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Association of pan-immune inflammation value with mortality in patients with pulmonary embolism: a cohort study

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Pan-immune inflammation value (PIV) is associated with prognosis in immune and inflammatory diseases, and inflammation is a hallmark of pulmonary embolism (PE). Nonetheless, the link between PIV and prognosis in PE remains unclear. However, few studies have specifically focused on critically ill patients with PE in ICUs. This study retrospectively analyzed electronic health data of patients with PE from the Medical Information Mart for Intensive Care (MIMIC-IV) database. The primary outcome was 28-day ACM; secondary outcomes were 90-day, 1-year, ICU, and in-hospital mortality. The study population included 213 patients with PE. Multivariate Cox proportional hazards regression showed that elevated PIV was significantly associated with ACM at 28 days (adjusted hazard ratio [aHR]: 1.93; 95% confidence interval [CI]: 1.02–3.63) and 90 days (aHR: 1.96; 95% CI: 1.10–3.47). Further, multivariate logistic regression analysis showed that PIV was significantly and positively associated with the risk of ACM. Kaplan-Meier survival curves showed that PIV was positively associated with ACM. Subgroup and interaction analyses corroborated this correlation. PIV was significantly correlated with ACM in critically ill ICU patients with PE. This correlation highlights the potential utility of PIV for stratifying patients with PE according to their risk of death.

Keywords Pan-immune inflammation value, Pulmonary embolism, Mortality, Cohort studies

Abbreviations

PIV	pan-immune-inflammation value
PE	pulmonary embolism
ACM	all-cause mortality
BIDMC	Beth Israel Deaconess Medical Center
HR	hazard ratio
CI	confidence interval
INR	international normalized ratio
WBC	white blood cell count
PT	prothrombin time
PPT	partial thromboplastin time
ALT	alanine aminotransferase
AST	aspartate aminotransferase
PO_2	partial pressure of oxygen
CCI	Charlson Comorbidity Index
SAPS II	simplified Acute Physiology Score II
SOFA	sequential Organ Failure Assessment
AKI	acute kidney injury
ECMO	extra-corporeal membrane oxygenation
CRRT	continuous renal replacement therapy
VSMC	vascular smooth muscle cell
sPESI	simplified pulmonary embolism severity index

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The annual incidence of pulmonary embolism (PE) is 60–120 per 100,000 people, and 60,000 to 100,000 patients die from PE each year in the US[1]. Furthermore, PE is the leading cause of in-hospital death and the third most frequent cause of cardiovascular death[2,3]. The incidence of PE is increasing because of population aging and higher cancer rates, posing a significant challenge to healthcare[4]. The pathophysiology of PE is complex and involves pulmonary vascular blockage, acute inflammation, and vasospasm[5]. Pulmonary vasoconstriction, triggered by the release of vasoactive mediators from activated platelets[6], is closely tied to inflammatory processes. Stratifying patients according to the risk of PE is challenging[7]. For patients with acute PE, assessing prognosis can improve disease management[8]. Furthermore, quantifying the risk of in-hospital mortality for critically ill patients may reduce medical costs and improve resource allocation[9]. Thus, identifying simple, user-friendly, and cost-effective indicators for predicting adverse outcomes of PE in clinical practice is crucial.

A few reliable prognostic biomarkers for PE have been identified, including lymphopenia and elevated neutrophil counts, which can predict pro-inflammatory states associated with an increased risk of thrombotic events. Platelet levels are significantly reduced after a thrombotic event[10].

The pan-immune inflammation value (PIV), a blood biomarker encompassing neutrophil, platelet, monocyte, and lymphocyte counts, provides insights into the physiological state and is linked to the prognosis of immune and inflammatory conditions, including hypertension[11], breast cancer[12], Gram-negative bloodstream infections in patients undergoing solid organ transplants[13], and nasopharyngeal carcinoma[14]. Furthermore, high PIV independently predicts coronary no-reflow in patients with ST-segment elevation myocardial infarction[15]. Although the relationship between PIV and PE is well known[16,17], few studies have assessed this relationship in critically ill intensive care unit (ICU) patients with PE.

We hypothesized that increased PIV was associated with poor prognosis in patients with PE. This study evaluated the association between PIV levels and all-cause mortality (ACM) in critically ill ICU patients with PE by retrospectively analyzing electronic health data from the Medical Information Mart for Intensive Care (MIMIC)-IV database. The results can help improve disease management and treatment in high-risk populations.

Materials and methods

Study population

This retrospective study analyzed electronic health data from the MIMIC-IV database (version 2.2) developed by the MIT Computational Physiology Laboratory. The Institutional Review Board at the Beth Israel Deaconess Medical Center (BIDMC) granted a waiver of informed consent and approved the sharing of the research resource[18]. Weihong Zhao (Access ID: 60,177,085) extracted data after receiving specialized training, complying with protocols. The study adhered to STROBE guidelines for observational studies.

The inclusion criteria included subjects aged 18 years or older admitted to ICUs and individuals diagnosed with PE based on the International Classification of Diseases 9th edition (codes 415.12 and 415.19) and 10th edition (codes I26, I26.0, I26.01, I26.09, I26.9, I26.90, I26.93, I26.94, and I26.99). The exclusion criteria were (1) subjects with multiple ICU admissions for PE, with data from the first admission retained only, (2) patients without data on PIV within 24 h of ICU admission, (3) patients with a lymphocyte count of 0, and (4) patients with a PIV of 0.

Data collection

Data were extracted using PostgreSQL version 13.7.2 and Navicat Premium version 16. The following data were analyzed: demographic characteristics (sex, age, and race) vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature), laboratory parameters (hemoglobin and anion gap), comorbidities (congestive heart failure, chronic pulmonary disease, diabetes, renal disease, and cancer), Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA), sepsis, acute kidney injury (AKI), need for mechanical ventilation, vasoactive drug use, continuous renal replacement therapy, smoking history, biochemical and blood laboratory parameters (creatinine, glucose, cell counts [white blood cells, neutrophils, platelets, monocytes, and lymphocytes], international normalized ratio [INR], prothrombin time [PT], alanine aminotransferase [ALT], lactate, and PO_2), Simplified Pulmonary Embolism Severity Index (sPESI)[19], and Charlson Comorbidity Index (CCI). The observation span for each subject began at the point of admission and extended to the morality event. PIV was calculated using the formula PIV = (neutrophil count × platelet count × monocyte count) / lymphocyte count[20]. Analyses relied on laboratory values and ICU admission severity scores within 24 h. Variables with more than 50% missing data were excluded, and missing values were handled using multiple imputation.

Clinical outcomes

The primary outcome was 28-day ACM, and the secondary outcomes were 90-day, 1-year, ICU, and in-hospital mortality.

Statistical analysis

Log_{10} transformation was performed to achieve a normal distribution and stabilize the variance since PIV levels were skewed to the left. Continuous variables were expressed as mean ± standard deviation (normally distributed data) or median and interquartile range (IQR) (non-normally distributed data) and were compared using a *t*-test or one-way analysis of variance. Categorical variables were expressed as numbers and percentages and were compared using the chi-square test or Fisher's exact test. The incidence of ACM was determined for each tertile.

Kaplan–Meier survival curves were used to determine the incidence of endpoints in each group defined by Log_{10} of PIV. Survival curves were compared using the log-rank test. The relationship between PIV and endpoints was analyzed using univariate and multivariate logistic regression analysis. Multivariate analysis was

adjusted for age, sex, race, body temperature, hemoglobin, neutrophil count, INR, PT, ALT, lactate, PO_2, chronic pulmonary disease, cancer, CCI, SAPS II, SOFA, sepsis, creatinine, AKI, need for mechanical ventilation, vasoactive drug use, continuous renal replacement therapy, and sPESI. Variables eligible for inclusion in the multivariate model were selected based on three criteria[21–25]: p-values of less than 0.1 in the univariate analysis, a change in the hazard ratio (HR) of at least 10% after including a variable in the model, and clinical relevance based on previous evidence. Adjusted HRs and corresponding 95% confidence intervals (CI) were calculated. The variance inflation factor did not indicate the presence of multicollinearity.

Log_{10} (PIV) was analyzed as a continuous variable or a categorical variable using the first tertile as the reference. Trends across tertiles were analyzed by calculating p-values. The correlation between Log_{10} (PIV) and ACM at 28 days, 90 days, and 1 year was evaluated using a Cox proportional hazards model.

Stratification and interaction analyses were performed to evaluate the influence of SAPS II (< 40 or ≥ 40), the presence of diabetes, vasoactive drug use, the need for mechanical ventilation, and AKI. Interactions were assessed using likelihood ratio tests. HRs in subgroups were the same as those adjusted for the multivariate model.

Sensitivity analyses were conducted to assess the robustness of the findings. Effect sizes and p-values from all models were calculated and compared.

Statistical analysis was conducted using R statistical software version 4.2.2 (http://www.R-project.org, The R Foundation) and Free Statistics analysis platform version 1.9.2 (Beijing, China, http://www.clinicalscientists.cn/freestatistics). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

The study population comprised 213 critically ill ICU patients with PE, with a median age of 61.3 ± 17.6 years. Of these, 112 (52.6%) were female. The median PIV was 1220.5 (IQR: 428.8–3126.2). The ICU, in-hospital, 28-day, 90-day, and 1-year mortality rates were 14.6%, 20.7%, 23.9%, 30.5%, and 36.6%, respectively. The cohort was divided into three tertiles ($n = 71$ per tertile) based on Log_{10} (PIV) on the first day of ICU admission. The flowchart of patient selection is shown in Fig. 1.

Baseline characteristics

Baseline demographic and clinical characteristics stratified by PIV tertiles are shown in Table 1. The tertiles were T1 (0.30–627.55), T2 (655.14–2107.80), and T3 (2154.58–35911.94). The median PIV in each tertile was 259.0 (IQR: 115.6–425.8), 1220.5 (IQR: 930.6–1502.4), and 4687.2 (IQR: 3131.0–7836.7). Individuals in the highest tertile tended to be older and Caucasian and had a higher incidence of chronic pulmonary disease, diabetes, kidney disease, and oncological diseases. These patients had higher heart and respiratory rates, anion gap, creatinine, blood glucose, PTT, ALT, neutrophil count, platelet count, monocyte count, CCI, and SAPS II than the other tertiles. Furthermore, PIV was positively associated with the need for mechanical ventilation, vasoactive drug use, sepsis during ICU stay, and AKI.

Clinical outcomes

PIV was positively correlated with ICU, in-hospital, 28-day, 90-day, and 1-year mortality (Table 2). The incidence of ACM in PIV subgroups was evaluated using Kaplan–Meier survival curves (Fig. 2). The results showed that PIV was positively associated with 28-day, 90-day, and 1-year mortality. Furthermore, there was a significant difference in mortality rates between high and low PIV levels during ICU stay and hospitalization (**Supplementary Fig. 1**). Log_{10} (PIV) as a continuous variable accurately predicted the risk of 28-day mortality in the univariate model (HR: 2.18, 95% CI: 1.38–3.45, $P = 0.001$) and adjusted multivariate model (aHR: 1.93, 95% CI: 1.02–3.63, $P = 0.042$) (Table 3). This result suggests a 93% increased risk of mortality for every 10-fold increase in PIV.

The analysis of Log_{10} (PIV) as a categorical variable showed that individuals in the highest tertile had a significantly higher risk of 28-day mortality in the univariate model (HR: 5.55, 95% CI: 2.44–12.62, $P < 0.001$) and multivariate model (aHR: 5.19; 95% CI: 1.63–16.49; $P = 0.005$) (P for trend = 0.003) than those in the lowest tertile, suggesting an increased risk of death with increasing PIV levels. Similar results were obtained using the Cox proportional hazard models for 90-day and 1-year mortality (Table 3). The association between the highest Log_{10} (PIV) tertile and the increased risk of ICU and in-hospital mortality was significant in these models (Supplementary Table S1).

Subgroup analysis

Subgroup analyses confirmed that PIV was a good predictor of 28-day mortality in critically ill patients with PE, and the risk was considerably higher in those with AKI (HR: 2.26; 95% CI: 1.0001–5.11). This association was also found in the groups stratified by SAPS II, diabetes, vasoactive drug use, and need for mechanical ventilation (Fig. 3A). The stratification factors did not significantly alter this association. PIV also predicted an increased risk of 90-day and 1-year mortality, especially in patients with AKI (HR: 2.57, 95% CI: 1.25–5.26 at 90 days; HR: 2.07, 95% CI: 1.07– 3.98 at 1 year). These results were consistent across stratifications (Fig. 3B, C) and indicate that PIV can accurately predict mortality in various patient populations.

Discussion

The results showed that PIV was significantly associated with short- and long-term mortality in critically ill ICU patients with PE from a US cohort. The correlation persisted after adjusting for confounders, and no significant effect modification was observed. These data suggest that PIV is an independent risk factor for PE.

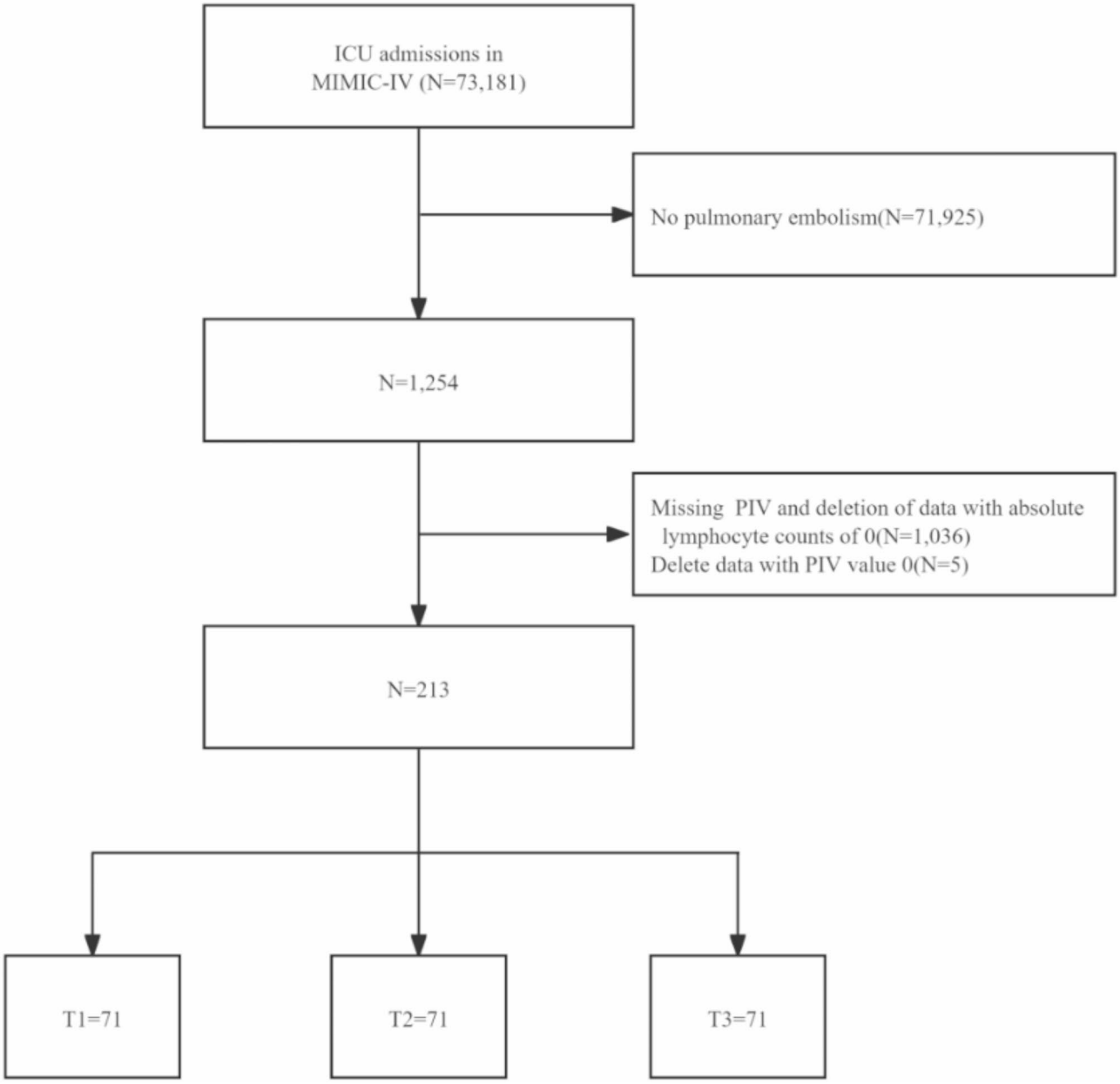

Fig. 1. The flow diagram of identifying eligible studies.

Peripheral blood counts indicate the systemic immune and inflammatory status. PIV is used as a prognostic biomarker for cancer patients treated with immune checkpoint inhibitors[26]. PIV is strongly linked to prognosis in patients with metastatic colorectal cancer undergoing first-line treatment[27]. Elevated PIV may also correlate with abdominal aortic calcification[28]. Moreover, the platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are markers of systemic inflammation and correlate with worsened prognosis in acute PE[10].

The relationship between PIV and PE is well established; however, few studies have evaluated this correlation in critically ill ICU patients with PE. A study conducted in a tertiary care hospital found that PIV accurately predicted in-hospital mortality in patients with acute PE (OR: 1.756, 95% CI: 1.418–2.176, $P < 0.001$)[16]. Another study found that PIV was significantly higher in non-survivors of PE than in survivors ($P < 0.001$)[17]. Multivariate Cox proportional hazard regression showed that PIV was significantly correlated with the risk of 28-day mortality (aHR: 1.93, 95% CI: 1.02–3.63, $P = 0.042$). PIV predicted the risk of 28-day, 90-day, and ICU mortality (Table 3). Moreover, Log_{10} (PIV) was associated with an increased risk of 1-year mortality (Table 3).

The results revealed that PIV was positively correlated with ACM at ICU admission and at 28 days, 90 days, and 1 year (Table 3), supporting the conclusion that increased PIV is an independent risk factor for mortality[29]. However, the relationship between PIV and PE in ICU patients is unclear. Thus, routine monitoring of PIV in critically ill patients with PE is essential for guiding early treatment and improving risk stratification and patient

Variables	All patients (n = 213)	PIV T1 (n = 71)	T2 (n = 71)	T3 (*n* = 71)	*P* -value
Demographics					
Age, years	61.3 ± 17.6	59.1 ± 18.4	60.2 ± 18.5	64.5 ± 15.5	0.155
Sex, n (%)					0.590
Female	112 (52.6)	40 (56.3)	38 (53.5)	34 (47.9)	
Male	101 (47.4)	31 (43.7)	33 (46.5)	37 (52.1)	
Race, n (%)					0.523
Caucasian	136 (63.8)	47 (66.2)	49 (69)	40 (56.3)	
African descent	29 (13.6)	8 (11.3)	8 (11.3)	13 (18.3)	
Other	48 (22.5)	16 (22.5)	14 (19.7)	18 (25.4)	
Vital Signs, Mean ± SD					
Heart rate, bpm	111.6 ± 21.3	109.6 ± 21.2	109.1 ± 20.7	116.2 ± 21.4	0.081
Systolic pressure, mmHg	90.3 ± 18.4	91.6 ± 17.4	89.4 ± 17.1	89.9 ± 20.7	0.751
Diastolic pressure, mmHg	48.3 ± 14.2	48.7 ± 14.9	49.4 ± 11.7	46.8 ± 15.7	0.520
Respiratory rate, bpm	31.1 ± 7.6	31.1 ± 8.3	30.4 ± 5.7	31.7 ± 8.5	0.589
Temperature, ℃	37.0 ± 0.5	36.9 ± 0.4	37.0 ± 0.4	37.0 ± 0.5	0.389
Laboratory tests					
Hemoglobin, g/dl	11.2 ± 2.3	11.3 ± 2.3	11.4 ± 2.6	10.8 ± 2.2	0.297
anion gap, mmol/l	17.5 ± 5.9	16.6 ± 4.5	16.8 ± 5.4	19.2 ± 7.3	**0.013**
Creatinine, mg/dl	1.0 (0.8, 1.6)	1.0 (0.8, 1.4)	1.0 (0.7, 1.6)	1.2 (0.8, 1.8)	0.179
Glucose, mg/dl	143.0 (119.0, 185.0)	136.0 (116.5, 184.0)	143.0 (115.5, 182.5)	156.0 (128.5, 220.0)	**0.035**
WBC, 10^9/L	14.9 (11.0, 20.9)	10.9 (8.4, 16.9)	13.8 (11.4, 18.1)	19.8 (15.8, 25.2)	**< 0.001**
INR, sec	1.4 (1.2, 1.7)	1.4 (1.2, 1.6)	1.4 (1.2, 1.7)	1.4 (1.2, 1.7)	0.488
PT, sec	14.9 (13.3, 18.3)	14.6 (13.3, 17.6)	14.7 (13.3, 18.4)	15.4 (13.4, 18.6)	0.450
PTT, sec	43.2 (30.6, 109.6)	38.4 (29.2, 93.6)	41.3 (32.5, 85.8)	57.6 (31.8, 112.8)	0.274
ALT, IU/L	29.0 (15.0, 75.8)	29.5 (15.5, 54.0)	27.0 (13.5, 63.5)	33.0 (17.0, 88.0)	0.588
AST, IU/L	36.0 (22.0, 86.0)	30.0 (20.0, 68.5)	40.0 (21.5, 89.0)	35.5 (23.0, 169.8)	0.450
Neutrophil count, 10^9/L	10.8 (6.8, 15.3)	6.2 (4.7, 9.0)	10.5 (7.6, 13.2)	15.9 (12.3, 21.2)	**< 0.001**
Platelet count, 10^9/L	189.0 (130.0, 247.0)	139.0 (74.0, 182.5)	193.0 (132.0, 234.0)	245.0 (191.0, 352.0)	**< 0.001**
Monocyte count, 10^9/L	0.8 (0.5, 1.2)	0.4 (0.2, 0.8)	0.8 (0.5, 1.1)	1.3 (0.9, 1.7)	**< 0.001**
Lymphocyte count, 10^9/L	1.2 (0.7, 1.9)	1.7 (0.7, 2.5)	1.2 (0.8, 1.9)	1.1 (0.7, 1.6)	0.087
PIV	1220.5 (428.8, 3126.2)	259.0 (115.6, 425.8)	1220.5 (930.6, 1502.4)	4687.2 (3131.0, 7836.7)	**< 0.001**
Lactate, mmol/l	2.4 (1.6, 4.2)	3.0 (2.0, 5.0)	2.0 (1.3, 3.8)	2.4 (1.6, 3.9)	0.254
PO_2, mmHg	79.3 ± 35.5	95.0 ± 41.6	70.9 ± 31.3	73.4 ± 29.4	**0.002**
Comorbidity disease, n (%)					
Congestive heart failure, n (%)	69 (32.4)	23 (32.4)	22 (31)	24 (33.8)	0.938
Chronic pulmonary disease, n (%)	51 (23.9)	12 (16.9)	18 (25.4)	21 (29.6)	0.197
Diabetes, n (%)	50 (23.5)	17 (23.9)	11 (15.5)	22 (31)	0.093
Renal disease, n (%)	32 (15.0)	9 (12.7)	10 (14.1)	13 (18.3)	0.620
Cancer, n (%)	63 (29.6)	18 (25.4)	15 (21.1)	30 (42.3)	**0.014**
Smoking history, n (%)	90 (42.3)	24 (33.8)	33 (46.5)	33 (46.5)	0.210
Events					
Sepsis, n (%)	131 (61.5)	40 (56.3)	42 (59.2)	49 (69)	0.265
AKI, n (%)	141 (66.2)	46 (64.8)	39 (54.9)	56 (78.9)	**0.010**
Interventions, n (%)					
Mechanical ventilation	83 (39.0)	27 (38)	24 (33.8)	32 (45.1)	0.380
Vasoactive drug	85 (39.9)	27 (38)	25 (35.2)	33 (46.5)	0.361
CRRT	11 (5.2)	5 (7)	3 (4.2)	3 (4.2)	0.806
Continued					

Variables	All patients (n = 213)	PIV			*P* -value
		T1 (n = 71)	T2 (n = 71)	T3 (*n* = 71)	
Severity of illness scores at admission					
CCI	6.0 (3.0, 9.0)	5.0 (2.0, 7.5)	5.0 (3.0, 7.0)	7.0 (5.0, 10.0)	**< 0.001**
SAPSII	38.2 ± 15.9	34.7 ± 16.5	37.6 ± 15.7	42.4 ± 14.7	**0.014**
SOFA	4.0 (2.0, 7.0)	5.0 (2.2, 7.0)	4.0 (2.0, 7.5)	4.0 (1.5, 8.0)	0.892
sPESI	3.0 (3.0,4.0)	3.0 (2.0,4.0)	3.0 (3.0,4.0)	4.0 (3.0,5.0)	0.071

Table 1. Baseline characteristics of participants. [a] T1-T3: Tertile according to Pan-Immune-Inflammation Value. PIV: T1: 0.3-627.55; T2: 655.14-2107.8; T3: 2154.58-35911.94. PIV, pan-immune-inflammation value; WBC, white blood cell count; PT, prothrombin time; PPT, partial thromboplastin time; ALT, alanine aminotransferase; AST: aspartate aminotransferase; PO_2, partial pressure of oxygen; CCI, Charlson Comorbidity Index; SAPSII: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; sPESI: Simplified Pulmonary Embolism Severity Index; AKI, acute kidney injury; ECMO, extra-corporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

PIV	All patients (*n* = 213)	PIV			*P* -value
		T1 (*n* = 71)	T2 (*n* = 71)	T3 (*n* = 71)	
Clinical Outcomes					
ICU ACM, n (%)	31 (14.6)	3 (4.2)	8 (11.3)	20 (28.2)	**< 0.001**
In-hospital ACM, n (%)	44 (20.7)	8 (11.3)	10 (14.1)	26 (36.6)	**< 0.001**
28 days ACM, n (%)	51 (23.9)	7 (9.9)	13 (18.3)	31 (43.7)	**< 0.001**
90 days ACM, n (%)	65 (30.5)	10 (14.1)	16 (22.5)	39 (54.9)	**< 0.001**
1 year ACM, n (%)	78 (36.6)	17 (23.9)	19 (26.8)	42 (59.2)	**< 0.001**

Table 2. ICU, in-hospital, 28 days, 90 days, and 1 year ACM. [a] T1-T3: Tertile according to Pan-Immune-Inflammation Value. ACM: all-cause mortality.

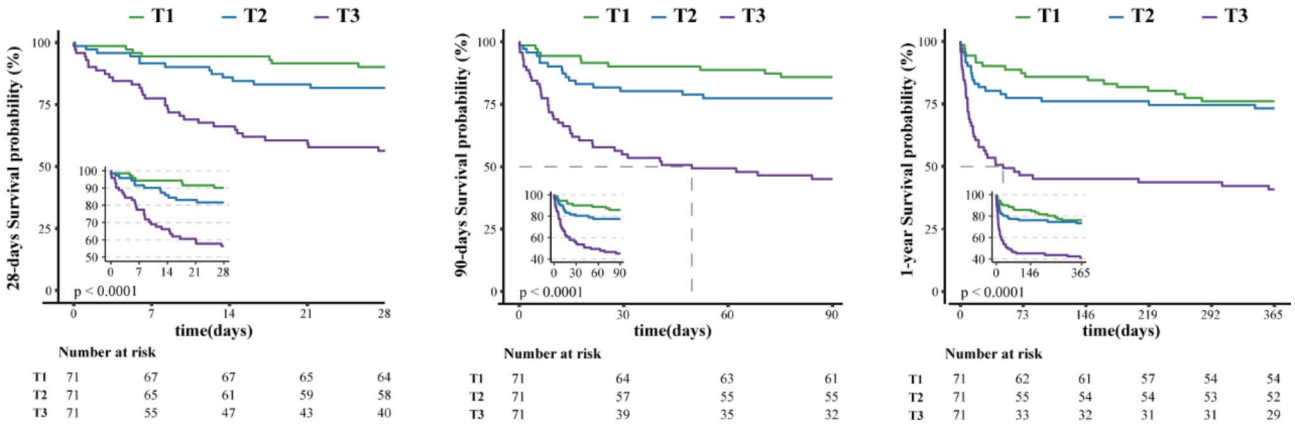

Fig. 2. Kaplan-Meier survival analysis curves for 28-day, 90-day, and 1-year ACM.

outcomes. Our results demonstrate that PIV is associated with ACM at ICU admission and at 28 and 90 days, highlighting its potential to identify high-risk individuals and improve clinical management.

This study has several strengths. First, we found that elevated PIV was a good independent predictor of ACM in a US cohort of critically ill ICU patients with PE. Second, we used Kaplan–Meier survival curves to analyze ACM across PIV tertiles and employed Cox proportional hazards models, logistic regression models, and subgroup analyses to mitigate confounding effects.

This study has several limitations. First, due to the limitations of a retrospective study, residual confounding factors are difficult to avoid although we did our best to adjust for confounders. Second, PIV was measured only at baseline and was not evaluated for changes during hospitalization and ICU stay. Future studies focusing on the dynamic changes of PIV during hospital stay are needed. Third, although the sample size is relatively small, the effect size observed in this study is sufficiently large to warrant further exploration in a larger multicenter cohort. Fourth, given that MIMIC-IV is a public database, patients can be queried according to ICD-9 and

Variable	univariate analysis		multivariate analysis	
	HR (95%CI)	*P*- value	HR (95%CI)	*P*- value
28 days mortality				
$\log_{10}$(PIV)	2.18 (1.38 ~ 3.45)	0.001	1.93 (1.02 ~ 3.63)	0.042
Tertile_$\log_{10}$(PIV)*				
T1(n = 71)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
T2(n = 71)	1.96 (0.78 ~ 4.9)	0.153	1.88 (0.62 ~ 5.69)	0.262
T3(n = 71)	5.55 (2.44 ~ 12.62)	< 0.001	5.19 (1.63 ~ 16.49)	0.005
P for Trend		< 0.001		0.003
90 days mortality				
$\log_{10}$(PIV)	2.14 (1.43 ~ 3.22)	< 0.001	1.96 (1.10 ~ 3.47)	0.022
Tertile_$\log_{10}$(PIV)*				
T1(n = 71)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
T2(n = 71)	1.71 (0.78 ~ 3.78)	0.181	2.61 (0.98 ~ 6.91)	0.054
T3(n = 71)	5.28 (2.63 ~ 10.59)	< 0.001	7.07 (2.51 ~ 19.91)	< 0.001
P for Trend		< 0.001		< 0.001
1 year mortality				
$\log_{10}$(PIV)	1.56 (1.10 ~ 2.23)	0.013	1.29 (0.83 ~ 2.01)	0.253
Tertile_$\log_{10}$(PIV)*				
T1(n = 71)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
T2(n = 71)	1.2 (0.62 ~ 2.3)	0.592	1.54 (0.69 ~ 3.46)	0.293
T3(n = 71)	3.51 (1.99 ~ 6.18)	< 0.001	3.75 (1.55 ~ 9.06)	0.003
P for Trend		< 0.001		0.002

Table 3. Cox proportional hazard ratios for PE at 28 days, 90 days, and 1 year. **$\log_{10}$(PIV)**, PIV after $\log_{10}$ transformation. *The term 'Tertile_$\log_{10}$(PIV)' refers to the tertiles of the values of the variable PIV after being transformed using the base-10 logarithm. Multivariate analysis was adjusted for age, sex, race, temperature, hemoglobin, neutrophil count, international normalized ratio, prothrombin time, alanine aminotransferase, lactate, PO_2, chronic pulmonary disease, cancer, Charlson Comorbidity Index, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment, sepsis, creatinine, acute kidney injury, mechanical ventilation, vasoactive drug, continuous renal replacement therapy, and sPESI.

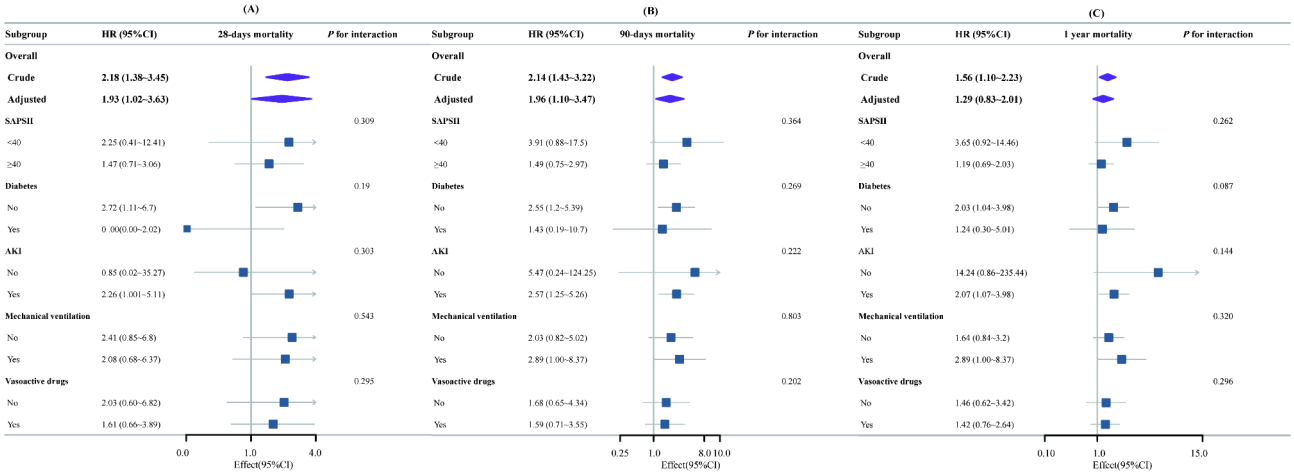

Fig. 3. Forest plots of hazard ratios for the primary endpoint in different subgroups. (**A**) 28-day mortality, (**B**) 90-day mortality, (**C**) 1-year mortality. The model was adjusted for age, sex, race, Temperature, anion gap, creatinine, international normalized ratio, prothrombin time, alanine aminotransferase, neutrophil count, lactate, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment, sepsis, chronic pulmonary disease, cancer, Charlson Comorbidity Index, acute kidney injury, mechanical ventilation, vasoactive drug, continuous renal replacement therapy, and sPESI.

ICD-10 codes; however, it is unclear whether patients were admitted to the ICU because of PE. Nonetheless, we found a strong correlation between PIV and the prognosis of PE in critically ill ICU patients. Fifth, caution is warranted when generalizing these findings to other countries or ICU settings, given the US-specific study cohort. Therefore, prospective multicenter studies are necessary to validate our findings.

Conclusions

The results demonstrated that PIV was positively correlated with ACM in critically ill ICU patients with PE, indicating the potential utility of PIV to stratify these patients according to their risk of death. Moreover, PIV can improve disease management and treatment.

Data availability

The data utilized in this study is derived from the MIMIC database, a publicly accessible and extensive critical database managed by the Computational Physiology team at the Massachusetts Institute of Technology. The database can be obtained from the following link: (https://physionet.org/content/mimiciv/2.2/).

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WZ (First author): Conceptualization, Data curation, Methodology, Software, Validation, Writing - original draft& editing.QL: Supervision, Validation, Writing - review & editing.YF: Supervision.FD: Validation, Writing - review & editing.ZL: Data curation, Visualization.XC: Supervision, Investigation.XL: Investigation, Software.YG: Supervision, Investigation.MZ: Data curation, Visualization.YZ: Data curation, Visualization.XL: Data curation, Visualization.FX (Corresponding author): Project administration, Conceptualization, Supervision, Methodology, Writing - review & editing.All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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