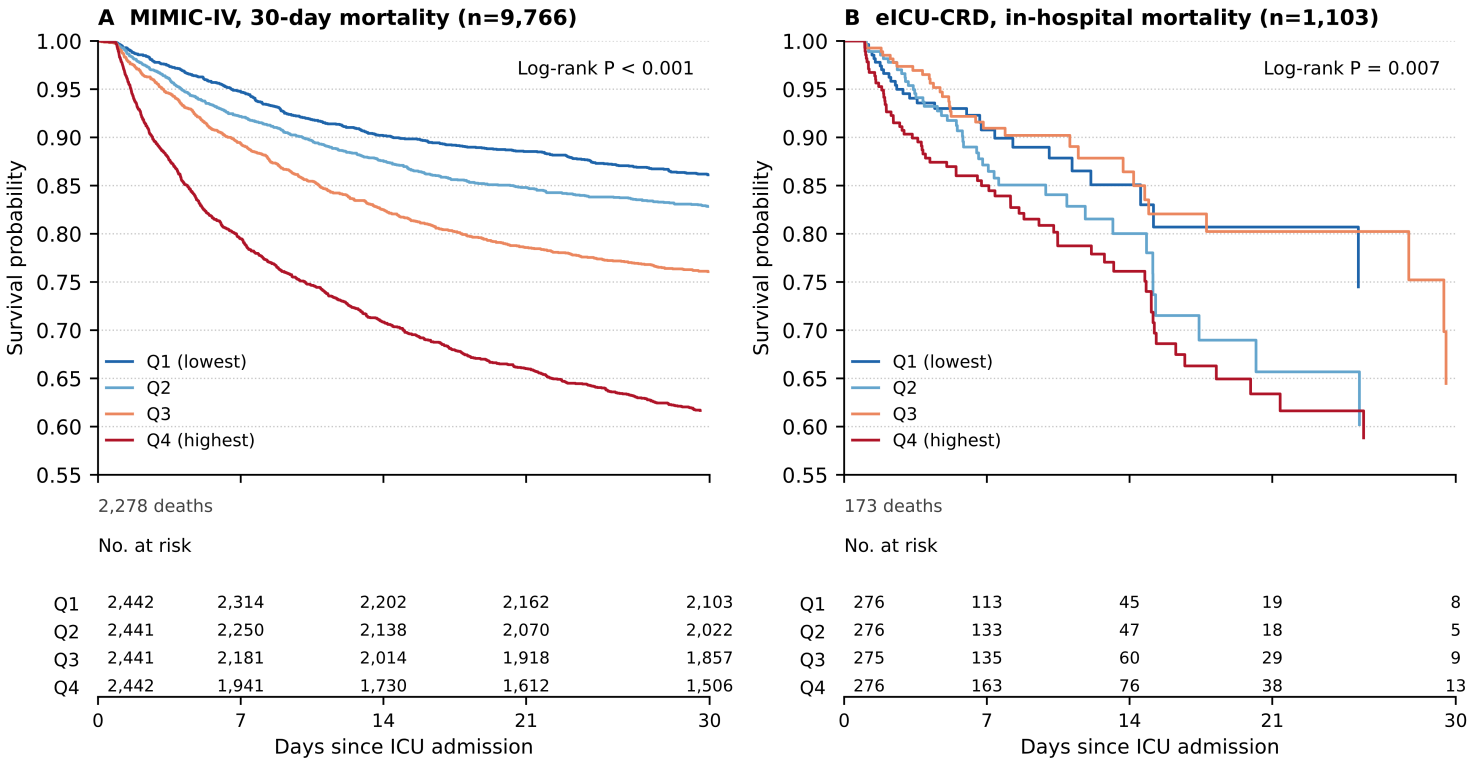


Figure 5

Subgroup analyses. Subgroup analyses. Hazard ratios for EASIX (per doubling) at 30 days within pre-specified subgroups, from model M4 with an additional EASIX × subgroup interaction. Squares, point estimates; horizontal lines, 95% confidence intervals; vertical line, hazard ratio of 1. P for interaction is from a joint likelihood ratio test including the main and the time-varying interaction terms (2 df per dummy variable, 4 df for admission era). CI, confidence interval; CKM, cardiovascular–kidney–metabolic; EASIX, Endothelial Activation and Stress Index; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.



Both panels censored at day 30. MIMIC-IV: all-cause death over 30 days. eICU-CRD: in-hospital death, censored at hospital discharge.

Figure 6

Survival by EASIX quartile in two cohorts. Survival by EASIX quartile in the derivation and validation cohorts, first 30 days. (A) MIMIC-IV (n = 9,766), all-cause mortality over 30 days, unadjusted Kaplan–Meier curves for the four EASIX quartiles defined within that cohort (cut-points 1.02, 2.06 and 4.98). (B) eICU-CRD (n = 1,103), in-hospital mortality over the same 30-day window, quartiles defined within the validation cohort (cut-points 1.33, 2.88 and 8.44). Patients still alive in hospital at day 30 and patients discharged alive before day 30 were censored at day 30 and at hospital discharge, respectively; the number at risk declines (median hospital stay 6.9 days; 1,068 of 1,103 patients, 96.8%, left hospital within 30 days, 903 of them alive, 81.9% of the cohort). Quartile colours are common to both panels; Q1, lowest EASIX; Q4, highest. Log-rank P was calculated over the 0–30-day window in each cohort separately, and the number of patients at risk is given below each panel. EASIX, Endothelial Activation and Stress Index; ICU, intensive care unit; Q, quartile.

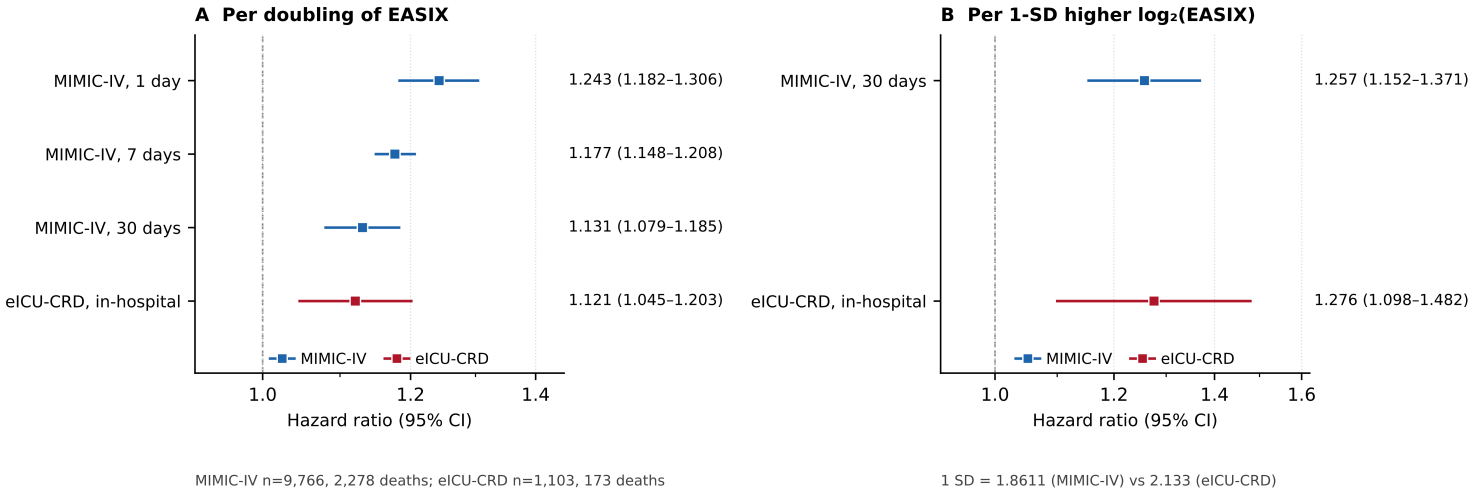


Figure 7

Hazard ratios for EASIX in two cohorts. Hazard ratios for EASIX in the derivation and validation cohorts. (A) Hazard ratio per doubling of EASIX. For the derivation cohort (MIMIC-IV, n = 9,766; 2,278 deaths): model M4, at the pre-specified time points of 1, 7 and 30 days after ICU admission; log2(EASIX) carried a time-varying coefficient, and the hazard ratio at day t is exp(β + γ ln t). Validation cohort (eICU-CRD, n = 1,103; 173 deaths): a single hazard ratio for in-hospital death from a model adjusted for age, sex, Glasgow Coma Scale, lowest mean arterial pressure and mechanical ventilation. (B) The same estimates per 1-SD increment in log2(EASIX); the standard deviation was 1.8611 in MIMIC-IV and 2.133 in eICU-CRD. Squares, point estimates; horizontal lines, 95% confidence intervals; dashed vertical line, hazard ratio of 1. CI, confidence interval; EASIX, Endothelial Activation and Stress Index; HR, hazard ratio; ICU, intensive care unit; SD, standard deviation.

Supplementary Files

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