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Research Article

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Association between EASIX and all-cause mortality in patients with ventilator-associated pneumonia: a retrospective cohort study from the MIMIC-IV database

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Abstract

Background Ventilator-associated pneumonia (VAP) is a common ICU-acquired infection with high mortality. The Endothelial Activation and Stress Index (EASIX), a marker of endothelial dysfunction, has shown prognostic value in various critical illnesses, including respiratory diseases such as ARDS and COPD. However, its association with all-cause mortality in patients with VAP remains unclear. This study aimed to evaluate the prognostic value of EASIX in VAP patients using the MIMIC-IV database.

Methods Data were retrieved from the Medical Information Mart for Intensive Care IV (MIMIC-IV) version 3.1 database. Adult patients diagnosed with VAP and an ICU stay of more than 24 hours were eligible. EASIX was calculated using the standard formula and log2-transformed before analysis. Subjects were stratified by tertiles of log2-EASIX. The primary endpoint was 28-day all-cause mortality, and the secondary endpoint was 90-day all-cause mortality. The Boruta algorithm was used for covariate selection. Multivariable Cox proportional hazards regression, Kaplan–Meier survival curves, and restricted cubic spline (RCS) analyses were performed to assess the relationship between EASIX and prognosis.

Results The analytic cohort comprised 1673 patients with VAP, including 343 (20.5%) non-survivors and 1330 (79.5%) survivors. Non-survivors exhibited significantly higher log2-EASIX levels than survivors (median [IQR]: 1.74 [0.77–2.99] vs. 1.12 [0.15–2.25]; $P < 0.001$). In the fully adjusted Cox model, each 1-unit increase in log2-EASIX was independently associated with higher 28-day and 90-day mortality ($P < 0.001$). Relative to the lowest tertile, the highest tertile of log2-EASIX was associated with a greater risk of 28-day mortality (HR 1.68, 95% CI 1.15–2.46; $P = 0.008$) and 90-day mortality (HR 2.11, 95% CI 1.54–2.88; $P < 0.001$). Kaplan–Meier analysis demonstrated that patients with higher EASIX tertiles had significantly lower survival. RCS modelling indicated a near-linear relationship. Stratified analyses indicated that the association remained robust across subgroups.

Conclusions Elevated EASIX levels were independently associated with an increased risk of 28-day and 90-day all-cause mortality in critically ill patients with VAP. EASIX may serve as a simple, readily available, and useful prognostic marker for risk stratification in this population. Further prospective studies are warranted to validate its clinical utility.

Keywords Ventilator-associated pneumonia; endothelial activation and stress index; EASIX; MIMIC-IV; mortality; critically ill; retrospective cohort study.

Introduction

Severe infections in critically ill patients are complex to diagnose and manage and remain a leading cause of morbidity and mortality in the United States. They include sepsis, drug-resistant infections, opportunistic infections in immunocompromised patients, community-acquired pneumonia, ventilator-associated pneumonia, complicated genitourinary infections, and others[1]. Among these, VAP is one of the most common ICU-acquired infections, affecting 20–36% of critically ill patients, and remains associated with substantial morbidity, prolonged mechanical ventilation, elevated healthcare costs, and persistently high mortality. Despite advances in critical care, reported mortality rates for VAP remain as high as 27%, with case fatality rates reaching 36.07% in some cohorts. The pathobiological heterogeneity and diagnostic challenges associated with VAP remain of major significance in the global healthcare landscape[2]. Recent studies have redefined VAP as a dynamic ecological process, with its development contingent upon the interaction between the microbial community and the host's immune status, with sepsis-associated immune paralysis further accelerating this process[3]. Unsupervised clustering analyses have identified distinct Hospital-Acquired Pneumonia（HAP）subphenotypes in critically ill patients, each characterized by distinct differences in respiratory failure severity, systemic inflammatory response, degree of respiratory microbiome dysbiosis, mortality risk, and responsiveness to antibiotic

therapy[4]. Nevertheless, validated indicators for early risk stratification in VAP remain limited. In this setting, the primary potential utility of procalcitonin (PCT) lies in informing decisions to stop antibiotics and reducing the duration of antibiotic exposure[5]. Therefore, early identification of patients with VAP who are at high risk of death is clinically important for optimizing treatment and resource allocation. This study aimed to investigate the association between EASIX and all-cause mortality in patients with VAP.

Endothelial dysfunction plays a central role in the pathophysiology of critical illness, such as infection[6], inflammation[7, 8], coagulation activation[9], microcirculatory impairment[10], and multiple organ failure[11]. The Endothelial Activation and Stress Index (EASIX) is a composite biomarker derived from lactate dehydrogenase (LDH), creatinine, and platelet count[12]. It reflects endothelial activation, cellular injury, renal function, and coagulation status. Elevated serum LDH levels have been reported to be associated with poor prognosis in numerous diseases, particularly in the contexts of tumors and inflammation[13–15].Creatine plays a pivotal role in maintaining and regulating endothelial function, and serves as a dynamic marker of systemic endothelial activation and kidney injury induced by the progression of critical illness[16].The platelet count serves as an indicator of coagulation profile and endothelial homeostasis.

EASIX is a scoring tool functioning as a biological marker tied to impaired endothelial function; it can be readily computed from routine laboratory measurements[17]. This metric can be applied to predict endothelial-associated complications and death after allogeneic stem cell transplantation and acute graft-versus-host disease (GvHD)[18]. EASIX is been independently associated with increased all-cause mortality in several critically ill populations, including patients with atrial fibrillation[19], sepsis[20], heart failure[21], and acute myocardial infarction[22]. EASIX also shows prognostic value

in acute respiratory distress syndrome (ARDS)[23], chronic obstructive pulmonary disease [13, 24], and acute ischemic stroke[25]. Recent evidence indicates that EASIX is an independent risk factor for acute kidney injury (AKI) in critically ill patients with cancer[16].

However, to our knowledge, no study has specifically investigated the association between EASIX and all-cause mortality in patients with VAP. In light of the research gaps and prior evidence, we examined the association between EASIX and mortality in critically ill patients with VAP. Using the MIMIC-IV database, we conducted a retrospective cohort study to assess the association between EASIX and 28- and 90-day all-cause mortality in this population. Our findings could aid in identifying potential biomarkers for early risk stratification in these vulnerable patients.

Materials and methods

Sources of data and ethics declarations

For this investigation, data were drawn from MIMIC-IV (v3.1), an openly accessible and comprehensive repository established by the Computational Physiology Laboratory at the Massachusetts Institute of Technology. This repository contains over 90,000 ICU admissions to Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2022. It encompasses various types of information, including laboratory findings, medication records, and other pertinent clinical variables[26]. By addressing previous data-related limitations, MIMIC-IV markedly enhances data precision and completeness, thereby providing a more reliable, large-scale public database for clinical research. Such improvements are essential for disease prediction, treatment response evaluation, and numerous analyses, ultimately driving progress in medicine. All patient data had been de-identified; therefore, no additional ethical approval or informed consent was required for this retrospective analysis. One author, who met the

database access criteria, completed the data extraction while ensuring compliance with the ethical standards governing research data use.

Selection criteria

Patients with VAP admitted to the ICU were identified from the MIMIC-IV 3.1 database. The present study focused on patients diagnosed with ventilator-associated pneumonia (VAP), with diagnoses confirmed using ICD-9 codes (4957 and 99731) and ICD-10 code (J95851)[27]. Patients were excluded if they: (1)had more than one ICU admission (only the initial ICU stay was retained); (2) had a hospital stay shorter than 24 h; (3) did not meet the VAP diagnostic criteria; (4) were younger han 18 or older than 100 years; (5) had absent measurements of LDH, creatinine, or platelets during the first 24 hours after admission. The final analysis comprised 1673 patients. Outliers were identified based on quantile-based interquartile range (IQR) criteria, with observations outside the first quartile(Q1) −1.5IQR or the third quartile(Q3) +1.5IQR classified as extreme values. Although missing values existed, the proportion of missing values for each variable was below 5%. These missing values were retained without imputation. The final study population comprised 1673 patients, divided into tertile groups based on EASIX scores (Figure 1).

Data collection

Data extraction from the MIMIC-IV database was carried out using PostgreSQL (version 9.6). Demographics characteristics included age, gender, race, weight, and height. Medical history included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes, renal disease, malignant cancer, and AIDS. Vital signs included temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, and SpO_2. Laboratory data included white blood cell count, red blood cell count, platelet count,

lymphocytes, neutrophils, hemoglobin, hematocrit, red cell distribution width (RDW), albumin, glucose, creatinine, blood urea nitrogen (BUN). chloride, calcium, potassium, sodium, PT, PTT, INR, total bilirubin, ALT, ALP, AST, LDH, lactate, FiO_2, PO_2, PCO_2, $PaO_2/Fi\ O_2$ ratio, base excess, and pH. Clinical events and interventions included delirium, acute kidney injury (AKI), sepsis-3, continuous renal replacement therapy (CRRT), and medication sincluding: as vasopressors, glucocorticoids, antibiotics, propofol, fentanyl, midazolam, dexmedetomidine, heparin, enoxaparin, prednisone, dexamethasone, prednisolone, methylprednisolone, hydrocortisone, albuterol, ipratropium bromide, acetylcysteine, and budesonide. Disease severity scores included the Sequential Organ Failure Assessment (SOFA), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Model for End-Stage Liver Disease (MELD), Glasgow Coma Scale (GCS), Logistic Organ Dysfunction Score (LODS), Systemic Inflammatory Response Syndrome (SIRS) criteria, and Richmond Agitation-Sedation Scale (RASS). When a variable had repeated measurements during the first 24 h after ICU admission, only the initial value was retained. The EASIX score was derived using the equation: LDH [U/L] × creatinine [mg/dl] / platelet count [10^9/L][28].

Management of missing data and outliers

Missing values were handled through multiple imputation using the mice package in R. Specifically, variables with >20% missing data were excluded, variables with 5–20% missing data were imputed, and variables with <5% missing data were not imputed.

Feature selection

We sought to determine whether EASIX is associated with clinical outcomes via variable selection while concurrently choosing covariates for incorporation into the subsequent multivariable-adjusted model. To this end, we used the Boruta algorithm. Boruta algorithm: a machine learning approach built upon

Random Forest that identifies variables by evaluating their significance relative to that of randomly shuffled "shadow" variables. Variable importance, quantified using indicators such as the Gini impurity or mean decrease accuracy, mirrors their influence on the model's predictive capability. Variables with elevated Z-scores (computed as the disfference between the variable's importance and the average importance of shadow variables, normalized by their standard deviation) are kept, whereas those with lower importance are eliminated[29].

Expose variable and clinical outcome

The exposure variable was log2 EASIX, where EASIX was calculated as: EASIX = LDH (U/L) × creatinine (mg/dL) / platelet count (×10⁹/L). The log2 EASIX value was used for analysis, and patients were divided into tertiles according to log2 EASIX. The endpoints of the present study were 28-day and 90-day ICU mortality. Follow-up started at ICU admission and continued to the corresponding time point (day 28 or day 90), or until death.

Statistical and analysis

Continuous data were presented as mean ± standard deviation (SD) or median (interquartile range), whereas categorical variables were reported as counts (%). Because EASIX had a skewed distribution, it was subjected log2-transformed prior to analysis[6]. All participants were categorized into three groups according to tertiles of log2EASIX. Intergroup comparisons among the three groups were conducted using one-way ANOVA or the Kruskal-Wallis test for continuous variables, and the $\chi 2$ test or Fisher's exact test for categorical variables, as appropriate. The 28-day and 90-day survival probabilities were estimated via the Kaplan-Meier approach for the three tertile groups and compared with the log-rank test. The relationship between log2EASIX and 28-day and 90-day mortality was examined using Cox proportional hazards models. Multicollinearity was evaluated by calculating the variance inflation factor

(VIF), with a VIF greater than 5 indicating multicollinearity. Both unadjusted and multivariable-adjusted models were constructed to assess the robustness of the findings. Covariates for adjustment were selected based on clinical significance and a minimum 10% change in the effect estimate. Model 1 was unadjusted; Model 2 included adjustments for age, gender, race, and weight. Model 3 was adjusted for age, gender, weight, race, temperature, SpO_2, mean blood pressure, white blood cell count, neutrophils, lymphocytes, glucose, BUN, chloride, PT, INR, ALT, myocardial infarction, congestive heart failure, renal disease, delirium, sepsis-3, vasopressors, hydrocortisone, and RASS. Restricted cubic spline analysis was performed to assess the potential non-linear relationship between log2 EASIX and survival outcome. Subgroup analyses were conducted to evaluate the consistency of the association. Sensitivity analyses, including propensity score matching and Love plots, were performed to assess the robustness of the findings. A two-sided P value < 0.05 was considered statistically significant. If a non-linear relationship was detected, a two-piecewise linear regression model would be applied to identify the threshold effect of log2 EASIX on sepsis prognosis. Subgroup analyses were also performed to evaluate the robustness of our results, including age, gender, race, congestive heart failure, myocardial infarction, malignant cancer, chronic pulmonary disease, cerebrovascular disease, and diabetes. Data analyses were performed using R software (version 4.5.2; R Foundation for Statistical Computing, http://www.R-project.org).

Results

Baseline characteristics

The initial cohort comprised 2,974 patients with VAP. Of these, 816 were excluded because they had a hospital stay of less than 24 hours. An additional 485 patients were excluded because of missing laboratory variables (LDH, creatinine, and platelet counts) required for EASIX computation. The final study sample comprised 1,673 patients (Figure. 1).

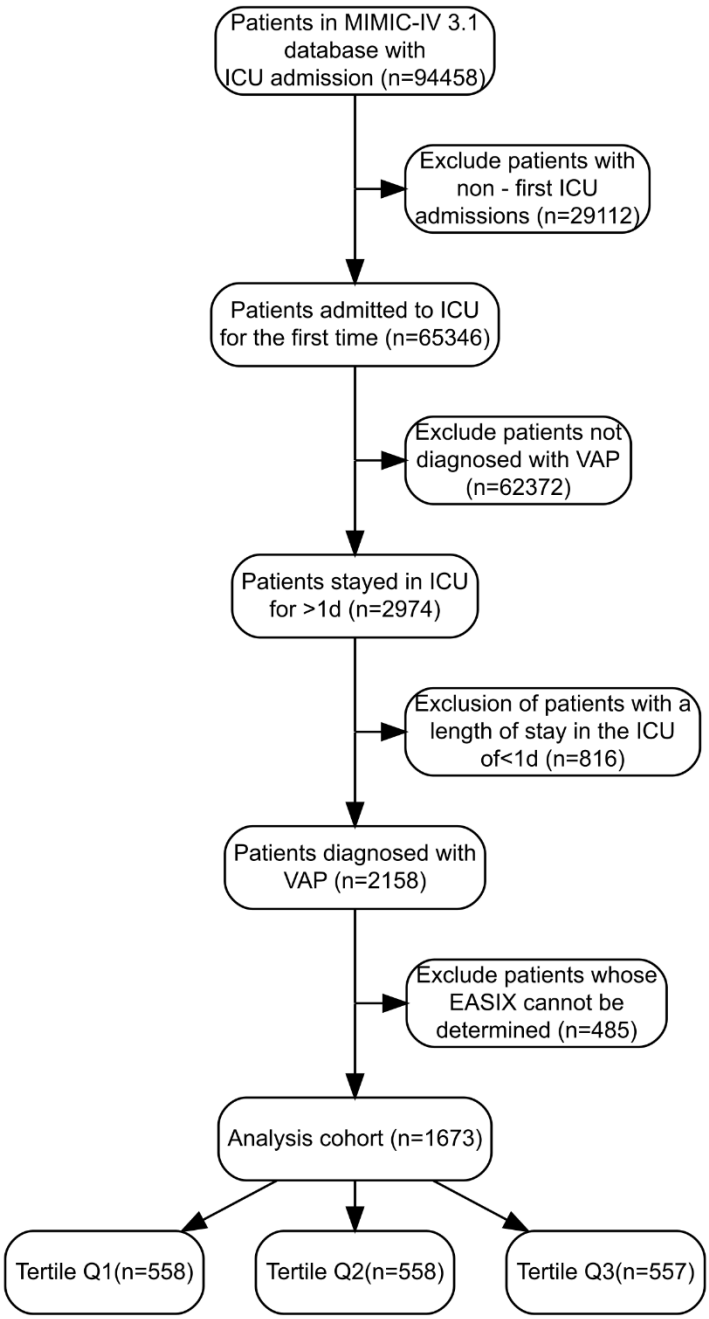


Figure. 1 Selection flowchart of patients with VAP from the MIMIC-IV database.

The present analysis included 1,673 patients diagnosed with VAP. Among them, 343 individuals (20.5%) died, whereas 1,330 (79.5%) survived (Table 1). Relative to survivors, non-survivors were significantly older (median age, 68.85 [59.75–77.14] vs. 62.75 [51.72–72.97] years; $P < 0.001$). No marked disparity was observed in sex distribution ($P = 0.522$), although racial composition differed significantly ($P = 0.016$). Non-survivors exhibited a higher prevalence of myocardial infarction,

congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, and renal disease (all $P < 0.05$). Regarding vital signs, non-survivors had a higher respiratory rate (21 vs. 20 bpm; $P = 0.012$), lower diastolic blood pressure (67 vs. 69 mmHg; $P = 0.027$), and lower SpO2 (97% vs. 98%; $P = 0.030$). Laboratory findings revealed that non-survivors had increased white blood cell count, neutrophil count, glucose, creatinine, blood urea nitrogen, chloride, potassium, sodium, prothrombin time, partial thromboplastin time, INR, ALT, ALP, AST, and LDH, along with decreased lymphocyte count and calcium levels (all $P < 0.05$). Notably, log2EASIX was significantly higher in non-survivors (1.74 [0.77–2.99] vs. 1.12 [0.15–2.25]; $P < 0.001$). Furthermore, non-survivors had greater illness severity, as reflected by higher SOFA, APS III, SAPS II, MELD, LODS, and RASS scores (all $P < 0.001$). They also had a higher incidence of complications, including delirium, AKI, and sepsis3 (all $P < 0.05$), and were more frequently treated with vasopressors, glucocorticoids, fentanyl, midazolam, dexmedetomidine, and hydrocortisone, as well as CRRT (all $P < 0.05$).

Table 1. Baseline characteristics of the study population stratified by survival status.

Variables	Total(1673)	Survivors(n=1330)	Non-survivors(n=343)	p-value
Demographics				
Age(years),n(%)	64.21 [53.08, 73.85]	62.75 [51.72, 72.97]	68.85 [59.75, 77.14]	<0.001
Gender,n(%)				0.522
Female	1085 (64.9)	857 (64.4)	228 (66.5)	
Male	588 (35.1)	473 (35.6)	115 (33.5)	
Race,n(%)				0.016
White	877 (52.4)	710 (53.4)	167 (48.7)	
Black	183 (10.9)	156 (11.7)	27 (7.9)	
Hispanic	30 (1.8)	23 (1.7)	7 (2.0)	
Others	583 (34.8)	441 (33.2)	142 (41.4)	
Weight (kg)	84.30 [70.00, 100.00]	85.00 [70.00, 100.77]	81.40 [68.75, 99.15]	0.109
Height (cm)	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	170.00 [163.00, 178.00]	0.193
Past history,n(%)				

Myocardial infarct				<0.001
No	1327 (79.3)	1080 (81.2)	247 (72.0)	
Yes	346 (20.7)	250 (18.8)	96 (28.0)	
Congestive heart failure				<0.001
No	1100 (65.8)	912 (68.6)	188 (54.8)	
Yes	573 (34.2)	418 (31.4)	155 (45.2)	
Peripheral vascular				0.035
No	1472 (88.0)	1182 (88.9)	290 (84.5)	
Yes	201 (12.0)	148 (11.1)	53 (15.5)	
Cerebrovascular				0.014
No	1295 (77.4)	1047 (78.7)	248 (72.3)	
Yes	378 (22.6)	283 (21.3)	95 (27.7)	
Chronic pulmonary				0.003
No	1213 (72.5)	987 (74.2)	226 (65.9)	
Yes	460 (27.5)	343 (25.8)	117 (34.1)	
Diabetes				0.101
No	1104 (66.0)	891 (67.0)	213 (62.1)	
Yes	569 (34.0)	439 (33.0)	130 (37.9)	
Renal				<0.001
No	1277 (76.3)	1045 (78.6)	232 (67.6)	
Yes	396 (23.7)	285 (21.4)	111 (32.4)	
Vital signs				
Temperature (℃)	36.83 [36.44, 37.22]	36.83 [36.44, 37.22]	36.78 [36.33, 37.11]	0.024
Heart rate (bpm)	91.00 [76.00, 106.00]	91.00 [76.00, 106.00]	89.00 [75.00, 107.00]	0.933
Resp rate (bpm)	20.00 [17.00, 25.00]	20.00 [16.00, 25.00]	21.00 [18.00, 26.00]	0.012
MBP(mmHg)	84.00 [71.00, 97.00]	84.00 [72.00, 97.00]	83.00 [70.00, 94.00]	0.17
Spo2 (%)	98.00 [94.00, 100.00]	98.00 [95.00, 100.00]	97.00 [93.00, 100.00]	0.03
Laboratory data				
WBC (10^9/L)	12.10 [8.40, 16.80]	11.70 [8.20, 16.30]	13.50 [9.50, 18.35]	<0.001
RBC (10^9/L)	3.59 [3.01, 4.23]	3.59 [3.02, 4.23]	3.56 [2.95, 4.21]	0.562
Platelet (10^9/L)	206.23 (109.23)	205.76 (107.63)	208.06 (115.34)	0.728
Lymphocytes (10^9/L)	0.98 [0.61, 1.56]	0.99 [0.62, 1.57]	0.90 [0.53, 1.44]	0.015

Neutrophils (10^9/L)	9.79 [6.59, 14.38]	9.60 [6.35, 13.93]	10.78 [7.82, 16.09]	<0.001
Hemoglobin (g/dL)	10.80 (2.47)	10.80 (2.46)	10.78 (2.51)	0.903
Hematocrit (%)	32.80 [27.80, 38.20]	32.85 [27.90, 38.30]	32.40 [27.45, 37.95]	0.836
RDW (%)	14.70 [13.50, 16.30]	14.60 [13.50, 16.20]	14.90 [13.50, 16.75]	0.136
Albumin (g/dL)	2.90 [2.50, 3.30]	2.90 [2.50, 3.30]	2.90 [2.40, 3.30]	0.672
Glucose (mg/dL)	142.00 [112.00, 191.00]	141.00 [112.00, 186.75]	151.00 [116.00, 199.50]	0.035
Creatinine(mg/dL)	1.10 [0.80, 1.80]	1.10 [0.80, 1.70]	1.40 [0.90, 2.40]	<0.001
Bun(mg/dL)	22.00 [15.00, 38.00]	21.00 [14.00, 35.00]	27.00 [17.00, 50.50]	<0.001
Chloride(mmol/L)	104.00 [99.00, 108.00]	104.00 [99.00, 108.00]	102.00 [97.00, 107.00]	<0.001
Calcium (mmol/L)	8.30 [7.70, 8.80]	8.30 [7.70, 8.80]	8.30 [7.80, 8.80]	0.046
Potassium(mmol/L)	4.20 [3.70, 4.70]	4.10 [3.70, 4.70]	4.30 [3.90, 4.80]	<0.001
Sodium (mmol/L)	139.00 [135.00, 142.00]	139.00 [136.00, 142.00]	138.00 [134.00, 141.00]	<0.001
PT (s)	14.00 [12.60, 17.10]	13.90 [12.60, 16.80]	14.50 [12.70, 18.15]	0.047
PTT (s)	31.40 [27.60, 39.90]	31.10 [27.60, 39.20]	32.10 [27.60, 43.05]	0.035
INR	1.30 [1.10, 1.60]	1.30 [1.10, 1.50]	1.30 [1.20, 1.60]	0.038
Bilirubin total (mg/dL)	0.60 [0.40, 1.10]	0.60 [0.40, 1.10]	0.60 [0.40, 1.30]	0.096
ALT(IU/L)	32.00 [18.00, 66.00]	31.00 [18.00, 62.75]	37.00 [21.00, 85.50]	0.003
ALP(IU/L)	79.00 [58.00, 114.00]	77.00 [56.00, 110.00]	88.00 [65.00, 132.00]	<0.001
AST(IU/L)	48.00 [28.00, 98.00]	47.00 [27.00, 91.75]	54.00 [32.00, 123.00]	0.002
LDH(IU/L)	335.00 [240.00, 514.00]	323.00 [233.25, 485.75]	393.00 [260.00, 634.50]	<0.001
Lactate(mmol/L)	1.60 [1.20, 2.70]	1.60 [1.10, 2.70]	1.70 [1.20, 3.00]	0.056
Fio2 (%)	60.00 [50.00, 100.00]	60.00 [50.00, 100.00]	60.00 [50.00, 100.00]	0.176
Po2 (mmHg)	95.00 [59.00, 171.00]	96.00 [60.00, 175.00]	90.00 [55.00, 152.00]	0.186
Pco2(mmHg)	42.00 [36.00, 52.00]	42.50 [36.00, 52.00]	42.00 [36.00, 51.00]	0.755
Pao2fio2ratio (mmHg)	165.00 [96.67, 287.00]	166.00 [97.50, 288.25]	160.00 [87.75, 275.50]	0.306
Baseexcess(mmol/L)	-1.82 (5.90)	-1.70 (5.99)	-2.30 (5.51)	0.09
Ph	7.35 [7.28, 7.41]	7.35 [7.28, 7.42]	7.35 [7.28, 7.40]	0.263
Log2EASIX	1.24 [0.23, 2.42]	1.12 [0.15, 2.25]	1.74 [0.77, 2.99]	<0.001
EASIX (median [IQR])	2.36 [1.17, 5.34]	2.18 [1.11, 4.75]	3.34 [1.71, 7.97]	<0.001
Events,n(%)				
Delirium				0.001
No	258 (15.4)	185 (13.9)	73 (21.3)	

Yes	1415 (84.6)	1145 (86.1)	270 (78.7)	
AKI				0.003
No	63 (3.8)	60 (4.5)	3 (0.9)	
Yes	1610 (96.2)	1270 (95.5)	340 (99.1)	
Sepsis3				0.003
No	78 (4.7)	73 (5.5)	5 (1.5)	
Yes	1595 (95.3)	1257 (94.5)	338 (98.5)	
Medication,n(%)				
Vaso (%)				0.001
No	542 (32.4)	457 (34.4)	85 (24.8)	
Yes	1131 (67.6)	873 (65.6)	258 (75.2)	
Glucocorticoid				<0.001
No	1229 (73.5)	1016 (76.4)	213 (62.1)	
Yes	444 (26.5)	314 (23.6)	130 (37.9)	
Heparin				0.089
No	132 (7.9)	113 (8.5)	19 (5.5)	
Yes	1541 (92.1)	1217 (91.5)	324 (94.5)	
Methylprednisolone				0.481
No	1432 (85.6)	1143 (85.9)	289 (84.3)	
Yes	241 (14.4)	187 (14.1)	54 (15.7)	
Hydrocortisone				<0.001
No	1424 (85.1)	1176 (88.4)	248 (72.3)	
Yes	249 (14.9)	154 (11.6)	95 (27.7)	
Albuterol				0.508
No	829 (49.6)	665 (50.0)	164 (47.8)	
Yes	844 (50.4)	665 (50.0)	179 (52.2)	
Ipratropium bromide				0.589
No	1130 (67.5)	903 (67.9)	227 (66.2)	
Yes	543 (32.5)	427 (32.1)	116 (33.8)	
Acetylcysteine				0.549
No	1515 (90.6)	1201 (90.3)	314 (91.5)	
Yes	158 (9.4)	129 (9.7)	29 (8.5)	

Budesonide				0.83
No	1649 (98.6)	1310 (98.5)	339 (98.8)	
Yes	24 (1.4)	20 (1.5)	4 (1.2)	
Evaluation scores				
SOFA	7.00 [4.00, 10.00]	7.00 [4.00, 10.00]	8.00 [5.00, 11.00]	<0.001
APSIII	54.00 [41.00, 71.00]	52.00 [40.00, 68.00]	63.00 [49.00, 82.00]	<0.001
SAPSII	42.00 [32.00, 52.00]	40.00 [31.00, 51.00]	47.00 [39.00, 56.00]	<0.001
MELD	15.00 [9.00, 23.00]	14.00 [9.00, 22.25]	18.00 [10.00, 25.80]	<0.001
GCS	15.00 [15.00, 15.00]	15.00 [15.00, 15.00]	15.00 [15.00, 15.00]	0.57
LODS	7.00 [5.00, 9.00]	7.00 [5.00, 9.00]	8.00 [6.00, 10.00]	<0.001
SIRS	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	0.368
RASS	2.00 [1.00, 2.00]	2.00 [1.00, 3.00]	2.00 [0.00, 2.00]	<0.001
Intervention,n(%)				
CRRT				<0.001
No	1285 (76.8)	1089 (81.9)	196 (57.1)	
Yes	388 (23.2)	241 (18.1)	147 (42.9)	

Data are presented as means ± SD, median (interquartile range), or n (%).

AKI, acute kidney injury; **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **APS-III**, Acute Physiology Score III; **AST**, aspartate aminotransferase; **CRRT**, continuous renal replacement therapy; **EASIX**, endothelial activation and stress index; **GCS**, Glasgow Coma Scale; **Hct**, hematocrit; **INR**, international normalized ratio; **LDH**, lactate dehydrogenase; **LODS**, logistic organ dysfunction score; **MBP**, mean blood pressure; **MELD**, Model for End-Stage Liver Disease; **PT**, prothrombin time; **PTT**, partial thromboplastin time; **RASS**, Richmond Agitation-Sedation Scale; **RBC**, red blood cell; **RDW**, red cell distribution width; **SAPS-II**, Simplified Acute Physiology Score II; **SIRS**, systemic inflammatory response syndrome; **SOFA**, Sequential Organ Failure Assessment; **SpO2**, oxyhemoglobin saturation; **WBC**, white blood cell.

In the baseline analysis stratified by EASIX tertiles (Table 2), patients with higher EASIX levels (Q3) exhibited a more severe clinical profile than those with lower EASIX levels (Q1). The three groups differed significantly in log2EASIX (Q1, −0.44 ± 0.86; Q2, 1.26 ± 0.38; Q3, 3.44 ± 1.39; $P < 0.001$). Age, lymphocyte count, chloride, sodium, Po2, GCS, and RASS did not differ significantly among the groups (all $P > 0.05$), whereas sex and racial distributions differed significantly ($P = 0.001$ and $P = 0.005$, respectively). Patients in Q3 had a higher prevalence of myocardial infarction (28.7% vs 13.4%), congestive heart failure (42.4% vs 24.9%), peripheral vascular disease (15.1% vs 8.8%), diabetes (37.0% vs 29.2%), and renal disease (41.5% vs 7.9%) compared with Q1 (all $P < 0.05$). They also exhibited higher respiratory rate and heart rate, and lower SpO2, SBP, DBP, and MBP (all $P < 0.05$). Laboratory findings revealed that Q3 patients had higher WBC, neutrophil count, RDW, glucose, creatinine, BUN, potassium, PT, PTT, INR, total bilirubin, ALT, ALP, AST, LDH, lactate, and FiO2, but lower RBC, platelet count, hemoglobin, hematocrit, albumin, calcium, pH, base excess, and PaO2/FiO2 ratio (all $P < 0.05$). In addition, Q3 showed higher CCI, SOFA2, SOFA, MELD, LODS, SIRS, APSIII, SAPSII, and OASIS scores (all $P < 0.001$). Regarding therapeutic interventions, the Q3

group patients were more likely to receive CRRT (47.8% vs 4.1%), vasopressors (77.2% vs 59.3%), glucocorticoids (33.2% vs 22.0%), fentanyl (90.1% vs 78.9%), midazolam (60.7% vs 52.7%), and hydrocortisone (23.0% vs 9.1%) than Q1 patients (all $P < 0.05$). Conversely, enoxaparin use was lower in Q3 than in Q1 (5.6% vs 19.2%; $P < 0.001$), and dexmedetomidine use was also lower in Q3 (9.9% vs 15.6%; $P = 0.017$). For clinical outcomes, the highest EASIX tertile exhibited significantly higher 28-day ICU mortality (29.4% vs 19.7%; $P = 0.001$) and 90-day ICU mortality (43.1% vs 28.3%; $P < 0.001$) than the lowest tertile. Collectively, these findings suggest that elevated EASIX is accompanied by greater disease severity and poorer survival in critically ill patients with VAP.

Table 2. Baseline characteristics of the population according to log2EASIX tertiles.

Variables	Total(n=1673)	Q1(n=558)	Q2(n=558)	Q3(n=557)	P-value
Demographics					
Age(years),n(%)	62.60 (15.41)	61.81 (15.73)	62.96 (15.36)	63.04 (15.12)	0.331
Gender,n(%)					
Female	1085 (64.9)	329 (59.0)	385 (69.0)	371 (66.6)	0.001
Male	588 (35.1)	229 (41.0)	173 (31.0)	186 (33.4)	
Race,n(%)					0.005
White	877 (52.4)	306 (54.8)	295 (52.9)	276 (49.6)	
Black	183 (10.9)	42 (7.5)	56 (10.0)	85 (15.3)	
Hispanic	30 (1.8)	8 (1.4)	11 (2.0)	11 (2.0)	
Others	583 (34.8)	202 (36.2)	196 (35.1)	185 (33.2)	
Weight (kg)	88.00 (27.95)	84.05 (28.01)	89.66 (28.40)	90.31 (27.04)	<0.001
Height (cm)	170.03 (10.21)	168.95 (10.65)	170.84 (9.62)	170.32 (10.27)	0.006
BMI(kg/m2)	30.54 (9.30)	29.31 (9.16)	31.12 (9.65)	31.12 (8.99)	0.002
Past history,n(%)					
Myocardial infarct					<0.001
No	1327 (79.3)	483 (86.6)	447 (80.1)	397 (71.3)	
Yes	346 (20.7)	75 (13.4)	111 (19.9)	160 (28.7)	
Congestive heart failure					<0.001
No	1100 (65.8)	419 (75.1)	360 (64.5)	321 (57.6)	
Yes	573 (34.2)	139 (24.9)	198 (35.5)	236 (42.4)	
Peripheral vascular					0.005
No	1472 (88.0)	509 (91.2)	490 (87.8)	473 (84.9)	
Yes	201 (12.0)	49 (8.8)	68 (12.2)	84 (15.1)	
Cerebrovascular					0.162

No	1295 (77.4)	421 (75.4)	428 (76.7)	446 (80.1)	
Yes	378 (22.6)	137 (24.6)	130 (23.3)	111 (19.9)	
Chronic pulmonary					0.103
No	1213 (72.5)	388 (69.5)	406 (72.8)	419 (75.2)	
Yes	460 (27.5)	170 (30.5)	152 (27.2)	138 (24.8)	
Diabetes					0.013
No	1104 (66.0)	395 (70.8)	358 (64.2)	351 (63.0)	
Yes	569 (34.0)	163 (29.2)	200 (35.8)	206 (37.0)	
Renal					<0.001
No	1277 (76.3)	514 (92.1)	437 (78.3)	326 (58.5)	
Yes	396 (23.7)	44 (7.9)	121 (21.7)	231 (41.5)	
Malignant cancer					0.272
No	1509 (90.2)	495 (88.7)	511 (91.6)	503 (90.3)	
Yes	164 (9.8)	63 (11.3)	47 (8.4)	54 (9.7)	
Aids					0.926
No	1660 (99.2)	554 (99.3)	553 (99.1)	553 (99.3)	
Yes	13 (0.8)	4 (0.7)	5 (0.9)	4 (0.7)	
Vital signs					
Temperature (℃)	36.76 (1.09)	36.82 (0.94)	36.81 (1.10)	36.63 (1.20)	0.005
Resp rate (bpm)	21.38 (6.38)	20.90 (6.12)	21.19 (6.39)	22.04 (6.57)	0.008
Heart rate (bpm)	91.94 (21.84)	90.06 (21.62)	91.73 (21.50)	94.03 (22.24)	0.01
Spo2	96.19 (5.08)	96.64 (4.59)	96.05 (5.65)	95.89 (4.94)	0.035
MBP(mmHg)	84.89 (19.97)	86.86 (19.05)	86.10 (21.67)	81.71 (18.69)	<0.001
Laboratory data					
WBC (10^9/L)	13.67 (11.17)	13.43 (7.11)	12.85 (6.22)	14.74 (16.85)	0.015
RBC (10^9/L)	3.63 (0.85)	3.73 (0.77)	3.70 (0.88)	3.45 (0.87)	<0.001
Platelet(10^9/L)	206.23 (109.23)	272.90 (114.73)	194.96 (85.81)	150.73 (87.40)	<0.001
Lymphocytes (10^9/L)	1.45 (6.84)	1.28 (0.99)	1.24 (1.39)	1.83 (11.72)	0.274
Neutrophils (10^9/L)	11.27 (7.14)	10.91 (6.13)	10.89 (6.06)	12.02 (8.84)	0.01
Hemoglobin (g/dL)	10.80 (2.47)	11.00 (2.28)	11.07 (2.53)	10.33 (2.52)	<0.001
Hematocrit (%)	33.21 (7.27)	33.86 (6.37)	33.91 (7.54)	31.88 (7.67)	<0.001
RDW(%)	15.26 (2.42)	14.96 (2.22)	14.95 (2.27)	15.87 (2.64)	<0.001

Albumin (g/dL)	2.89 (0.61)	2.94 (0.65)	2.92 (0.61)	2.82 (0.57)	0.003
Glucose (mg/dL)	164.83 (84.42)	151.84 (65.40)	166.60 (79.91)	176.08 (102.22)	<0.001
Creatinine	1.68 (1.80)	0.81 (0.37)	1.36 (0.76)	2.87 (2.60)	<0.001
Bun(mg/dL)	31.22 (25.68)	19.59 (13.61)	28.76 (21.30)	45.34 (31.64)	<0.001
Chloride(mmol/L)	103.44 (7.63)	103.46 (7.28)	103.80 (7.23)	103.05 (8.33)	0.252
Calcium (mmol/L)	8.25 (1.03)	8.39 (0.91)	8.22 (0.97)	8.14 (1.17)	<0.001
Potassium(mmol/L)	4.30 (0.85)	4.08 (0.69)	4.25 (0.76)	4.56 (1.01)	<0.001
Sodium (mmol/L)	138.70 (6.25)	139.04 (5.77)	138.73 (6.15)	138.33 (6.80)	0.161
PT (s)	16.75 (10.50)	15.01 (9.27)	16.18 (8.80)	19.05 (12.62)	<0.001
PTT (s)	40.61 (27.08)	35.31 (20.53)	40.92 (28.39)	45.61 (30.37)	<0.001
INR	1.52 (0.91)	1.35 (0.67)	1.46 (0.63)	1.76 (1.25)	<0.001
Bilirubin_total (mg/dL)	1.38 (2.93)	0.80 (1.84)	1.34 (2.84)	1.99 (3.68)	<0.001
ALT(IU/L)	140.00 (602.47)	45.90 (63.79)	58.60 (108.20)	315.80 (1014.51)	<0.001
ALP(IU/L)	103.21 (86.78)	101.05 (73.43)	96.44 (89.04)	112.15 (95.77)	0.008
AST(IU/L)	247.62 (1208.89)	52.32 (69.85)	89.28 (144.24)	601.89 (2044.46)	<0.001
LDH(IU/L)	559.59 (1151.05)	267.25 (104.30)	389.23 (192.58)	1023.10 (1898.97)	<0.001
Lactate(mmol/L)	2.42 (2.23)	1.78 (1.49)	2.32 (1.96)	3.17 (2.82)	<0.001
Fio2 (%)	66.34 (24.70)	61.02 (23.60)	67.66 (25.02)	70.36 (24.57)	<0.001
Po2 (mmHg)	133.74 (109.75)	128.51 (99.81)	137.26 (110.35)	135.45 (118.31)	0.373
Pco2(mmHg)	45.41 (14.28)	46.92 (15.04)	45.03 (14.27)	44.29 (13.39)	0.006
Pao2fio2ratio (mmHg)	208.99 (152.59)	217.81 (144.62)	214.08 (157.13)	195.05 (155.03)	0.028
Baseexcess(mmol/L)	-1.82 (5.90)	0.61 (5.29)	-1.85 (5.26)	-4.22 (6.09)	<0.001
Ph	7.34 (0.11)	7.37 (0.10)	7.34 (0.11)	7.31 (0.12)	<0.001
Log2EASIX	1.42 (1.86)	-0.44 (0.86)	1.26 (0.38)	3.44 (1.39)	<0.001
EASIX	9.55 (56.40)	0.85 (0.39)	2.49 (0.67)	25.33 (95.86)	<0.001
Events,n(%)					
Delirium					0.076
No	258 (15.4)	101 (18.1)	83 (14.9)	74 (13.3)	
Yes	1415 (84.6)	457 (81.9)	475 (85.1)	483 (86.7)	
AKI					<0.001
No	63 (3.8)	35 (6.3)	18 (3.2)	10 (1.8)	
Yes	1610 (96.2)	523 (93.7)	540 (96.8)	547 (98.2)	

Sepsis3					0.008
No	78 (4.7)	37 (6.6)	26 (4.7)	15 (2.7)	
Yes	1595 (95.3)	521 (93.4)	532 (95.3)	542 (97.3)	
CRRT					<0.001
No	1285 (76.8)	535 (95.9)	459 (82.3)	291 (52.2)	
Yes	388 (23.2)	23 (4.1)	99 (17.7)	266 (47.8)	
Medication,n(%)					
Vaso					<0.001
No	542 (32.4)	227 (40.7)	188 (33.7)	127 (22.8)	
Yes	1131 (67.6)	331 (59.3)	370 (66.3)	430 (77.2)	
Glucocorticoid					<0.001
No	1229 (73.5)	435 (78.0)	422 (75.6)	372 (66.8)	
Yes	444 (26.5)	123 (22.0)	136 (24.4)	185 (33.2)	
Heparin					0.226
No	132 (7.9)	49 (8.8)	48 (8.6)	35 (6.3)	
Yes	1541 (92.1)	509 (91.2)	510 (91.4)	522 (93.7)	
Methylprednisolone					0.782
No	1432 (85.6)	477 (85.5)	482 (86.4)	473 (84.9)	
Yes	241 (14.4)	81 (14.5)	76 (13.6)	84 (15.1)	
Hydrocortisone					<0.001
No	1424 (85.1)	507 (90.9)	488 (87.5)	429 (77.0)	
Yes	249 (14.9)	51 (9.1)	70 (12.5)	128 (23.0)	
Albuterol					0.583
No	829 (49.6)	272 (48.7)	271 (48.6)	286 (51.3)	
Yes	844 (50.4)	286 (51.3)	287 (51.4)	271 (48.7)	
Ipratropium bromide					0.916
No	1130 (67.5)	375 (67.2)	375 (67.2)	380 (68.2)	
Yes	543 (32.5)	183 (32.8)	183 (32.8)	177 (31.8)	
Acetylcysteine					0.892
No	1515 (90.6)	504 (90.3)	508 (91.0)	503 (90.3)	
Yes	158 (9.4)	54 (9.7)	50 (9.0)	54 (9.7)	
Budesonide					0.413

No	1649 (98.6)	547 (98.0)	551 (98.7)	551 (98.9)	
Yes	24 (1.4)	11 (2.0)	7 (1.3)	6 (1.1)	
Evaluation scores					
CCI	5.04 (2.97)	4.35 (2.77)	5.01 (2.94)	5.76 (3.02)	<0.001
SOFA2	8.66 (3.71)	6.70 (2.92)	8.44 (3.32)	10.85 (3.61)	<0.001
SOFA	7.22 (3.94)	4.86 (3.05)	6.92 (3.35)	9.88 (3.64)	<0.001
MELD	16.76 (8.64)	10.88 (5.36)	16.00 (7.30)	23.40 (7.93)	<0.001
GCS	14.42 (2.01)	14.47 (1.86)	14.51 (1.77)	14.27 (2.35)	0.11
LODS	7.16 (2.96)	5.82 (2.76)	6.85 (2.51)	8.82 (2.78)	<0.001
SIRS	2.87 (0.90)	2.75 (0.95)	2.85 (0.91)	3.00 (0.82)	<0.001
APSIII	57.82 (23.68)	48.09 (20.65)	55.68 (20.71)	69.69 (24.28)	<0.001
SAPSII	43.37 (14.90)	37.50 (13.59)	42.08 (12.97)	50.54 (15.05)	<0.001
OASIS	37.57 (7.79)	36.06 (7.01)	36.95 (7.84)	39.69 (8.05)	<0.001
RASS	1.57 (1.39)	1.51 (1.38)	1.63 (1.34)	1.55 (1.46)	0.331
Intervention,n(%)					
CRRT					<0.001
No	1285 (76.8)	535 (95.9)	459 (82.3)	291 (52.2)	
Yes	388 (23.2)	23 (4.1)	99 (17.7)	266 (47.8)	
Outcomes,n(%)					
Icu outcome 28d					0.001
No	1265 (75.6)	448 (80.3)	424 (76.0)	393 (70.6)	
Yes	408 (24.4)	110 (19.7)	134 (24.0)	164 (29.4)	
Icu outcome 90d					<0.001
No	1080 (64.6)	400 (71.7)	363 (65.1)	317 (56.9)	
Yes	593 (35.4)	158 (28.3)	195 (34.9)	240 (43.1)	

Data are presented as means ± SD, median (interquartile range), or n (%).

AKI, acute kidney injury; **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **APS-III**, Acute Physiology Score III; **AST**, aspartate aminotransferase; **CRRT**, continuous renal replacement therapy; **EASIX**, endothelial activation and stress index; **GCS**, Glasgow Coma Scale; **Hct**, hematocrit; **INR**, international normalized ratio; **LDH**, lactate dehydrogenase; **LODS**, logistic organ dysfunction score; **MBP**, mean blood pressure; **MELD**, Model for End-Stage Liver Disease; **PT**, prothrombin time; **PTT**, partial thromboplastin time; **RASS**, Richmond Agitation-Sedation Scale; **RBC**, red blood cell; **RDW**, red cell distribution width; **SAPS-II**, Simplified Acute Physiology Score II; **SIRS**, systemic inflammatory response syndrome; **SOFA**, Sequential Organ Failure Assessment; **SpO2**, oxyhemoglobin saturation; **WBC**, white blood cell.

Feature selection

The Boruta algorithm identified 32 of the 91 candidate variables as showing the strongest associations with 28-day ICU all-cause mortality (Figure. 2A). The Boruta algorithm identified 26 of the 89 candidate variables as showing the strongest associations with 90-day ICU all-cause mortality (Figure. 2B).

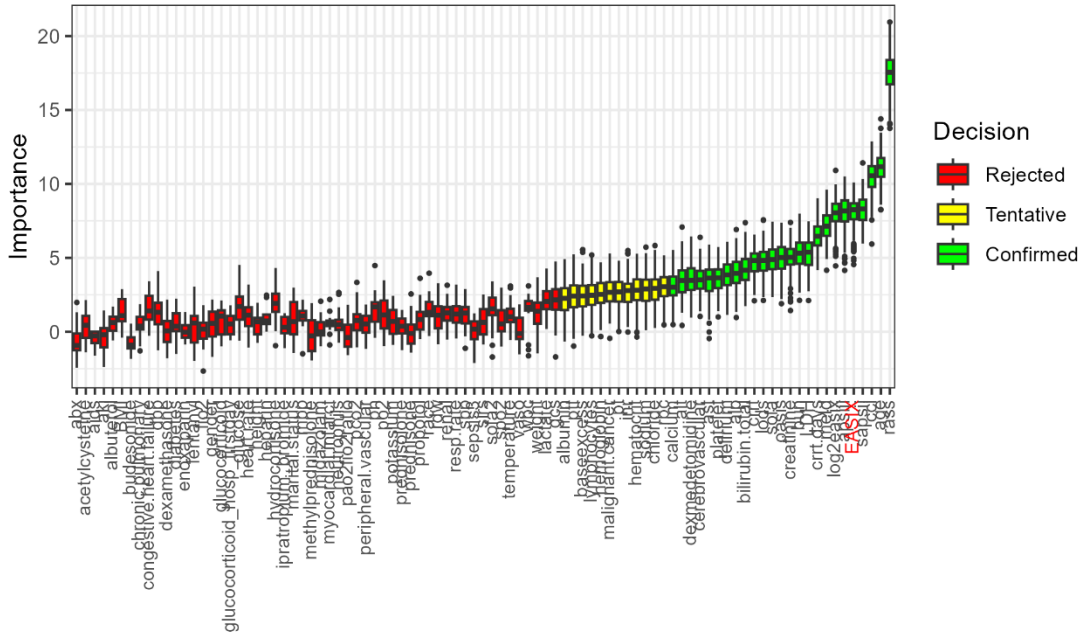
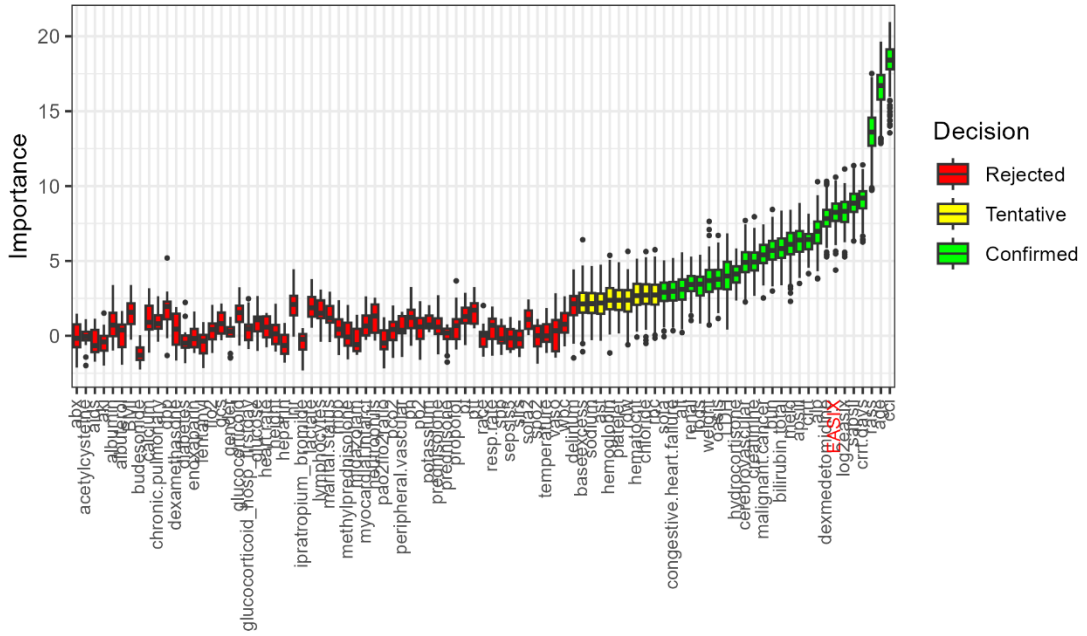


Figure. 2 Boruta-based predictor screening for the relationship between EASIX and ICU mortality. **(A)** 28-day ICU all-cause mortality.



(B) 90-day ICU all-cause mortality. The horizontal axis presents the variable names, while the vertical axis represents the Z value of each variable. The boxplot depicts the Z-score of each variable in the model calculation, with green boxes representing important variables, yellow representing tentative attributes, and red representing unimportant variables.

Kaplan-Meier survival analysis and survival outcome

Kaplan-Meier curves for 28-day overall survival stratified by EASIX tertiles are shown in Figure 3A. The Q3 group, which had the highest EASIX level, exhibited the lowest survival rate, suggesting the greatest mortality risk. In contrast, the Q1 group, with the lowest EASIX level, exhibited the highest survival rate, indicating the lowest mortality risk (log-rank P = 0.001). A comparable trend was noted for 90-day overall survival (Figure.3B), where Q3 patients exhibited a significantly lower survival rate than those in Q1 or Q2 (log-rank P < 0.001).

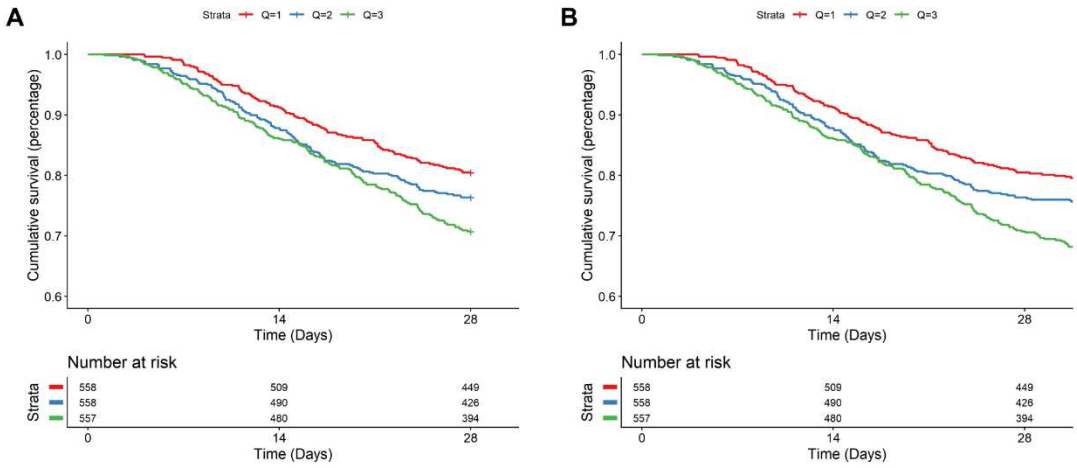


Figure.3 Kaplan–Meier survival curves for 28-day **(A)** and 90-day **(B)** all-cause mortality according to log2 EASIX tertiles. Q1, Q2, and Q3 represent the lowest, middle, and highest tertiles of log2 EASIX, respectively. The numbers at risk at 0, 14, and 28 days are shown below the curves. The log-rank test was used to compare survival among the three groups.

Cox regression analysis

Multivariable Cox proportional hazards regression models were fitted to examine the independent associations of EASIX with 28-day and 90-day mortality in patients with VAP (Table 3). When EASIX was entered as a continuous variable (log2EASIX), higher levels were significantly associated with an increased hazard of 28-day mortality across all three models. The corresponding hazard ratios (HR) with 95% confidence intervals (CI) were 1.10 (1.05–1.15), 1.13 (1.07–1.18), and 1.12 (1.05–1.19) for Models 1, 2, and 3, respectively (all $P < 0.05$). In the categorical analysis by EASIX tertiles, patients in the highest tertile (Q3) had a higher risk of 28-day mortality than those in the lowest tertile (Q1). The unadjusted HR (95% CI) were 1.52 (1.11–2.08) for Q2 and 2.20 (1.63–2.99) for Q3 ($P = 0.009$ and $P < 0.001$, respectively). These associations persisted after adjustment for covariates in Model 2 (Q2: HR 1.49, 95% CI 1.06–2.02, $P = 0.02$; Q3: HR 2.20, 95% CI 1.54–2.88, $P < 0.001$) and Model 3 (Q2: HR 1.45, 95% CI 1.03–2.05, $P = 0.033$; Q3: HR 1.68, 95% CI 1.15–2.46, $P = 0.008$). A significant graded trend across tertiles was observed in all models (P for trend < 0.05).

For 90-day mortality, similar results were obtained. As a continuous variable, log2 EASIX was positively associated with 90-day mortality in Models 1–3, with HRs (95% CIs) of 1.10 (1.06–1.14), 1.12 (1.08–1.17), and 1.12 (1.08–1.17), respectively (all $P < 0.001$). When analyzed categorically, compared with Q1, the HRs (95% CIs) for Q2 were 1.52 (1.11–2.08), 1.49 (1.08–2.06), and 1.46 (1.06–2.02) across Models 1–3, respectively, and for Q3 were 2.20 (1.63–2.99), 2.20 (1.62–3.01), and 2.10 (1.54–2.88), respectively (all $P < 0.05$). The test for trend also revealed a significant dose–response relationship ($P < 0.001$ for all models).

Table 3.Cox regression analysis of EASIX levels and mortality in VAP patients.

Characteristic	Model 1			Model 2			Model3		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
28-day mortality									
Log2easix	1.1	1.05, 1.15	<0.001	1.13	1.07, 1.18	<0.001	1.12	1.05, 1.19	0.001
Tertile of Log2easix									
Q1	Reference			Reference			Reference		
Q2	1.52	1.11, 2.08	0.009	1.49	1.06, 2.02	0.02	1.45	1.03, 2.05	0.033
Q3	2.2	1.63, 2.99	<0.001	2.2	1.54, 2.88	<0.001	1.68	1.15, 2.46	0.008
Test for trend	1.15	1.07, 1.24	<0.001	1.16	1.07, 1.24	<0.001	1.1	1.01, 1.20	0.032
90-day mortality									
Log2easix	1.1	1.06, 1.14	<0.001	1.12	1.08, 1.17	<0.001	1.12	1.08, 1.17	<0.001
Tertile of Log2easix									
Q1	Reference			Reference			Reference		
Q2	1.52	1.11, 2.08	0.009	1.49	1.08, 2.06	0.02	1.46	1.06, 2.02	0.02
Q3	2.2	1.63, 2.99	<0.001	2.2	1.62, 3.01	<0.001	2.1	1.54, 2.88	<0.001
Test for trend	1.17	1.10, 1.24	<0.001	1.18	1.10, 1.25	<0.001	1.18	1.10, 1.25	<0.001

Model 1 was unadjusted.

Model 2 was adjusted for age, gender, race, and weight.

Model 3 was adjusted for age, gender, race, weight, temperature, SpO2, MBP, WBC, neutrophils, lymphocytes, glucose, BUN, chloride, PT, INR, ALT, myocardial infarction, congestive heart failure, renal disease, delirium, Sepsis-3, vasopressors, hydrocortisone, and RASS.

Restricted cubic spline analysis

Restricted cubic spline (RCS) analysis was performed to evaluate the association between log2EASIX and 28-day all-cause mortality in the ICU (Figure. 4). In the unadjusted model (Model A), a significant nonlinear association was observed between log2EASIX and the outcome (P for overall < 0.001; P for nonlinearity = 0.037). However, after adjusting for demographic and clinical covariates (Models B and C), the nonlinear component became non-significant (P for nonlinearity = 0.334 and 0.485, respectively). The restricted cubic spline (RCS) curves displayed a monotonic, linear increase in hazard ratio (HR) across the continuum of log2EASIX in the fully adjusted models.

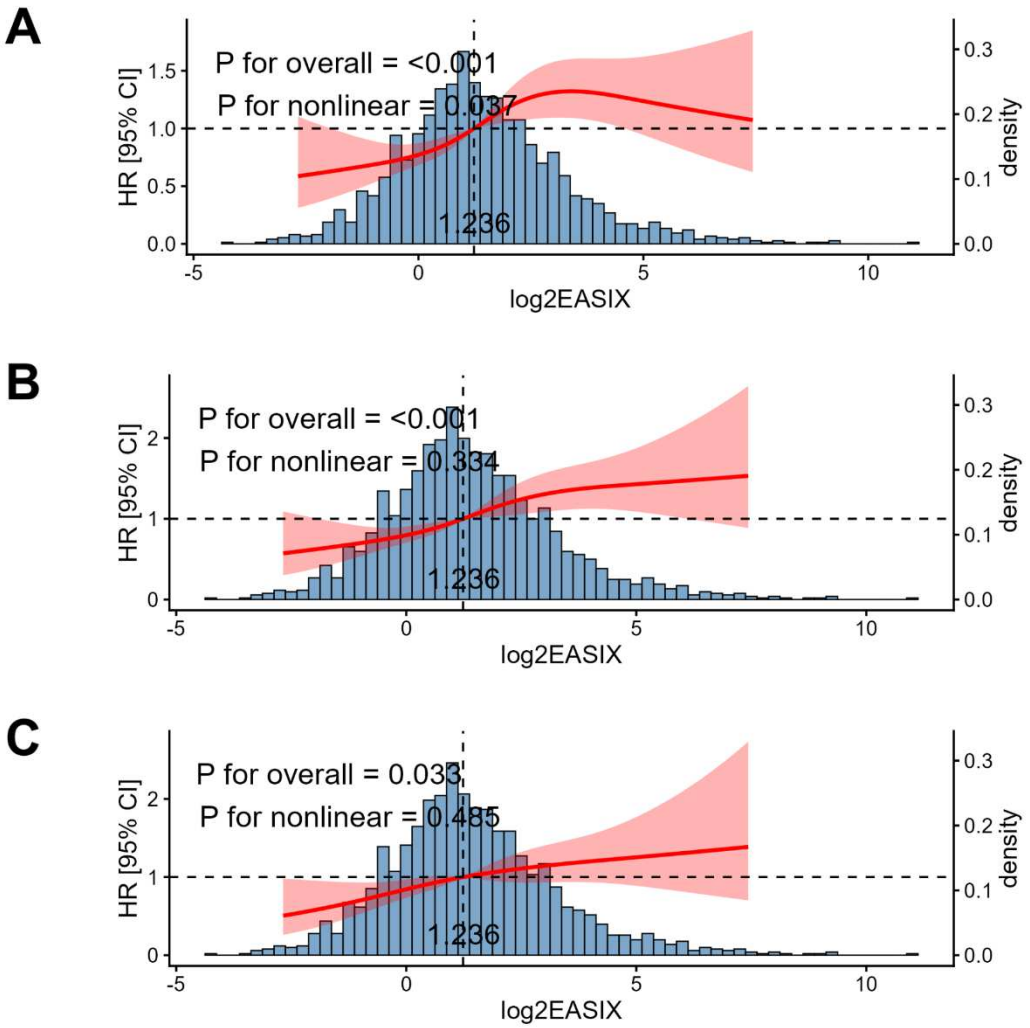


Figure.4 Restricted cubic spline analysis of 28-day ICU all-cause mortality. (A) Model 1 was unadjusted. (B) Model 2 was adjusted for age + gender + race + weight. (C) Model 3 was adjusted for age, gender, weight, race, temperature, spo2, mbp, wbc, neutrophils, lymphocytes, glucose, bun, chloride, pt, inr, alt, myocardial infarct, congestive heart failure, renal, sepsis3, vaso, hydrocortisone, rass.

Restricted cubic spline (RCS) analysis was performed to evaluate the association between log2EASIX and 28-day all-cause mortality in the ICU (Figure. 5). In the unadjusted model (Model 1), the RCS curve revealed a significant U-shaped nonlinear relationship (P for overall < 0.001; P for nonlinearity = 0.001), with an inflection point observed at a log2EASIX value of 1.236. As covariates were progressively added (Models 2 and 3), the nonlinear trend was attenuated but remained statistically significant in Model 2 (P

for nonlinearity = 0.039). However, in the fully adjusted model (Model 3), the nonlinear component was no longer significant (P for nonlinearity = 0.407), indicating that the association between log2EASIX and 28-day ICU mortality was better described as a linear positive trend (P for overall = 0.005). All variance inflation factor (VIF) values were below 10, precluding significant multicollinearity and confirming the stability of the models.

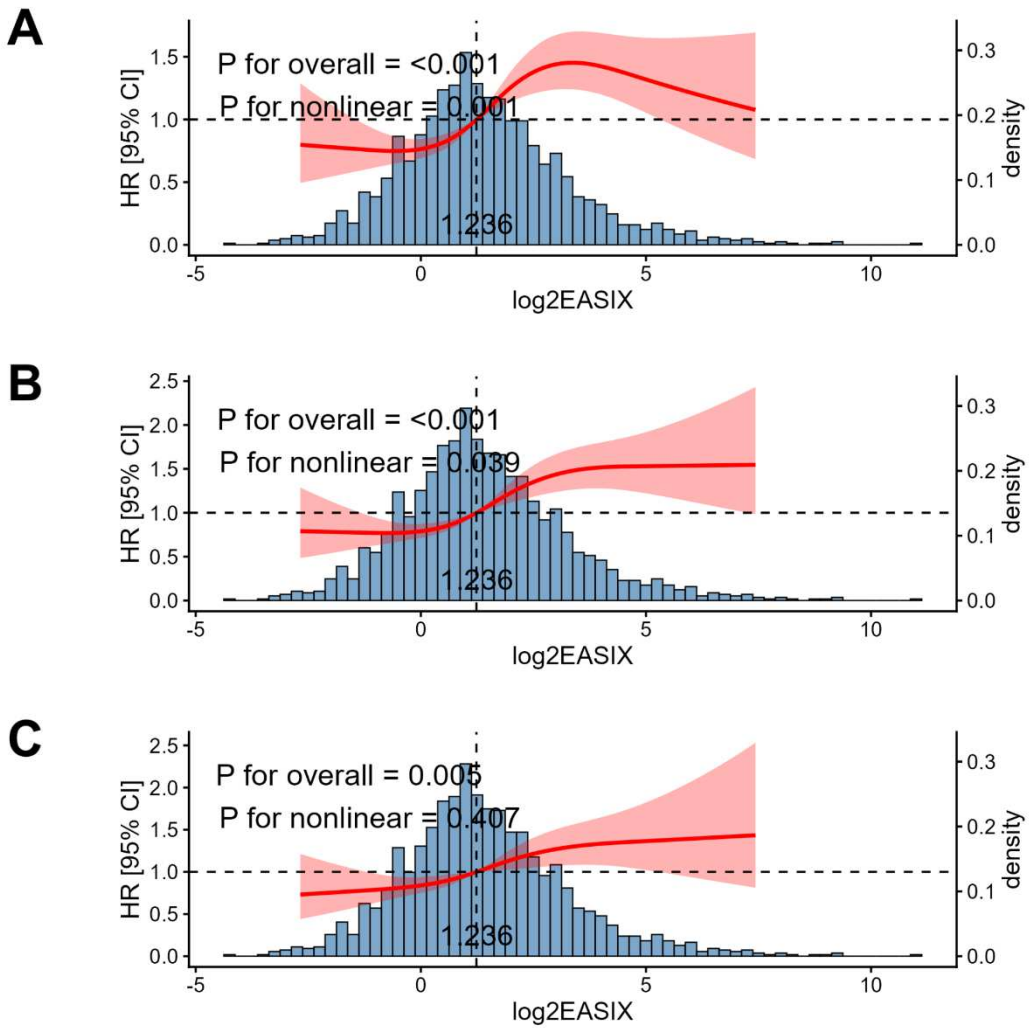


Figure.5 Restricted cubic spline analysis of 90-day ICU all-cause mortality. (A)Model 1 was unadjusted. (B) Model 2 was adjusted for age, gender, race, weight. (C) Model 3 was adjusted for age, gender, weight, race, temperature, spo2, mbp, wbc, neutrophils, lymphocytes, glucose, bun, chloride, pt, inr, alt, myocardial infarct, congestive heart failure, renal, sepsis3, vaso, hydrocortisone, rass.

Subgroup Analyses of 28-Day and 90-Day Mortality

Stratified analyses were performed to evaluate the consistency of the association between EASIX and mortality across clinically relevant subgroups (Figure.6 and Figure.7).

For 28-day mortality (Figure.6), the association between EASIX and mortality remained significant across all subgroups. However, significant interaction effects were observed for renal failure (P for interaction = 0.027), renal replacement treatment (CRRT) (P for interaction = 0.000), and SOFA score (P for interaction = 0.013). Specifically, the prognostic value of EASIX was attenuated in patients with renal failure (HR 0.97, 95% CI 0.87–1.09) compared to those without (HR 1.12, 95% CI 1.05–1.18). Similarly, in patients receiving CRRT, EASIX did not significantly predict mortality (HR 0.92, 95% CI 0.83–1.01), whereas a significant association persisted in those not receiving RRT (HR 1.14, 95% CI 1.07–1.23). Furthermore, a more pronounced association was observed in patients with a lower SOFA score (<8: HR 1.19, 95% CI 1.09–1.30) compared to those with a higher SOFA score (>=8: HR 1.03, 95% CI 0.96–1.11). Borderline interactions were noted for age (P for interaction = 0.085) and delirium (P for interaction = 0.074).

Fig.6 Subgroup analysis for the association between EASIX and 28d- mortality in critically ill patients with VAP.

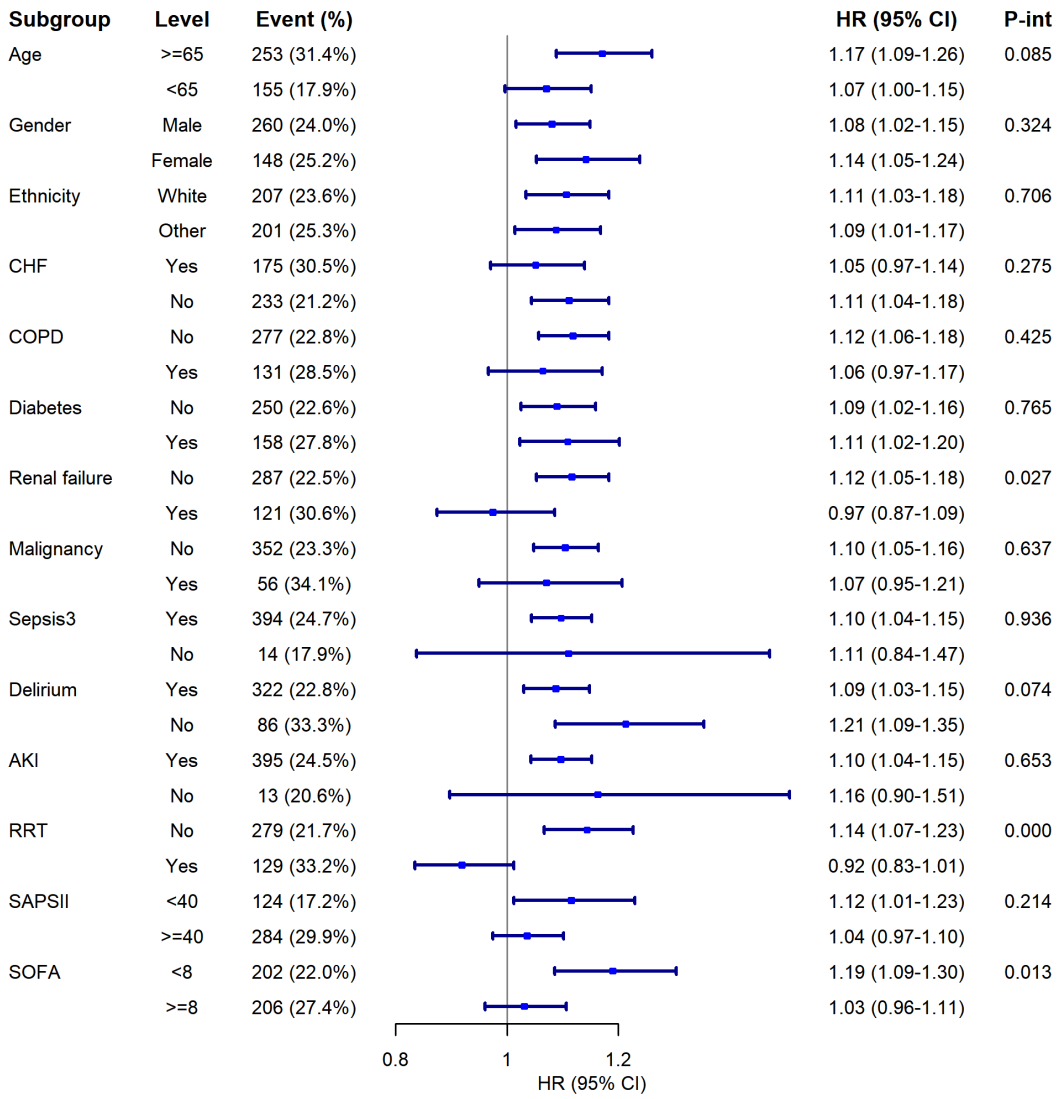


Figure.6 Subgroup analysis for the association between EASIX and 28d- mortality in critically ill patients with VAP.

For 90-day mortality (Figure.7), consistently significant associations were observed across most subgroups. Significant interactions were identified for chronic pulmonary disease (P for interaction = 0.036), renal failure (P for interaction = 0.021), malignant cancer (P for interaction = 0.036), delirium (P for interaction = 0.018), CRRT (P for interaction = 0.001), and SOFA score (P for interaction = 0.005). Notably, the presence of chronic pulmonary disease (HR 1.03, 95% CI 0.95–1.11), renal failure (HR 0.98, 95% CI 0.90–1.07), malignant cancer (HR 1.00, 95% CI 0.91–1.11), and CRRT (HR 0.95, 95% CI 0.88–

1.02) attenuated the association between EASIX and long-term mortality. Conversely, the association remained robust in patients without these comorbidities or interventions. The predictive value of EASIX was also stronger in patients with a lower SOFA score (<8: HR 1.20, 95% CI 1.11–1.29) compared to those with a higher SOFA score (>=8: HR 1.04, 95% CI 0.98–1.11).

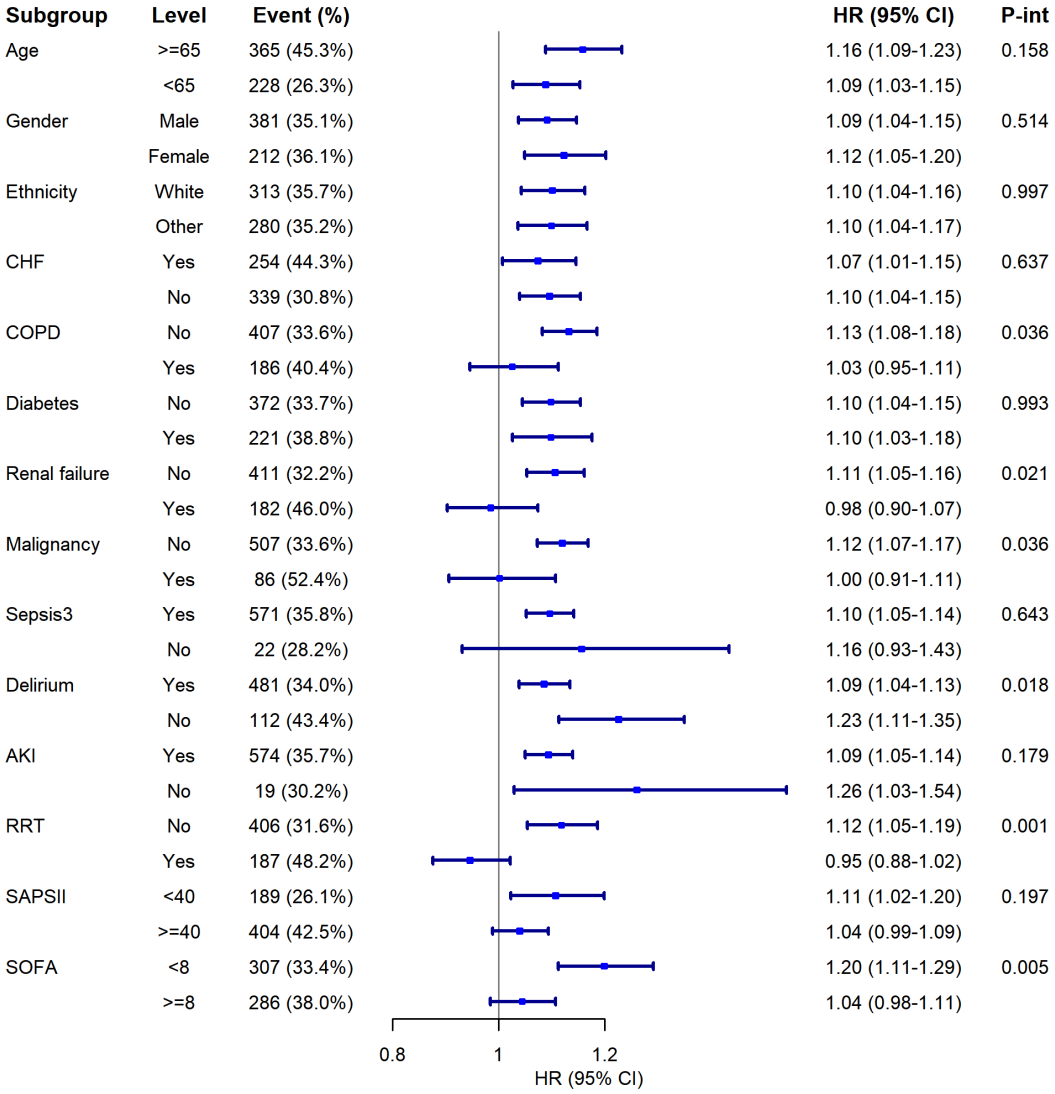


Figure.7 Subgroup analysis for the association between EASIX and 90d-mortality in critically ill patients with VAP.

Overall, these findings suggest that while EASIX is a robust prognostic indicator for both short-term and long-term mortality in the general ICU population, its predictive utility is significantly influenced by renal function, CRRT status, SOFA score, and certain comorbidities.

Discussion

This retrospective study, based on the MIMIC-IV database, was designed to investigate the association between EASIX and the risk of all-cause mortality in patients with VAP. Our findings demonstrated a significant positive association that persisted after adjustment for covariates and remained consistent across subgroups, thereby supporting the robustness of our results. To the best of our knowledge, this is the first study to elucidate the relationship between EASIX and the risk of all-cause mortality in patients with VAP. To ensure rigorous and scientifically valid feature selection, we employed the Boruta algorithm. EASIX emerged as a significant feature in this analysis, which corroborated the results of our Cox regression analysis. Our findings indicate that higher EASIX scores were independently associated with an increased risk of all-cause mortality at 28 and 90 days. On the basis of these observations, we propose that EASIX may serve as a promising and reliable biomarker for predicting mortality in patients with VAP. To the best of our knowledge, the present investigation is the first to explore the relationship between the EASIX score and clinical outcomes among patients with VAP. Our results suggest that elevated EASIX scores were independently associated with an increased risk of all-cause mortality at 28 and 90 days. Moreover, this relationship remained stable across diverse subgroups.

VAP remains one of the most common ICU-acquired infections and continues to pose a substantial clinical burden, given its considerable pathobiological heterogeneity and diagnostic challenges [2]. Recent evidence has reframed VAP as a dynamic ecological process driven by interactions between the microbial community and the host's immune status, with sepsis-associated immune paralysis further

compounding this dynamic.[3]. Unsupervised clustering analyses have further identified distinct HAP subphenotypes in critically ill patients, characterized by differences in respiratory failure severity, systemic inflammatory response, respiratory microbiome dysbiosis, mortality risk, and antibiotic responsiveness[4]. Despite advances in critical care, validated indicators for early risk stratification in VAP remain limited. Therefore, identifying patients at high risk of death is clinically critical for optimizing treatment strategies and resource allocation. As illustrated in the selection flowchart (Figure. 1), the final analytical cohort in the present study consisted of 1,673 patients with VAP.

In the present cohort, non-survivors exhibited a more severe baseline profile than survivors, including older age, a greater burden of cardiovascular, pulmonary, and renal comorbidities, higher disease severity scores, and more frequent use of vasopressors and CRRT (Table 1). Notably, EASIX was significantly higher in non-survivors than in survivors ($P < 0.001$). This elevation was accompanied by higher LDH and creatinine levels, two of the three core components of EASIX, whereas platelet counts did not differ significantly between groups. These findings suggest that the prognostic value of EASIX in VAP may be largely driven by cellular injury and renal impairment, while still reflecting a broader state of endothelial activation and systemic stress. Endothelial cells exhibit significant morphological heterogeneity, and their dysfunction can manifest in various characteristic forms, including vascular motility, hemostasis, adhesion, and angiogenesis[30].Endothelial dysfunction (ED) serves as a pivotal link in the pathophysiological processes of numerous diseases, playing a central role particularly in cardiovascular disorders[31]. In critical conditions such as sepsis, contemporary pathophysiological concepts regard the endothelium as a functionally active structure that integrates immune, hemostatic, and metabolic processes, rather than merely constituting an anatomical vascular barrier[30]. Endothelial dysfunction is not only a common component of both cardiovascular and

410 respiratory diseases but also acts as a key molecular hub connecting systemic inflammation with
411 microcirculatory dysfunction[32]. The Endothelial Activation and Stress Index (EASIX), derived from
412 conventional laboratory parameters, serves as a composite biomarker capable of effectively quantifying
413 both endothelial dysfunction and systemic stress status. During the progression of various acute and
414 chronic diseases, dynamic changes in EASIX are closely associated with systemic inflammatory
415 responses and microvascular damage. Elevated EASIX levels often indicate aggravated endothelial
416 injury and poorer clinical prognosis[33–35]. As a simple, cost-effective, and non-invasive assessment
417 tool, EASIX holds potentil for clinical application in risk stratification and prognostic prediction across
418 multiple disease spectra, including cardiovascular diseases, cerebrovascular diseases, severe infections,
419 and malignant tumors[36–38]. EASIX levels may therefore serve as a potential biomarker for predicting
420 overall survival in these patients[13]. Our study further extends these findings by demonstrating that
421 higher EASIX levels are independently associated with higher 28-day and 90-day all-cause mortality in
422 patients with VAP (Table 2), thereby supporting the potential utility of EASIX as a simple prognostic
423 marker for risk stratification in this population.

424 To ensure rigor and scientific validity in covariate selection, we employed the Boruta algorithm, a
425 random-forest-based wrapper method that identifies relevant features by comparing their importance
426 against randomly shuffled “shadow” variables. Unlike conventional regression-based approaches, the
427 Boruta algorithm iteratively evaluates all candidate variables and retains only those whose importance
428 significantly exceeds that of their randomized counterparts, thereby effectively capturing complex,
429 nonlinear relationships between predictors and outcomes. This method has been increasingly adopted in
430 critical care research using the MIMIC-IV database for variable selection and prognostic model
431 development[39].In the present study, the Boruta algorithm evaluated 91 candidate variables for 28-day

ICU all-cause mortality and 89 for 90-day ICU all-cause mortality. Among these, 32 and 26 variables were identified as significantly associated with the respective outcomes (Figure. 2). Notably, EASIX was confirmed as an important feature in both analyses, further supporting its independent prognostic relevance in patients with VAP. This finding is consistent with a recent study that applied the Boruta algorithm to evaluate EASIX in sepsis patients from the MIMIC-IV database, where EASIX was identified as the core variable in the prediction model[6]. The convergence between the Boruta-based feature selection and our multivariable Cox regression results reinforces the robustness of the association between EASIX and mortality in VAP. In the fully adjusted Cox model, each 1-unit increase in log2 EASIX was independently associated with higher 28-day and 90-day mortality ($P < 0.001$; Table 3). The discrepancy in nonlinearity across models highlights the profound impact of confounding factors. The apparent U-shaped curve and the biologically implausible protective effect at low log2EASIX levels (Figure. 5A) observed in the unadjusted model were likely driven by unmeasured baseline characteristics, such as age and disease severity. After comprehensive adjustment, this trend resolved into a monotonic linear increase, suggesting that the observed protective effect was a statistical artifact caused by confounding. Clinically, although an inflection point at a log2EASIX of 1.236 was identified in the unadjusted model, this threshold effect should be interpreted with caution, as the fully adjusted model revealed a linear increase without a clear threshold. Therefore, we recommend treating log2EASIX as a continuous variable in clinical prediction models rather than relying on arbitrary cut-offs derived from unadjusted curves. These findings were consistent across multiple time-to-event models and sensitivity analyses.

Stratified analyses showed that the association between EASIX and mortality remained largely robust across most subgroups (Figure. 6 and Figure. 7). However, significant effect modifications were observed

for renal function, continuous renal replacement therapy (CRRT), and SOFA score. Specifically, the prognostic value of EASIX was attenuated in patients with renal failure and in those receiving CRRT (Figure. 6). This may be explained by the inclusion of serum creatinine in EASIX: renal failure elevates EASIX scores and makes creatinine the dominant source of variation, while CRRT directly clears creatinine and causes marked fluctuations in EASIX. Consequently, the prognostic signal of EASIX may be diluted or distorted in these patients. Furthermore, EASIX demonstrated better performance in patients with lower SOFA scores than in those with higher scores, likely because profound multi-organ dysfunction dominates the prognosis in high SOFA patients. For 90-day mortality, additional interactions emerged for chronic pulmonary disease, malignant cancer, and delirium, suggesting that the long-term prognostic value of EASIX is more susceptible to modification by comorbidities (Fig. 7). Overall, EASIX remains a robust prognostic marker, but its interpretation should be approached with caution in patients with renal dysfunction, those receiving CRRT, those with high SOFA scores, or those wight the aforementioned comorbid ities.

This study has several limitations. First, it was a retrospective analysis conducted using data from the single-center MIMIC-IV database, which may introduce selection bias and limit generalizability. Second, despite comprehensive adjustment, residual confounding cannot be entirely excluded. Third, EASIX was assessed only at ICU admission, and changes in EASIX over the coures of the ICU stay were not evaluated; future studies should examine whether longitudinal EASIX trajectories offer additional prognostic value. Fourth, VAP was identified using ICD codes, which may be subject to misclassification or underdiagnosis. Fifth, the study did not distinguish early-onset from late-onset VAP, nor did it differentiate among causative pathogens or pneumonia subtypes. Sixth, missing data and extreme values were handled using prespecified approaches, but the influence of these factors cannot be fully eliminated.

Finally, external validation in multicenter cohorts is needed to confirm the robustness and broader applicability of these findings.

Conclusion

In conclusion, elevated EASIX was independently associated with increased 28-day and 90-day all-cause mortality in critically ill patients with VAP. EASIX may serve as a simple, readily available, and valuable prognostic marker for risk stratification in this population. Further prospective and multicenter studies are warranted to validate its clinical utility and to determine whether dynamic EASIX monitoring can enhance prognostic accuracy in patients with VAP.

Abbreviations

VAP: Ventilator-associated pneumonia

ICU: Intensive Care Unit

EASIX: Endothelial Activation and Stress Index

ARDS: acute respiratory distress syndrome

COPD: chronic obstructive pulmonary disease

RCS: restricted cubic spline

HAP: Hospital-Acquired Pneumonia

PCT: procalcitonin

LDH: lactate dehydrogenase

GvHD: graft-versus-host disease

BIDMC: Beth Israel Deaconess Medical Center

MIMIC-IV: Medical information mart for intensive care-IV

IQR: Interquartile Range

AKI: acute kidney injury

MBP: mean blood pressure;

WBC: white blood cell;

RBC: red blood cell;

RDW: red cell distribution width;

Hct: hematocrit;

PT: prothrombin time;

PTT: partial prothrombin time;

INR: international normalized ratio;

ALP: alkaline phosphatase;

ALT: alanine aminotransferase;

AST: aspartate aminotransferase;

LDH: lactate dehydrogenase;

SpO2: oxyhemoglobin saturation;

SOFA: sequential organ failure assessment;

APSIII: acute physiology score III;

SAPS II: simplified acute physiology score;

MELD: model for end-stage liver disease;

GCS: glasgow coma scale;

LODS: logistic organ dysfunction score ;

SIRS: systemic inflammatory response syndrome;

RASS: richmond agitation-sedation scale;

CRRT: continuous renal replacement therapy;

Declarations

Ethics approval and consent to participate

The MIMIC-IV database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. All patient records were de-identified to ensure patient privacy. Therefore, no additional ethics approval or informed consent was required for this retrospective study.and conducted in accordance with the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki/).

Consent for publication

Not applicable.

Availability of data and materials

The MIMIC-IV database is publicly accessible via PhysioNet (https://physionet.org/content/mimiciv/). The derived dataset and the analysis code employed in this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Linlin Lv was responsible for the study conception, methodological design, formal data analysis, software implementation, study execution, and data management. Weiqi Li drafted the initial manuscript,

and Gang Li performed substantive content revisions. Fangyi Li critically reviewed and approved the final manuscript. All authors provided feedback on previous versions of the manuscript and made corresponding revisions.

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Generative AI statement

The authors declare that no generative AI tools were used in generating the scientific content of this manuscript. If language editing was used, it did not affect the scientific interpretation or conclusions.

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Availability of data and materials

The data that support the findings of this study are available from the MIMIC-IV database (version 3.1), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The MIMIC-IV database is available from the PhysioNet repository at https://physionet.org/content/mimiciv/3.1/ upon completion of the required credentialing process, including human participant training and signing of the data use agreement. Data are however available from the corresponding author upon reasonable request and with permission of the PhysioNet repository.

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