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Association between the endothelial activation and stress index and all-cause mortality in patients receiving extracorporeal membrane oxygenation: a retrospective cohort study based on the MIMIC-IV database

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Abstract

Objective

To evaluate the association between the endothelial activation and stress index (EASIX) within 24 h of ICU admission and 28-day all-cause mortality in patients receiving extracorporeal membrane oxygenation (ECMO) support, and to examine whether this association can be used for early risk stratification.

Methods

A retrospective cohort study was conducted based on the MIMIC-IV v3.1 (2008–2022) database. Adult critically ill patients receiving ECMO support were included, the ECMO stay was designated as the index stay for each patient, and follow-up was counted from the time point of ICU admission of this stay. The exposure was the worst EASIX within 24 h of ICU admission, taken as the base-2 logarithm (each 1-unit increase meaning a doubling of EASIX). The primary endpoint was 28-day all-cause mortality, and the secondary endpoints were 90-day and 365-day all-cause mortality.

Results

A total of 155 patients were included in the analysis; 80 died at 28 days (51.6%), 90 at 90 days (58.1%) and 94 at 365 days (60.6%). The median EASIX was 12.14 (IQR 4.04–55.94), range 0.48–2589.5. After adjustment, each doubling of EASIX was associated with a 17% increase in the risk of 28-day all-cause mortality (HR 1.169, 95% CI 1.070–1.277, $P < 0.001$); the direction and magnitude of the results at 90 days and 365 days were consistent (HR 1.180, 95% CI 1.084–1.284; 1.182, 95% CI 1.087–1.285; both $P < 0.001$). Restricted cubic spline found no evidence of departure from linearity (P for non-linearity = 0.745), and the association rose monotonically over the interval of $\log_2$EASIX from 0 to 12. When grouped by cohort tertiles, 28-day mortality rose with increasing tertile (32.7%, 54.9%, 67.3%; log-rank $\chi^2 = 16.07$, $P < 0.001$); with T1 as the reference, the HR was 2.044 (1.080–3.871) for T2 and 3.347 (1.750–6.403) for T3, and the HR for trend per one-tertile increase was 1.805 (1.319–2.471). Within each subgroup of age, sex, ECMO mode, cardiogenic shock and SOFA the direction of the association was consistent, and none of the interaction tests was statistically significant (all $P > 0.05$). Among the eight sensitivity analyses, six had an HR still above 1 and statistically significant; only after excluding those with unknown ECMO mode (n = 74) and in those analysed for the VA mode only (n = 45) did the point estimate remain unchanged (1.163 and 1.201) while the confidence interval crossed 1.

Conclusions

In adult critically ill patients receiving ECMO support, a raised EASIX within 24 h of ICU admission was independently associated with 28-day all-cause mortality, and this association persisted at 90 days and 365 days and was consistent across multiple subgroups. EASIX is composed of three routine bedside indices at zero additional cost, and can serve as an auxiliary tool for early risk stratification of ECMO patients.

Introduction

The endothelial activation and stress index (EASIX) was proposed by Luft et al. and is defined as lactate dehydrogenase (LDH, U/L) × serum creatinine (mg/dL) ÷ platelet count (×10⁹/L) [1]. LDH corresponds to endothelial cell injury and red blood cell destruction, creatinine corresponds to the fall in renal perfusion and the abnormality of sodium and water excretion caused by endothelial dysfunction, and the platelet count corresponds to microthrombus formation and platelet consumption after endothelial activation; therefore, EASIX can be regarded as a composite readout of endothelial activation and injury in peripheral blood [1]. This index was initially established and validated in the allogeneic haematopoietic stem cell transplantation population [1][2], and was subsequently validated in a prospective cohort with risk cut-points determined [3].

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal life support technique that drains venous blood out of the body, completes oxygenation and carbon dioxide removal through a membrane oxygenator and then returns it to the body, and is used for severe respiratory and/or circulatory failure refractory to conventional treatment [4]. It does not itself treat the primary disease, but only buys time for organ recovery, bridging to transplantation or long-term support devices. Patients receiving ECMO support have a high mortality, and the judgement of illness severity early after ICU admission directly determines subsequent transfer, intensity of consultation and resource allocation. The ECMO circuit itself can cause continuous contact between blood and foreign surfaces, non-physiological shear stress, haemolysis and consumption of von Willebrand factor, and a systematic review has summarised evidence showing that ECMO support further causes endothelial injury (marked by elevation of angiopoietin-2, von Willebrand factor and extracellular vesicles) [5], while endothelial injury is in turn a core link in post-ECMO oedema, organ dysfunction and death [5][6]. In other words, what EASIX measures is precisely the downstream consequence of ECMO-related endothelial injury, and this layer of association has not yet been examined in the ECMO population.

On this basis, the present study used the MIMIC-IV database to investigate, in adult critically ill patients receiving ECMO support, the relationship between the EASIX level within 24 h of ICU admission and the risk of all-cause mortality, and to examine whether EASIX can divide patients according to within-cohort cut-points into strata whose absolute risks differ substantially.

Methods

Study design and data sources

This study was a single-centre retrospective cohort study. Data were obtained from MIMIC-IV v3.1, which contains all hospital admission and ICU records of the Beth Israel Deaconess Medical Center between 2008 and 2022, and includes the hosp and icu modules [7]. The study was reported according to the STROBE statement [8].

Study population

Inclusion criteria: age ≥ 18 years; ECMO record present; matchable to an ICU admission record; LDH, creatinine and platelet count all available within 24 h of ICU admission, so that EASIX could be calculated.

Exclusion criteria: for the same patient receiving ECMO more than once, only the first admission was retained; those in whom EASIX could not be constructed within the 24-h window of the index stay were excluded, without substituting values from other time windows and without imputing the exposure.

Study variables

Exposure variable: EASIX = LDH (U/L) × serum creatinine (mg/dL) ÷ platelet count ($\times 10^9$/L). All regression models used $\log_2$(EASIX), whose coefficient is interpreted as "for each doubling of EASIX". In the group analysis, patients were divided into three groups according to the tertile cut-points of the EASIX distribution in this cohort.

Outcome variables: the primary endpoint was 28-day all-cause mortality; the secondary endpoints were 90-day and 365-day all-cause mortality. The time origin was the time point of ICU admission of the index stay.

Covariates: age, sex, BMI, ECMO mode, cardiogenic shock, cardiac arrest, respiratory failure, cardiac surgery, SOFA score, arterial blood pH, PaO_2/FiO_2, norepinephrine use, mechanical ventilation, continuous renal replacement therapy, comorbidity (Charlson comorbidity index).

Missing data: missing values were not deleted variable by variable, nor were they single-imputed. All covariates entered one and the same multiple imputation model by chained equations at once (m = 20); the imputation model included all covariates, $\log_2$EASIX, the 28-day death indicator and the Nelson–Aalen cumulative hazard, and the results were combined according to Rubin's rules; after imputation the sample size remained consistent with that of the full cohort, and no splitting by variable was performed.

Statistical analysis

Continuous variables were described as median (interquartile range), and comparisons between groups used the Kruskal–Wallis test; categorical variables were described as frequency (percentage) and compared with the χ^2 test, and when the expected frequency was less than 5 an exact test with 5000

permutations was used instead. Survival curves of the tertile groups were estimated by the Kaplan–Meier method, and comparisons between groups used the log-rank test. The main model was a Cox proportional hazards model containing 8 parameters: $\log_2$EASIX, age, male sex, Charlson index, ECMO mode (2 dummy variables), cardiogenic shock, cardiac arrest. The upper limit of the number of parameters was taken as an events-per-variable of not less than 10. SOFA was not included in the main model. The dose–response shape was characterised with a restricted cubic spline with 4 knots fixed, the knot positions being taken at the 5th, 35th, 65th and 95th percentiles of the $\log_2$EASIX distribution and the reference point being taken at the cohort median; the null hypothesis of the non-linearity test was that the coefficients of the 2nd and 3rd spline terms were simultaneously 0. Effect modification was assessed on 5 variables (age, sex, ECMO mode, cardiogenic shock, SOFA) with the Wald test of interaction terms, and SOFA was divided into two strata at the cohort median; the HR for each doubling of EASIX within each stratum was also reported. The proportional hazards assumption was tested with Schoenfeld residuals, and for variables suggesting violation a sensitivity analysis was performed by way of stratification or a time-dependent covariate. There were 8 sensitivity analyses: excluding those who died within 24 h of ICU admission; excluding those who converted between VA and VV modes; including only those with an unequivocal ECMO mode (VA/VV/Central); analysing only the VA mode; stratifying by ECMO mode and allowing the Charlson index to vary with time; and three alternative exposure definitions (worst value in the 48-h window, first measured value, value from blood drawn at the same time point at the same moment). The alternative exposures were recalculated within the same set of patients, and no exposure value was imputed; for an alternative definition that could not be constructed in all patients, the model was fitted in the patients in whom it could be constructed. Two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Python 3.13.14 (Python Software Foundation, Wilmington, DE, USA) and Stata 19.0 (StataCorp, College Station, TX, USA).

Results

Cohort characteristics

Across the whole database, 216 ECMO admissions (215 patients) were identified, of which 210 admissions (209 patients) had an ICU stay (6 patients had no ICU record); 160 patients had all three EASIX components available within 24 h of the first ECMO stay, and 49 patients were excluded because the three components were incomplete; after the index stay was re-designated according to the ECMO stay, 5 patients were excluded because they had no complete EASIX within 24 h, and 155 patients were finally included. The selection process is shown in Fig. 1. Among the 155 patients, the median age was 53 (41–63) years, 105 were male (67.7%), and the median BMI was 30.5 (25.8–35.6) kg/m². ECMO mode: unknown 74, VA 45, VV 25, Central 4, VA + VV 3, unclassified 4. Cardiogenic shock was present in 89 (57.4%), cardiac arrest in 37 (23.9%), respiratory failure in 106 (68.4%) and cardiac surgery in 26 (16.8%). Within 24 h of ICU admission, the median SOFA was 15 (11–16) points, the median Charlson index 2 (1–4), arterial pH 7.19 (7.06–7.27) and PaO_2/FiO_2 102.5 (69.5–208.8) mmHg; norepinephrine was used in 105 (67.7%), mechanical ventilation in 146 (94.2%) and CRRT in 34 (21.9%).

The median EASIX was 12.14 (IQR 4.04–55.94), the 90th percentile 190.05, the range 0.48–2589.5, and the median $\log_2$ 3.60. The tertile cut-points were 5.598 and 38.521, and the three groups comprised 52, 51 and 52 patients respectively (the EASIX distribution is shown in detail in Fig. 2). When grouped by tertile, 28-day death occurred in 80 patients (51.6%), and in the three groups in 17 (32.7%), 28 (54.9%) and 35 (67.3%) respectively, P = 0.002. The three groups differed statistically significantly in LDH, creatinine, platelets, SOFA, pH, cardiogenic shock, norepinephrine use, mechanical ventilation and CRRT (all P < 0.001), and the differences in ECMO mode composition (P = 0.001) and age (P = 0.026) were also statistically significant; the differences in BMI, Charlson index, PaO_2/FiO_2, sex, cardiac arrest, respiratory failure and cardiac surgery were not statistically significant (see Table 1 for details).

Primary endpoint: EASIX and 28-day all-cause mortality

After adjustment for age, sex, Charlson index, ECMO mode, cardiogenic shock and cardiac arrest, the HR for 28-day all-cause mortality per doubling of EASIX was 1.169 (95% CI 1.070–1.277, P < 0.001; overall model likelihood ratio $\chi^2 = 30.29$, df = 8, P < 0.001) (see **Supplementary Table 1** for details). In the same model, the HR for cardiac arrest was 1.779 (1.092–2.899, P = 0.021) and the HR for male sex 0.552 (0.347–0.878, P = 0.012); the differences for age HR 1.003 (0.987–1.020, P = 0.706), Charlson index HR 1.077 (0.964–1.203, P = 0.191), ECMO mode (VV vs VA 0.788, 0.323–1.925; other vs VA 0.952, 0.569–1.592) and cardiogenic shock HR 0.988 (0.591–1.653, P = 0.963) were all not statistically significant. The 7 variables of the main model had zero missing values, and the complete cases were the full cohort of 155 patients. Complete-case Cox and multiple imputation (m = 20) pooled results: the HR was 1.1688 in both, and the standard error on the log scale was 0.0452 in both.

Table 1
Baseline characteristics by EASIX tertile

Characteristic	Overall (n = 155)	T1, low (n = 52)	T2, middle (n = 51)	T3, high (n = 52)	P value
Age, years	53.0 (41.0–63.0)	51.5 (37.0–59.2)	59.0 (47.5–69.5)	52.0 (40.2–61.0)	0.026
BMI, kg/m² (missing 19)	30.5 (25.8–35.6)	29.8 (25.8–33.6)	30.8 (26.5–37.1)	31.2 (25.9–37.4)	0.650
LDH, U/L	760.0 (415.5–1890.0)	354.5 (285.8–501.2)	752.0 (531.5–986.5)	3412.5 (1672.5–6534.0)	< 0.001
Creatinine, mg/dL	1.9 (1.0–2.7)	0.9 (0.8–1.3)	1.8 (1.2–2.5)	2.7 (2.2–3.5)	< 0.001
Platelets, ×10⁹/L	108.0 (71.0–168.0)	175.0 (109.5–244.8)	100.0 (65.5–142.0)	79.0 (53.0–117.2)	< 0.001
EASIX (LDH × creatinine ÷ platelets)	12.14 (4.04–55.94)	2.61 (1.59–4.03)	12.14 (8.90–22.97)	101.42 (56.29–236.97)	< 0.001
SOFA score (24 h)	15.00 (11.00–16.00)	10.50 (8.00–13.00)	15.00 (12.00–16.00)	17.00 (15.00–18.00)	< 0.001
Charlson comorbidity index	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.5 (1.8–4.0)	0.146
Arterial pH (missing 1)	7.19 (7.06–7.27)	7.27 (7.21–7.35)	7.16 (7.05–7.22)	7.12 (7.05–7.23)	< 0.001
PaO_2/FiO_2, mmHg (missing 8)	102.5 (69.5–208.8)	101.5 (67.6–182.5)	96.2 (70.0–209.3)	124.0 (70.0–221.9)	0.406
Male sex	105 (67.7)	30 (57.7)	38 (74.5)	37 (71.2)	0.153
ECMO mode†					0.001
VA	45 (29.0)	10 (19.2)	15 (29.4)	20 (38.5)	
VV	25 (16.1)	16 (30.8)	7 (13.7)	2 (3.8)	
Central	4 (2.6)	0 (0.0)	0 (0.0)	4 (7.7)	
VA + VV	3 (1.9)	1 (1.9)	1 (2.0)	1 (1.9)	
Unclassified	4 (2.6)	2 (3.8)	0 (0.0)	2 (3.8)	
Unknown	74 (47.7)	23 (44.2)	28 (54.9)	23 (44.2)	

Characteristic	Overall (n = 155)	T1, low (n = 52)	T2, middle (n = 51)	T3, high (n = 52)	P value
Cardiogenic shock	89 (57.4)	20 (38.5)	29 (56.9)	40 (76.9)	< 0.001
Cardiac arrest	37 (23.9)	10 (19.2)	16 (31.4)	11 (21.2)	0.300
Respiratory failure	106 (68.4)	30 (57.7)	38 (74.5)	38 (73.1)	0.125
Cardiac surgery (procedure codes)	26 (16.8)	5 (9.6)	10 (19.6)	11 (21.2)	0.233
Norepinephrine	105 (67.7)	24 (46.2)	37 (72.5)	44 (84.6)	< 0.001
Mechanical ventilation†	146 (94.2)	43 (82.7)	51 (100.0)	52 (100.0)	< 0.001
CRRT	34 (21.9)	4 (7.7)	7 (13.7)	23 (44.2)	< 0.001
28-day all-cause death	80 (51.6)	17 (32.7)	28 (54.9)	35 (67.3)	0.002
90-day all-cause death	90 (58.1)	20 (38.5)	33 (64.7)	37 (71.2)	0.002
365-day all-cause death	94 (60.6)	21 (40.4)	34 (66.7)	39 (75.0)	< 0.001

Continuous variables are median (IQR) with P values from the Kruskal–Wallis test; categorical variables are n (%) with P values from the χ^2 test. † indicates that at least one expected cell count was below 5, in which case a 5,000-permutation exact test was used instead.

BMI was missing in 19 patients, arterial pH in 1 and PaO_2/FiO_2 in 8; all other variables were complete. Missing SOFA components were scored as 0, which is the definitional rule of the score rather than an imputation.

Dose–response shape: the restricted cubic spline (4 knots, reference $\log_2$EASIX = 3.60) showed no evidence of departure from linearity ($\chi^2 = 0.59$, df = 2, P = 0.745). With the cohort median as the reference, the HR was 0.60 (0.21–1.68) at $\log_2$EASIX of 0 (EASIX about 1), 1.67 (1.02–2.72) at 6 (EASIX 64), 2.18 (1.11–4.26) at 9 (EASIX 512) and 2.69 (0.76–9.49) at 12 (EASIX 4096) (see Fig. 3 for details).

Tertile risk stratification: with T1 (EASIX < 5.598) as the reference, the HR for 28-day death was 2.044 (95% CI 1.080–3.871, P = 0.028) for T2 (5.598–38.521) and 3.347 (1.750–6.403, P < 0.001) for T3 (> 38.521); with the tertile as an ordinal variable, the HR for trend was 1.805 (1.319–2.471, P < 0.001) (see **Supplementary Table 2** for details). The 28-day absolute risks of the three groups were 32.7%, 54.9% and 67.3% respectively; log-rank $\chi^2 = 16.07$, df = 2, P < 0.001 (see Fig. 4 for details).

Secondary endpoints

The EASIX effect size of the same 8-parameter model at 90 days and 365 days: HR 1.180 (1.084–1.284, P < 0.001) at 90 days and HR 1.182 (1.087–1.285, P < 0.001) at 365 days (see **Supplementary Table 1** for details). The three endpoints used the same model and were fitted in the same 155 patients, with event counts of 80, 90 and 94 respectively. The HR for male sex was 0.559 and 0.587, and the HR for cardiac arrest 1.953 and 1.977, all P < 0.05.

Subgroup analysis

Within each stratum of age (< 60 / ≥ 60 years), sex, ECMO mode (VA / VV / other), cardiogenic shock (yes / no) and SOFA (≤ 15 / > 15 points), the point estimate of the HR per doubling of EASIX ranged from 1.064 to 1.216 (Fig. 5). Interaction tests: age P = 0.842, sex P = 0.977, ECMO mode P = 0.853 (VV vs VA) and 0.391 (other vs VA), cardiogenic shock P = 0.949, SOFA P = 0.698 (**Supplementary Table 3**). The VA mode (45 patients, 24 deaths) had an HR of 1.201 (0.970–1.487), and the SOFA > 15 stratum (56 patients, 40 deaths) had an HR of 1.064 (0.906–1.249), with the 95% CI crossing 1.

Sensitivity analysis

Excluding those who died within 24 h of ICU admission (145 patients, 70 deaths) the HR was 1.170 (1.064–1.286); excluding those who converted between VA and VV modes (152 patients, 78 deaths) 1.165 (1.065–1.274); stratifying by ECMO mode and allowing the Charlson index to vary with time 1.171 (1.070–1.281); worst value in the 48-h window 1.174 (1.073–1.283); first measured value 1.112 (1.010–1.225, P = 0.031); value from blood drawn at the same time point at the same moment 1.111 (1.008–1.225, P = 0.034). Including only those with an unequivocal ECMO mode (74 patients, 37 deaths) 1.163 (0.974–1.389, P = 0.094); analysing only the VA mode (45 patients, 24 deaths) 1.201 (0.970–1.487, P = 0.093), the latter being a subset of the former. The results of the eight sensitivity analyses are shown in **Supplementary Table 4**. Proportional hazards assumption (Schoenfeld residuals): the EASIX term $\rho = -0.149$, $\chi^2 = 1.65$, df = 1, P = 0.199; global $\chi^2 = 17.16$, df = 8, P = 0.029; the VV class $\rho = 0.311$, $\chi^2 = 7.93$, P = 0.005; Charlson index $\rho = 0.215$, $\chi^2 = 4.43$, P = 0.035; all the remaining items P > 0.17.

Discussion

Our study suggests: in 155 adult critically ill patients receiving ECMO support, EASIX within 24 h of ICU admission was independently associated with 28-day all-cause mortality: for each doubling of EASIX, the risk of death increased by 17% (HR 1.169, 95% CI 1.070–1.277). The magnitude of the association was almost unchanged at the 90-day and 365-day endpoints (1.180 and 1.182), suggesting that what it reflects is not a transient peri-ECMO-cannulation perturbation, but a stable characteristic related to the patient's overall prognosis. Restricted cubic spline found no evidence of non-linearity, and the association was monotonic over an exposure range of nearly four orders of magnitude; when grouped by cohort tertiles, the absolute mortality rose from 32.7% to 67.3%, and both the trend test and the log-rank test supported the validity of the stratification. Within the five prespecified subgroups the direction of the association was consistent, with no evidence of interaction. Six of the eight sensitivity analyses

remained statistically significant, and two crossed 1 in the confidence interval because the sample size was halved, but the point estimate did not change.

Comparison with previous studies

From 2024 onwards, EASIX began to enter the cardiovascular field: Finke et al. confirmed in a coronary artery disease cohort that it predicted long-term death independently of left ventricular ejection fraction and degree of coronary stenosis [9]; Estler et al. reported in a chronic heart failure outpatient cohort an HR for all-cause mortality per doubling of EASIX of 1.51 (training cohort) and 1.59 (validation cohort), and that it could still further stratify within the same quartile of NT-proBNP [10]; Rehn et al. reported in 7233 patients undergoing cardiac surgery with cardiopulmonary bypass an OR per $\log_2$ of preoperative EASIX of 2.08 [11]; in addition there are reports in directions such as coronary artery bypass grafting [12], transcatheter aortic valve replacement [13][14], critical atrial fibrillation [15] and endovascular repair of type B aortic dissection [16]. The common conclusion of these studies is: a raised EASIX is associated with adverse outcomes, the strength of the association is moderate, but the cut-points cannot be applied across populations.

The effect sizes reported by the various cohorts of previous studies differ greatly. In MIMIC-IV, 28-day death after cardiopulmonary bypass was HR 1.12 per $\log_2$ [17], and critical atrial fibrillation 1.21 (short-term) and 1.16 (365 days) [15]. The 1.169 of the present study falls within this range, and is clearly lower than the chronic heart failure (1.51 and 1.59) and coronary artery disease cohorts. The 28-day mortality of this cohort reached 51.6%; against such a high background risk, the relative risk that a single biomarker can contribute is necessarily compressed, and this contrasts with the absolute risk difference (a difference of 34.6 percentage points between T1 and T3), which is the clinical anchor of risk stratification. The timing of the exposure also differs: the chronic heart failure and coronary artery disease cohorts measured values in the stable phase or before elective angiography, reflecting a chronic endothelial state [9][10]; the present study measured the worst value within 24 h after ECMO establishment, which is mixed with the acute haemolysis and shear injury caused by the circuit itself [5], and the noise is greater. The comparability of the index is likewise limited: the median EASIX of this cohort was 12.14, one order of magnitude higher than published cardiovascular cohorts (critical atrial fibrillation 5.64 [15], cardiac surgery with cardiopulmonary bypass 2.32 [11], transcatheter aortic valve replacement 1.65 [13], coronary artery bypass grafting 1.16 [12]). ECMO-related haemolysis causing a marked rise in LDH is the main reason, followed by the rise in creatinine caused by the acute kidney injury that is widespread in ECMO patients [6]. This means that no literature cut-point is applicable in this cohort, and the present study therefore used cohort tertiles (5.598 and 38.521) throughout and did not cite an external threshold.

Mechanistic explanation

The intersection of the three components of EASIX with the pathophysiology of ECMO is the most reasonable explanation of this association. The 26 studies summarised in the systematic review show that ECMO support further causes endothelial injury, with elevation of angiopoietin-2, von Willebrand

factor and extracellular vesicles in the circulation, and that in healthy animals ECMO itself can lead to vascular leakage and oedema [5]. Against this background: the rise in LDH comes both from red blood cell destruction (haemolysis) and from the release of intracellular enzymes after endothelial cell injury; the rise in creatinine reflects both the fall in renal perfusion and the change in microcirculatory permeability caused by endothelial dysfunction [6]; the fall in platelets reflects activation, aggregation and consumption after contact of blood with foreign surfaces, as well as von Willebrand factor-mediated microthrombus formation. The three indices are therefore not three independent risk factors, but readouts of the same endothelium–coagulation–perfusion axis from different sides, and this is also the biological basis on which they can be combined into a single ratio and keep a consistent direction of discrimination.

It should be stated that the endothelial nature of EASIX in the cardiovascular field still belongs to inference rather than direct validation: none of the existing studies has compared it head-to-head with endothelial gold standards (such as syndecan-1, angiopoietin-2, soluble thrombomodulin) in the same cohort, and the original literature itself acknowledges this [5][9]. The present study likewise has no endothelial markers, so the above explanation should be regarded as a mechanistic hypothesis compatible with the data, rather than a proven causal pathway.

Clinical implications

The tools currently used in clinical practice to judge the severity of this kind of patient are mainly systemic organ function scores such as SOFA and APACHE II, as well as oxygenation and perfusion indices such as arterial blood pH and PaO_2/FiO_2. The common feature of these tools is: they add the injuries of multiple organ systems with equal weight, and there is no dedicated characterisation of "endothelium", the target that ECMO directly strikes. The anchor of the present study is stratification, not prediction. EASIX can be obtained within 24 h of ICU admission, and all three items are indices that ECMO patients are routinely tested for every day; it adds no blood sampling, no cost and no additional equipment, which is an essential difference from biomarkers that require dedicated testing. The absolute risk difference of the tertile stratification is also large enough: 28-day death was 32.7% in the T1 group and 67.3% in the T3 group, and this gap can support concrete clinical actions: starting multidisciplinary assessment earlier for the T3 group, more actively considering transfer to a centre with transplantation or long-term support capability, and giving a more conservative expectation when communicating with the family. The association still exists at 365 days, which shows that a high EASIX is not a marker that "disappears once the acute phase is survived", and it also has indicative significance for the intensity of follow-up of those discharged alive. It should be stated that in this study neither age nor the Charlson index was statistically significant after adjustment, and the same was true of ECMO mode and cardiogenic shock, which suggests that under the case composition of this cohort the ability of these traditional factors to discriminate 28-day death was limited, rather than that they are unimportant.

Limitations

This study still has some limitations: the ECMO mode could not be determined (74 patients, 47.7%), the main model could only take "other" as a combined category, and adjustment by mode was incomplete; this study has no external validation, and the cut-points and effect sizes need to be re-examined in an independent ECMO cohort. With 155 patients and 80 events, the events per variable of 10.0 is already at the lower limit, and no further confounding could be adjusted for; residual confounding under the observational design cannot be excluded either.

Declarations

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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

MIMIC-IV (version 3.1) is hosted on PhysioNet (https://physionet.org/content/mimiciv/3.1/). Access requires PhysioNet credentialing, including completion of a training course in human subjects research, and signature of the PhysioNet data use agreement; the data are therefore not redistributed by the authors. The cohort definition scripts and analysis code that produce every estimate reported in this article are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study is a secondary analysis of the MIMIC-IV database (version 3.1). The collection of patient information and the creation of the research resource were reviewed by the Institutional Review Board of the Beth Israel Deaconess Medical Center, which granted a waiver of informed consent and approved the data sharing initiative. All records used in the present analysis were de-identified; the study involved no intervention and no attempt to re-identify any individual, and accordingly no further ethical approval or informed consent was required.

Competing interests

The authors declare no competing interests.

Consent for publication

All the authors agree to publish.

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Figures

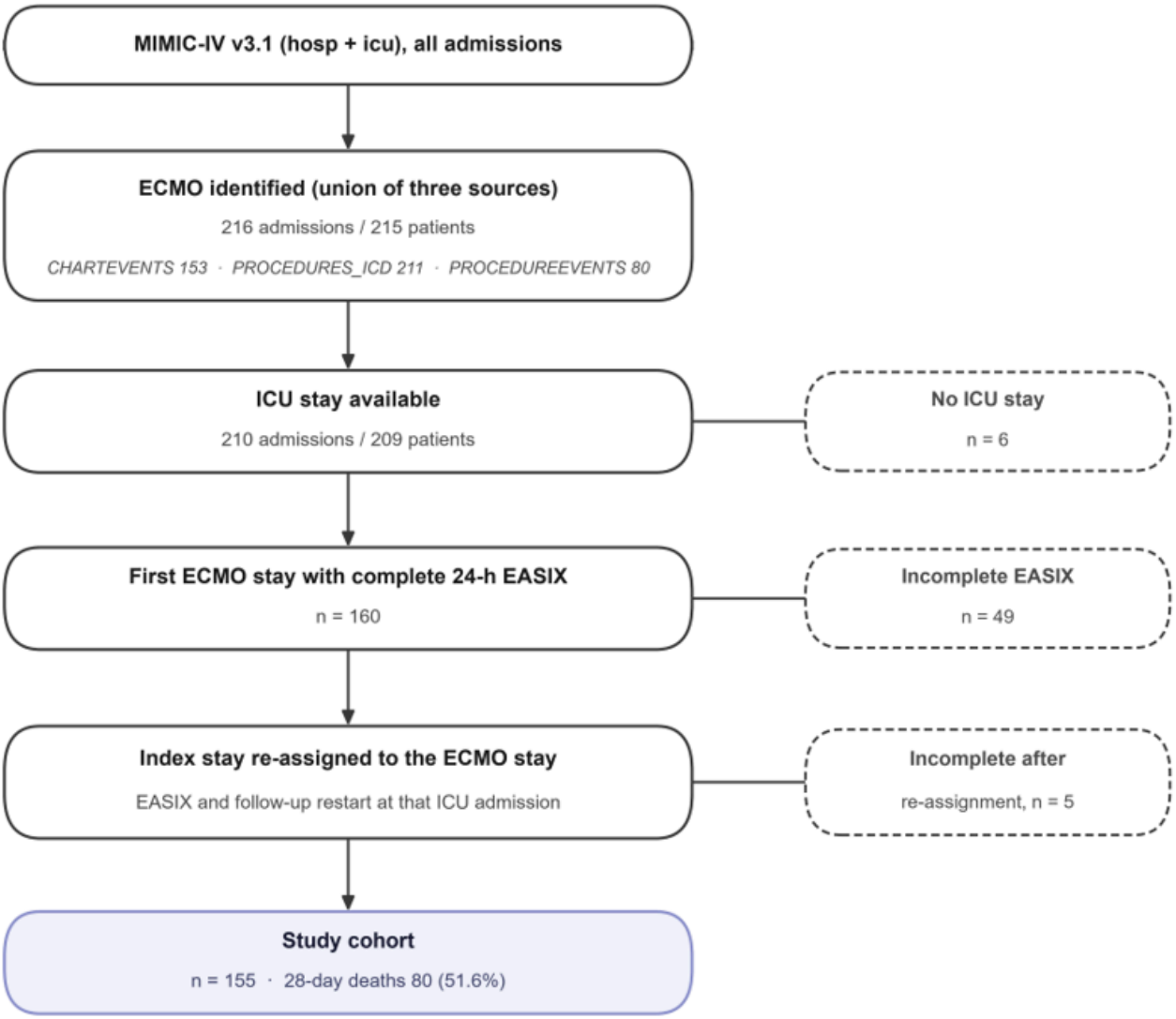


Figure 1

Selection of the study cohort.

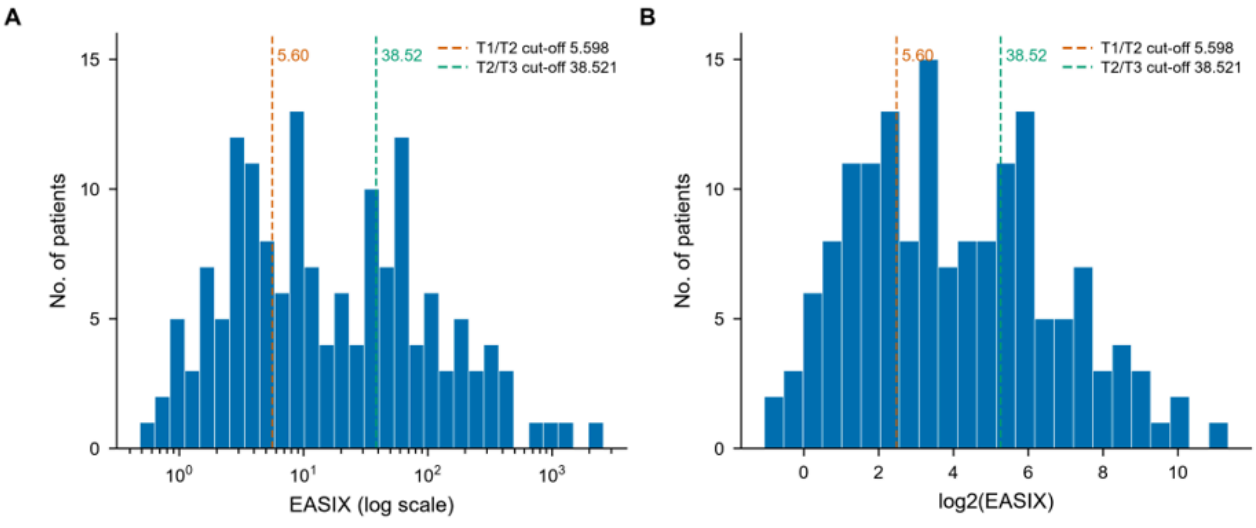


Figure 2

Distribution of EASIX in the cohort.

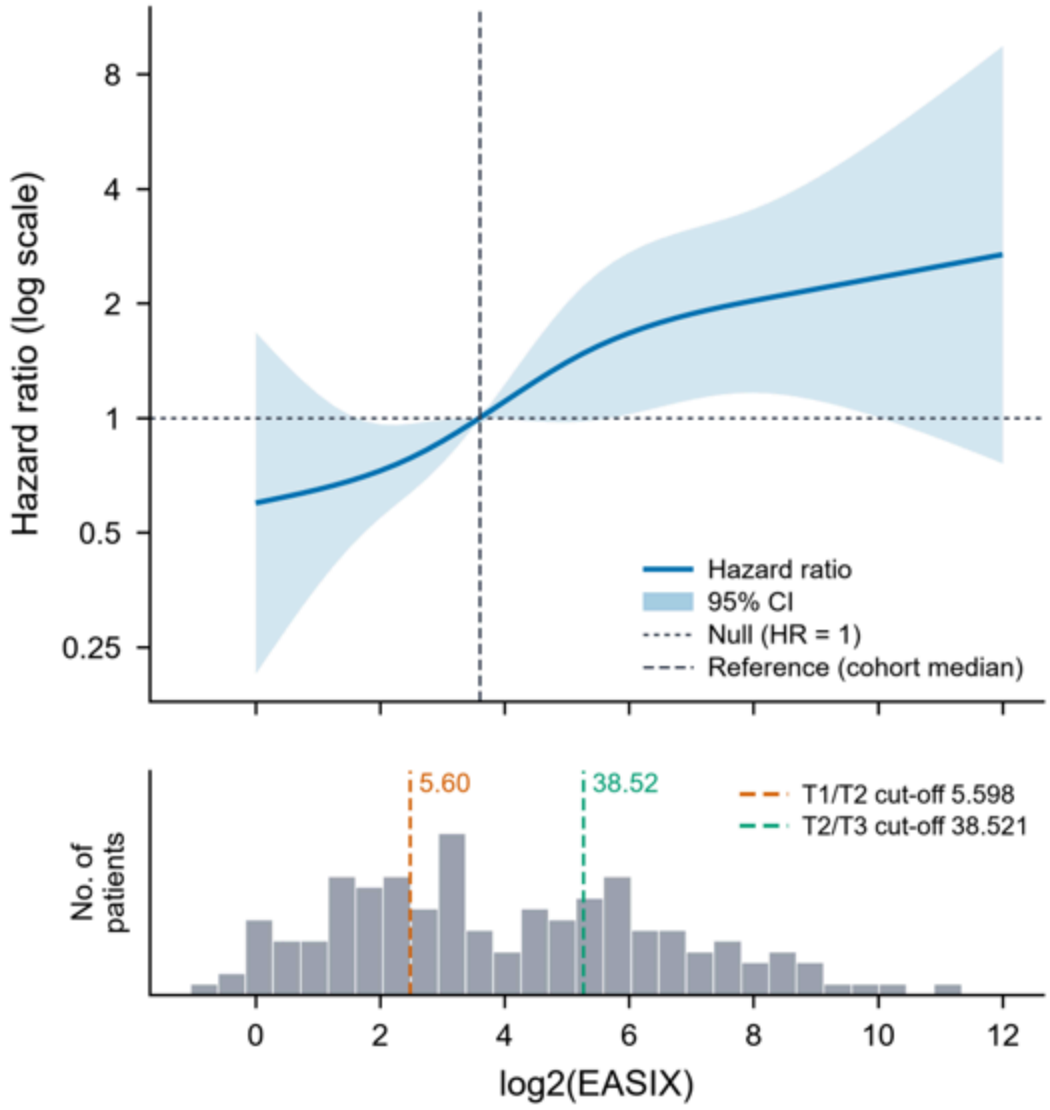


Figure 3

Dose–response association between EASIX and 28-day all-cause mortality.

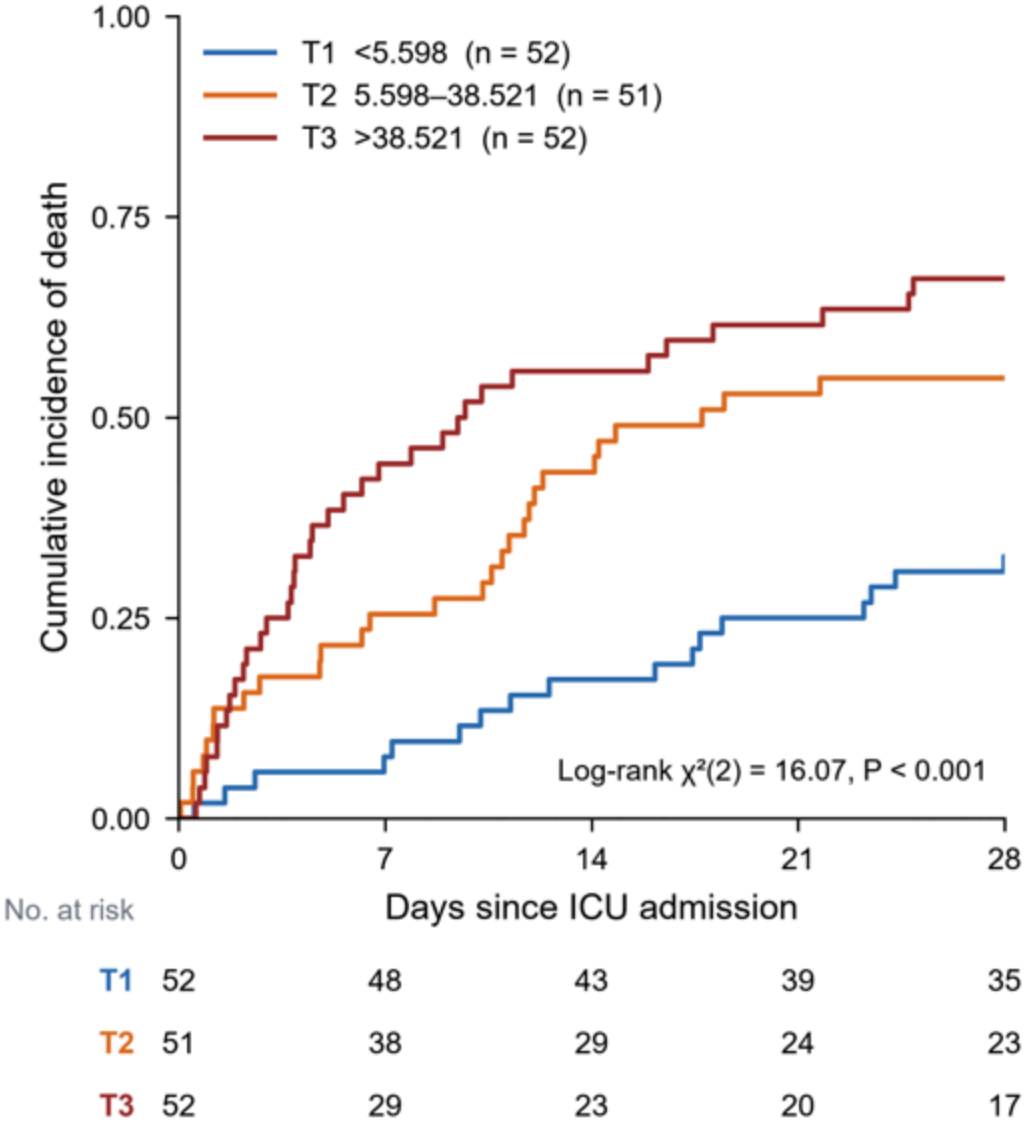


Figure 4

Cumulative incidence of 28-day all-cause death by EASIX tertile.

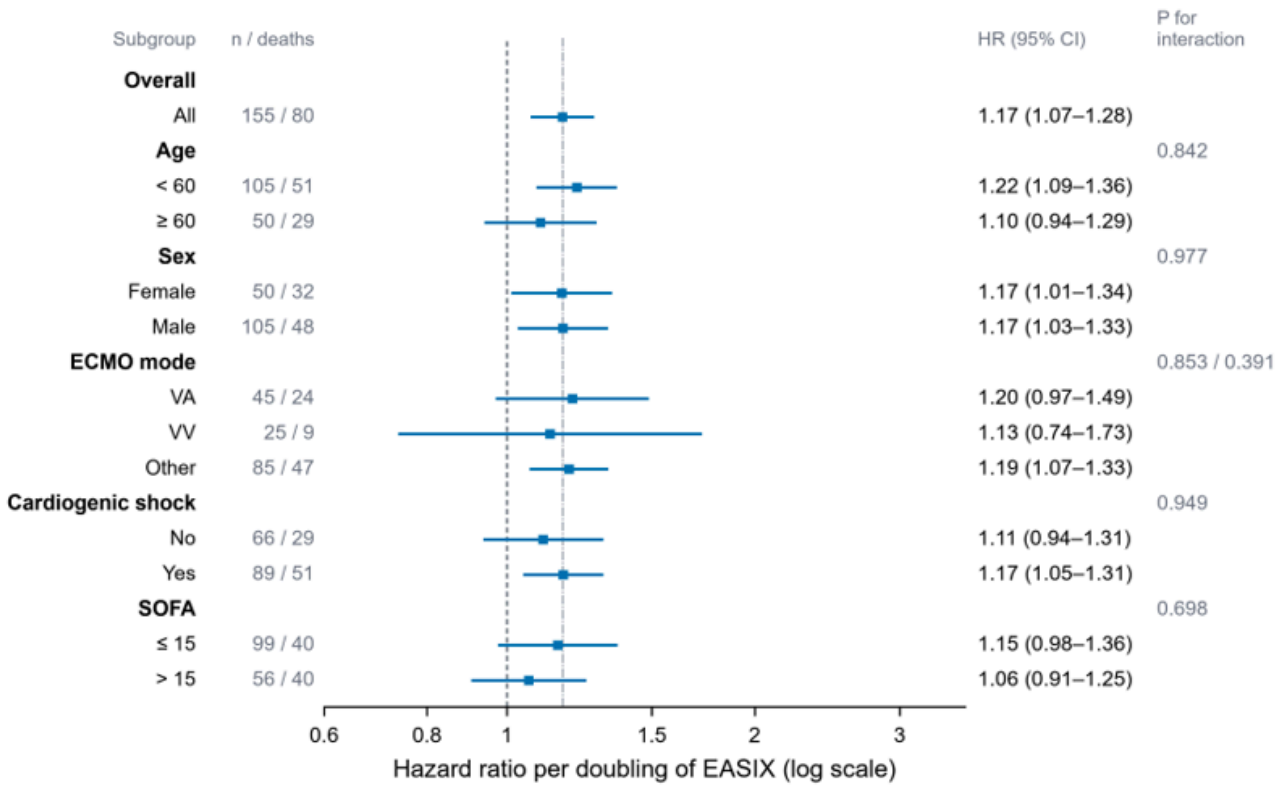


Figure 5

Association between EASIX and 28-day all-cause mortality within prespecified subgroups.

Supplementary Files

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