BMC Gastroenterology

RESEARCH

Open Access

Association between pan-immune-inflammation and in-hospital mortality in critically ill patients with acute pancreatitis: a cohort study from the MIMIC-IV database

Fei Zhang[1] and Weijuan Hu[1*]

Abstract

The pan-immune-inflammation value (PIV) is a novel, readily available biomarker that integrates neutrophil, monocyte, lymphocyte, and platelet counts. This study aimed to evaluate the association between the PIV and in-hospital mortality in critically ill patients with acute pancreatitis. This retrospective cohort study used information from the Medical Information Mart for Intensive Care-IV (MIMIC-IV version 3.1) database. Of 7510 patients screened, 277 fulfilled the inclusion criteria (mean [±SD] age 57.0 ± 17.7 years; 56.3% male). In-hospital and 90-day mortality were 18.4% and 24.9%, respectively. When analyzed as a continuous variable, each per-doubling (1-unit increase) of PIV corresponded to a 21% increase in the odds of in-hospital death across all models (fully adjusted OR 1.21 [95% CI 1.04–1.40]; $P = 0.015$);When analyzed as a categorical variable, patients in the highest tertile (T3) exhibited a significantly higher risk for in-hospital mortality compared with those in the lowest tertile (T1) (OR = 3.56 [95% CI 1.40–9.05], $P = 0.008$); the association with 90-day mortality lost significance after full adjustment. RCS revealed a linear relationship between $\log_2$-PIV and in-hospital mortality (P for nonlinearity = 0.868). Subgroup analyses revealed no significant interactions(all $P > 0.05$).Our findings indicate that an elevated PIV is an independent predictor of in-hospital mortality in critically ill patients with AP and may serve as a simple and reliable biomarker for early risk stratification and therapeutic guidance. Larger prospective multicenter studies are needed to validate these findings and explore interventions targeting PIV to improve outcomes.

Keywords Acute pancreatitis, Critically ill, Pan-immune-inflammation value, MIMIC IV database

*Correspondence:
Weijuan Hu
1305_weijuan@sina.com
[1]Department of Emergency Medicine, The Second Affiliated Hospital of Nanchang University, No.1 Minde Road, Donghu District, Nanchang, Jiangxi 330006, People's Republic of China

Acute pancreatitis (AP) is the most common pancreatic disorder worldwide and one of the leading causes of hospital admission among acute gastrointestinal diseases. Its incidence has risen markedly, with an estimated annual rate of 3.74 cases per 100,000 and a mortality rate of 1.6 deaths per 100,000 [1, 2]. Although the incidence of AP is similar among men and women, the risk for disease increases progressively with age [3]. The defining clinical hallmark of the disease is a pronounced local and systemic inflammatory response that closely dictates the clinical trajectory. Approximately 20% of patients progress to moderate or severe AP, characterized by persistent organ failure and infected pancreatic or peripancreatic necrosis, which carries a mortality rate of 20%–40% [4–7].Therefore, early assessment of disease severity and prompt institution of targeted interventions are pivotal for the management of AP. Although validated prognostic tools are widely accepted for many other disorders, reliable identification of individuals at risk for severe AP remains challenging. Currently recommended scoring systems for predicting AP severity include the Ranson criteria, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the Bedside Index for Severity in Acute Pancreatitis (i.e., "BISAP") [8–10]. However, most of these instruments require the collection of multiple variables, rendering them cumbersome for routine clinical use, and their predictive accuracy remains limited [11]. Consequently, there is an urgent need to identify a simple and readily accessible biomarker to evaluate the severity of AP.

It is well established that the pathological hallmark of AP is acinar cell injury, which precipitates an aberrant intracellular release of trypsinogen and its subsequent activation to trypsin, triggering a cascade involving other digestive enzymes, the kinin system, and the complement pathway, ultimately culminating in autodigestion of the pancreas [12, 13]. The pan-immune inflammation value (PIV) is a hematological biomarker derived from the complete blood count that integrates neutrophil, monocyte, lymphocyte, and platelet counts, thereby reflecting systemic inflammatory and immune activation; however, its prognostic utility remains unclear. Recent investigations have demonstrated that elevated PIV is closely associated with adverse clinical outcomes in a spectrum of critical illnesses, including sepsis [14], chronic obstructive pulmonary disease [15], acute decompensated heart failure [16], pulmonary embolism [17, 18], and acute myocardial infarction [19]. Building on these observations, we hypothesized that PIV may similarly correlate with an unfavorable prognosis in patients with AP. However, to the best of our knowledge, no study has directly addressed this question.

Accordingly, in the present study, we used information from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database to evaluate the association between the PIV and in-hospital mortality among critically ill patients with AP, thereby enabling clinicians to rapidly identify high-risk individuals and intensify therapeutic management.

Methods

Study design

This retrospective study was conducted using information from the publicly available MIMIC-IV version 3.1, database, which compiles comprehensive clinical data from patients admitted to the intensive care unit (ICU) of Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2008 and 2019 [20]. MIMIC-IV v3.1 is a de-identified, publicly accessible database. The institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center have waived the requirement for individual informed consent. Completion of the Collaborative Institutional Training Initiative (CITI) program and signing of the PhysioNet Data Use Agreement were the only prerequisites for data access.One of the authors (W-J H) successfully completed the Collaborative Institutional Training Initiative (CITI) program (certificate ID 14375401) and obtained the requisite access credentials.

Inclusion and exclusion criteria

Hospitalization records were extracted from the MIMIC-IV for all patients assigned an *International Classification of Diseases, Ninth Revision* (ICD-9) code of 577.0, or an ICD-10 code K85 of K85.92 for AP, yielding 7510 initial admissions. Subsequent exclusions were applied as follows: readmissions for AP; only data from the first ICU stay were retained; age < 18 years; ICU length of stay < 24 h; and missing or zero values for neutrophil, monocyte, lymphocyte, or platelet counts. After these criteria were applied, 277 patients constituted the final analytic cohort. A flow-diagram illustrating the inclusion and exclusion process is presented in Fig. 1.

Data collection

Data were extracted from the MIMIC-IV using PostgreSQL and comprised all first-available recordings obtained within the initial 24 h of ICU admission. Demographic information included sex, age, and race. Laboratory variables included neutrophil count,monocyte count,lymphocyte and platelet count,white blood cell count (WBC), hemoglobin, hematocrit, red cell distribution width (RDW), glucose, serum creatinine, blood urea nitrogen, anion gap, bicarbonate, sodium, potassium, total calcium, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, arterial pH, partial pressure of oxygen (PaO_2), activated partial thromboplastin time (APTT), international

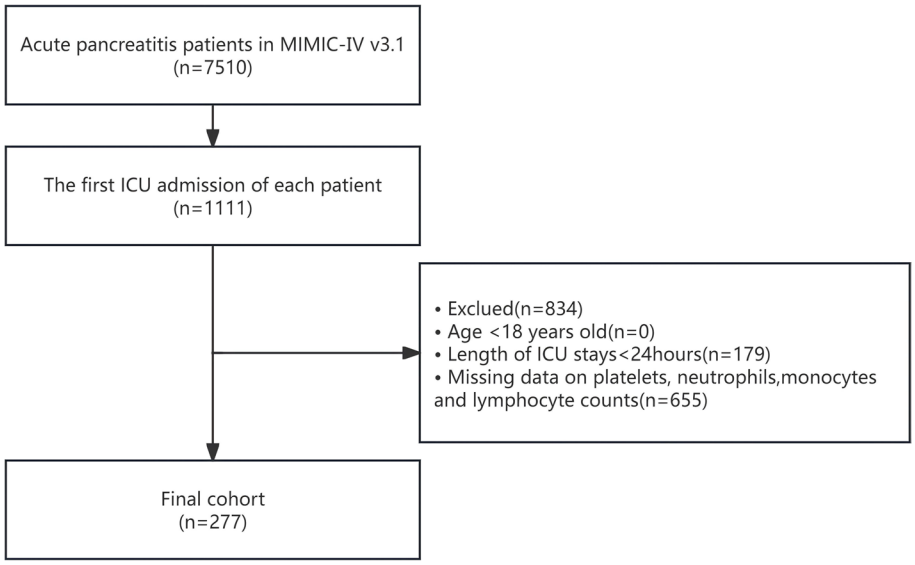

Fig. 1 Diagram of study sample selection steps. ICU, intensive care unit; MIMIC, Medical Information Mart for Intensive Care

normalized ratio (INR), and prothrombin time (PT). Severity scores included the Charlson Comorbidity Index (CCI), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II (SAPS II). Comorbid conditions recorded included congestive heart failure, chronic pulmonary disease, renal disease, and diabetes. The interventions included mechanical ventilation, renal replacement therapy, and vasopressor use. Vital signs included temperature, heart rate, respiratory rate, mean arterial pressure (MAP), and oxygen saturation (SpO_2). The length of ICU stay, total hospital length of stay, in-hospital mortality, and 90-day mortality were also documented. The PIV was calculated using the equation:

$$\begin{aligned}\mathrm{PIV} = {} & (\text{neutrophil count } [\mathrm{k}/\mu\mathrm{L}] \times \text{neutrophil count } [\mathrm{k}/\mu\mathrm{L}] \\ & \times \text{platelet count } [\mathrm{k}/\mu\mathrm{L}]) \ / \ \text{lymphocyte count } [\mathrm{k}/\mu\mathrm{L}]\end{aligned}$$

Outcomes

The primary endpoint was in-hospital mortality(any time during index hospitalisation); the secondary endpoint was 28-day mortality and 90-day mortality (from ICU admission to day 28 and 90, censored at last follow-up).

Statistical analysis

Participants were stratified into tertiles according to their log2-transformed PIV. Continuous variables were tested for normality. Normally distributed data are expressed as mean ± standard deviation (SD) and were compared using the independent-samples t-test. Non-normally distributed data are expressed as median (interquartile range) and were compared using the Mann–Whitney U test. Categorical variables are reported as frequency (percentage); comparisons were performed using Pearson's χ^2 test when expected cell counts were ≥ 5, and using Fisher's exact test when expected counts were < 5 or sample sizes were small. The association between PIV and the risk for each outcome were examined using both univariable and multivariable logistic regression. To investigate the potential linear or nonlinear relationship(s) between PIV and the outcomes, restricted cubic spline (RCS) regression curves were constructed. Finally, subgroup analyses were performed using stratified logistic regression to assess the stability of the PIV–outcome relationship across different clinical scenarios. Because the proportion of missing data for any variable was < 20%, missing values for hemoglobin, RDW, SOFA score, and total bilirubin were imputed using multiple imputation by chained equations (i.e., "MICE") with 5 imputed datasets [21], to enhance statistical power and minimize bias attributable to missing data.Hb, RDW, SOFA, and total bilirubin were all treated as continuous variables and imputed using predictive mean matching (PMM) to preserve their original distributions; five imputed datasets were created with ten iterations per imputation. Four sequential models were constructed: crude model, no covariate adjustment; Model 1, adjusted for age, sex, and race; Model 2, Model 1 plus diabetes mellitus, congestive heart failure, and renal disease; Model 3, Model 2 plus SOFA score, hemoglobin, RDW, and total bilirubin. Mechanical ventilation, RRT, and vasopressors was regarded as potential mediators of the association between PIV and in-hospital mortality; they were therefore excluded from the primary adjustment set and analysed only in an exploratory sensitivity model.Log_2-PIV was analyzed both as a continuous variable and as a categorical variable (tertile), with the

lowest tertile serving as the reference category. Effect estimates (odds ratio [OR] with corresponding 95% confidence interval [CI]) and *P* values were calculated, recorded, and compared across models. All analyses were performed using R version 4.4.1 (R Core Team; R Foundation for Statistical Computing, Vienna, Austria) and the Free Statistics Analysis platform(version 2.2.0). All statistical tests were two-sided and differences with $P < 0.05$ were considered to be significant.

Results

Patients' baseline and clinical data

The baseline characteristics of 277 critically ill patients with severe AP, stratified according to tertile (T1–T3) of the log_2-PIV are summarized in Table 1. The mean (± SD) age was 57.0 ± 17.7 years, and the cohort comprised 156 men and 121 women; 59.6% of participants were White. Patients in the higher log_2-PIV tertiles exhibited significantly higher SAPS II scores and a pronounced upward trend in WBC count ($P < 0.05$).At baseline, 130 patients (46.9%) presented with acute respiratory failure ($PaO_2 < 60$ mmHg within 24 h of ICU admission), 110 (39.7%) met criteria for shock (any vasopressor use within 24 h of ICU admission), and 207 (74.7%) developed acute kidney injury within 48 h of ICU admission, confirming that the cohort represents a population with severe acute pancreatitis."In the overall cohort, in-hospital mortality was 18.4% and 90-day mortality was 24.9%. Notably, the in-hospital mortality progressively with increasing log_2-PIV.

Multivariate analyses of PIV and in-hospital and 28-day and 90-day mortality

Several logistic regression models were constructed to evaluate the association between log_2-PIV and clinical outcomes in patients with AP (Table 2). When log_2-PIV was treated as a continuous variable, logistic regression demonstrated that each unit increment in log_2-PIV was independently associated with an increased risk for both in-hospital and 90-day mortality. For in-hospital mortality, log_2-PIV remained statistically significant across all models (unadjusted, OR 1.19 [95% CI 1.04–1.36], $P = 0.012$; Model 1, OR 1.21 [95% CI 1.05–1.39], $P = 0.008$); Model 2, OR 1.20 95% CI 1.05–1.39], $P = 0.009$; Model 3, OR 1.21 [95% CI 1.04–1.40], $P = 0.015$). Similarly, for 90-day mortality, log_2-PIV was a significant predictor in all but the fully adjusted model (unadjusted, OR 1.14 [95% CI 1.01–1.28], $P = 0.031$; Model 1, OR 1.14 [95% CI 1.01–1.29], $P = 0.040$; Model 2, OR 1.14 [95% CI 1.01–1.29], $P = 0.041$; Model 3, OR 1.12 [95% CI 0.97–1.29], $P = 0.126$). When log_2-PIV was analyzed as a categorical variable, a stepwise increase in the risk for in-hospital mortality was observed across the tertiles. In every model, patients in the highest tertile (T3) exhibited a significantly higher risk for in-hospital mortality compared with those in the lowest tertile (T1) (unadjusted, OR 3.01 [95% CI 1.35–6.71], $P = 0.007$; Model 1, OR 3.15 [95% CI 1.38–7.19], $P = 0.007$; Model 2, OR 3.17 [95% CI 1.38–7.25], $P = 0.006$; Model 3, OR 3.56 [95% CI 1.40–9.05], $P = 0.008$); however, no significant difference was observed between T2 and T1. In contrast, for 90-day mortality, only the unadjusted model revealed a significantly increased risk in T3 compared with T1 (OR 2.00 [95% CI 1.01–3.97]; $P = 0.048$); no significant intergroup differences were detected in the adjusted models. We aslo analysed 28-day mortality as an additional secondary endpoint. In the fully-adjusted model (Model 3) neither continuous log_2-PIV (HR 1.13, 95% CI 0.97–1.30, $P = 0.109$) nor the highest-tertile comparison (T3 vs T1: HR 1.75, 95% CI 0.70–4.36, $P = 0.227$) reached statistical significance (Supplementary Table S2).

To illustrate the clinical significance of the association between PIV and in-hospital mortality, we calculated predicted mortality risks and absolute risk differences (ARDs) across log_2-PIV tertiles using the fully adjusted model (Model 3). Patients in the highest log_2-PIV tertile (T3) had a predicted in-hospital mortality risk of 22.5% (95% CI: 13.1%–35.8%), which was 13.8 percentage points higher than those in the lowest tertile (T1: 8.7%; 95% CI: 4.2%–17.5%). The middle tertile (T2) showed a 5.6-percentage-point higher risk compared to T1 (14.3%; 95% CI: 7.8%–25.1%). For continuous log_2-PIV, each doubling of PIV was associated with an ARD of 3.2%–4.8% in predicted mortality, depending on baseline PIV (Supplementary Table 4).

211 patients (76.2%) had zero missing covariates.After excluding cases with missing data, the multivariable analysis was repeated; the odds ratio for in-hospital mortality remained 1.21, identical to the original estimate (Supplementary Table S8).

Restricted cubic splines

RCS regression was used to examine the shape of the relationship between log_2-PIV and in-hospital mortality. After adjusting for potential confounders, the association was found to be linear (*P* for nonlinearity = 0.868), as illustrated in Fig. 2.Reference point (Ref. point = 10.88) indicates the median log_2-PIV value of the study population.

Subgroup analysis

To assess the stability of the relationship between log_2-PIV and in-hospital mortality across clinically distinct populations, subgroup analyses stratified according to sex, age (< 65 [vs.] ≥ 65 years), congestive heart failure, chronic pulmonary disease, use of renal replacement therapy, and use of vasopressors were performed (Fig. 3). No significant interactions were detected in any of these

Table 1 Basic characteristics of included patients grouped according to log_2-PIV tertiles

Variables	Total(*n* = 277)	T1(*n* = 92)	T2(*n* = 92)	T3(*n* = 93)	*P value*
Sex,male,n(%)	156 (56.3)	54 (58.7)	52 (56.5)	50 (53.8)	0.795
Age(years)	57.0 ± 17.7	57.8 ± 17.6	57.4 ± 17.6	55.8 ± 18.0	0.723
Race,white,n(%)	165 (59.6)	46 (50)	55 (59.8)	64 (68.8)	0.064
Laboratory Parameters					
WBC,10^9/L	15.8 ± 8.3	10.3 ± 5.5	14.2 ± 4.6	22.8 ± 8.7	< 0.001
Hemoglobin,g/dL	11.0 ± 2.8	11.0 ± 2.7	11.1 ± 2.8	10.9 ± 2.8	0.847
Hematocrit,%	33.7 ± 8.2	33.3 ± 7.9	34.0 ± 8.3	33.7 ± 8.5	0.828
RDW	15.5 ± 2.8	15.4 ± 2.9	15.5 ± 2.8	15.7 ± 2.7	0.710
Glucose,mg/dL	155.4 ± 92.8	158.6 ± 120.8	152.8 ± 75.6	154.9 ± 75.6	0.911
Creatinine,mg/dL	1.3 (0.8, 2.2)	1.2 (0.8, 2.1)	1.1 (0.7, 1.9)	1.5 (0.8, 2.7)	0.214
Urea Nitrogen,mg/dL	21.0 (12.0, 37.0)	20.0 (11.0, 33.0)	16.5 (9.0, 29.2)	26.0 (15.0, 52.0)	< 0.001
Anion Gap,mEq/L	16.4 ± 5.3	16.8 ± 5.6	15.9 ± 5.1	16.4 ± 5.0	0.476
Bicarbonate,mEq/L	20.2 ± 5.4	19.3 ± 5.1	20.8 ± 5.4	20.5 ± 5.5	0.121
Sodium,mEq/L	137.6 ± 6.6	137.7 ± 6.4	137.0 ± 6.9	137.9 ± 6.6	0.592
Potassium,mEq/L	4.3 ± 1.0	4.3 ± 1.0	4.2 ± 0.9	4.3 ± 0.9	0.601
Calcium total,mEq/L	8.0 ± 1.2	8.1 ± 1.1	8.0 ± 1.3	7.8 ± 1.0	0.270
Albumin,g/dL	2.8 ± 0.7	2.9 ± 0.6	2.7 ± 0.6	2.7 ± 0.6	0.094
Alanine Aminotransferase,IU/L	46.5 (24.0,127.0)	42.0 (24.0,127.0)	64.5 (30.0,155.8)	40.0 (18.5,103.5)	0.060
Aspatate Aminotransferase,IU/L	76.0 (36.0,173.5)	81.0 (39.0,192.5)	86.0 (38.0,260.0)	56.0 (33.2,110.8)	0.049
Total bilirubin,mg/dL	1.1 (0.6,3.9)	1.2 (0.6,4.2)	1.1 (0.6,3.8)	1.1 (0.6,3.9)	0.981
pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	0.557
PO_2,mmHg	57.0 (40.2,94.2)	57.5 (42.8,91.2)	63.0 (41.0,99.0)	52.0 (38.0,83.0)	0.179
APTT(s)	37.6 ± 20.5	36.2 ± 18.3	40.4 ± 27.1	36.3 ± 13.8	0.302
INR	1.7 ± 1.0	1.6 ± 1.2	1.6 ± 1.0	1.7 ± 0.8	0.975
PT(s)	18.1 ± 11.3	18.1 ± 13.8	17.9 ± 11.0	18.2 ± 8.5	0.984
Comorbidities					
Congestive heart failure,n(%)	50 (18.1)	17 (18.5)	15 (16.3)	18 (19.4)	0.857
Chronic pulmonary disease,n(%)	41 (14.8)	11 (12)	17 (18.5)	13 (14)	0.443
Renal disease,n(%)	59 (21.3)	17 (18.5)	21 (22.8)	21 (22.6)	0.720
Diabetes,n(%)	78 (28.2)	26 (28.3)	23 (25)	29 (31.2)	0.646
Clinical severity					
Charlson comorbidity index	4.6 ± 3.0	4.6 ± 2.9	4.4 ± 3.1	4.8 ± 3.0	0.664
SAPS Ⅱ	41.3 ± 17.0	41.0 ± 17.2	38.2 ± 15.9	44.7 ± 17.4	0.033
SOFA	4.9 ± 2.6	5.1 ± 2.7	4.5 ± 2.4	5.2 ± 2.6	0.204
ARF	130 (46.9)	44 (15.9)	37 (13.4)	49 (17.7)	0.303
Shock	110 (39.7)	37 (40.2)	35 (38)	38 (40.9)	0.919
AKI	207 (74.7)	68 (73.9)	66 (71.7)	73 (78.5)	0.558
Intervention					
Ventilation,n(%)	4 (1.4)	2 (2.2)	1 (1.1)	1 (1.1)	0.855
RRT,n(%)	74 (26.7)	23 (25)	22 (23.9)	29 (31.2)	0.483
Norepinephrine,n (%)	110 (39.7)	37 (40.2)	35 (38)	38 (40.9)	0.919
Events					
ICU Los	5.1 (2.5,14.2)	5.0 (2.6,14.3)	5.0 (2.8,16.3)	5.1 (2.4,13.0)	0.903
Hospital Los	18.6 (9.7,30.6)	18.2 (8.1,27.3)	19.5 (9.9,30.6)	18.1 (9.9,33.9)	0.554
In-hospital mortality,n(%)	51 (18.4)	10 (10.9)	16 (17.4)	25 (26.9)	0.018
90 day mortality,n(%)	69 (24.9)	17 (18.5)	23 (25)	29 (31.2)	0.136

Continuous and categorical variables were presented as median (Interquartile range) or n (%). T1-T3:Grouped by tertiles according to the log_2-PIV

PIV Pan-Immune-Inflammation Value, *WBC* White Blood Cell Count, *RDW* Red Blood Cell distribution Width, *APTT* Activated Partial Thromboplastin Time, *pH* Potential of Hydrogen, *PaO2* Partial Pressure of Oxygen, *INR* International Normalized Ratio, *PT* Prothrombin Time, *CCI* Charlson Comorbidity Index, *RRT* Renal Replacement Therapy, *SOFA* Sequential Organ Failure Assessment, *SAPS II* Simplified Acute Physiology Score II, *ALT* Alanine Aminotransferase, *AST* Aspatate Aminotransferase, *ARF* Acute Respiratory Failure, *AKI* Acute Kidney Injury

Table 2 Association between PIV and in-hospital and 90-day mortality in patients with AP across different models

Variable	Crude Model		Model1		Model2		Model3	
	OR(95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
In-hospital mortality								
log_2-PIV(continuous variable)	1.19 (1.04 ~ 1.36)	0.012	1.21 (1.05 ~ 1.39)	0.008	1.2 (1.05 ~ 1.39)	0.009	1.21 (1.04 ~ 1.4)	0.015
log_2-PIV Tertiles								
T1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
T2	1.73 (0.74 ~ 4.04)	0.208	1.75 (0.74 ~ 4.15)	0.205	1.75 (0.74 ~ 4.17)	0.206	2.17 (0.82 ~ 5.78)	0.122
T3	3.01 (1.35 ~ 6.71)	0.007	3.15 (1.38 ~ 7.19)	0.007	3.17 (1.38 ~ 7.25)	0.006	3.56 (1.4 ~ 9.05)	0.008
P for trend		0.006		0.006		0.005		0.008
90 days mortality								
log_2-PIV(continuous variable)	1.14 (1.01 ~ 1.28)	0.031	1.14 (1.01 ~ 1.29)	0.040	1.14 (1.01 ~ 1.29)	0.041	1.12 (0.97 ~ 1.29)	0.126
log_2-PIV Tertiles								
T1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
T2	1.47 (0.73 ~ 2.98)	0.285	1.46 (0.7 ~ 3.05)	0.312	1.39 (0.66 ~ 2.93)	0.382	1.17 (0.48 ~ 2.85)	0.731
T3	2 (1.01 ~ 3.97)	0.048	1.96 (0.96 ~ 4.04)	0.066	1.96 (0.95 ~ 4.04)	0.069	1.72 (0.74 ~ 4.03)	0.210
P for trend		0.047		0.066		0.068		0.203

The crude Model was not adjusted for any variables

Model 1 was adjusted for Age,Sex and Race

Model 2 was adjust for Model 1 + Diabetes,Congestive heart failure,Renal disease

Model 3 was adjust for Model 2 + SOFA,Hemoglobin,RDW,Total Bilirubin

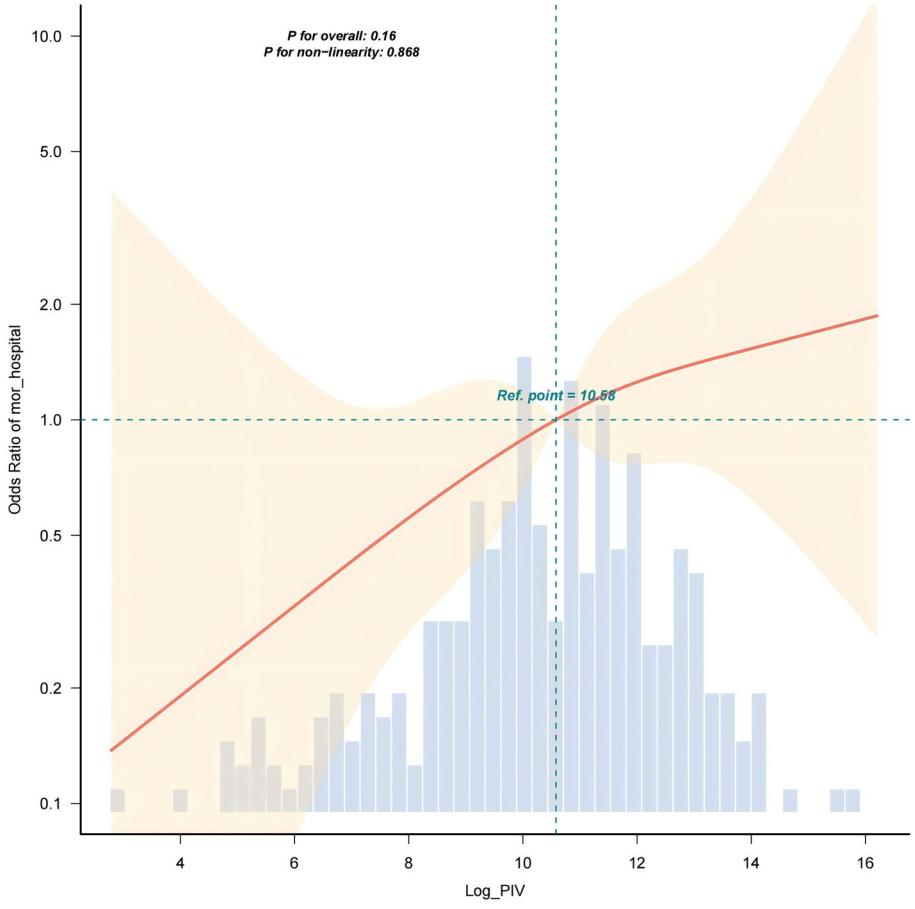

Fig. 2 Association between log_2-PIV and in-hospital mortality in acute pancreatitis patients. Data were fitted by a multivariable-adjusted restricted cubic spline Logistic regression. A linear association between log_2-PIV and in-hospital mortality was observed. log_2-PIV was entered as a continuous variable, the variables in model 3 of Table 2 were adjusted. The curves line and shaded ribbons around represented the estimated values and their corresponding 99% confidence intervals. PIV: Pan-immune-inflammation value

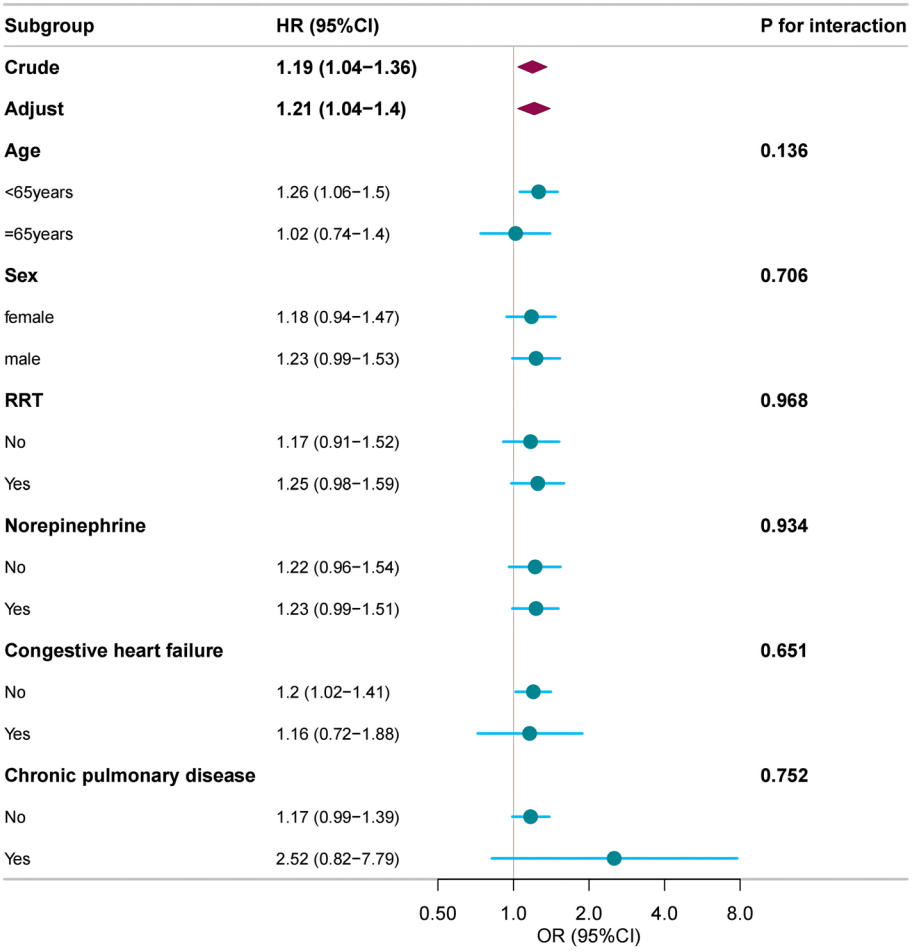

Fig. 3 Forest plot of subgroup analysis for the association between log2-PIV and in-hospital mortality in acute pancreatitis patients. OR: odds ratio; Pan-Immune inflammation value

subgroups (all $P > 0.05$), indicating that the association between elevated log_2-PIV and increased risk for in-hospital death remained consistent irrespective of these clinical characteristics.

Aetiology-proxy subgroup analyses

Because MIMIC-IV lacks narrative reports, we used two biochemical proxies to explore residual confounding by aetiology: Hypertriglyceridaemic AP: triglyceride ≥ 11.3 mmol/L within 24 h ($n = 165$ after excluding 112 missing);suspected biliary AP: total bilirubin ≥ 1 mg/dL, excluding severe liver disease ($n = 221$ after excluding 45 liver disease and 11 missing).In both subgroups the adjusted OR for in-hospital mortality remained essentially unchanged (hyper-TG stratum 1.26 vs non-hyper-TG 1.78, P-interaction$n = 0.204$; high-bilirubin 1.14 vs low-bilirubin 1.20, P-interaction$n = 0.683$; Supplementaly Table S3), indicating no significant heterogeneity in the prognostic value of PIV across these aetiologic proxies.

Prediction of in-hospital mortality in patients with AP using log_2-PIV

We constructed ROC curves for in-hospital mortality and calculated the area under the curve (AUC) for (1) PIV alone, (2) SOFA alone, (3) APACHE-II alone, (4) PIV added SOFA and APACHE-II,(5) PIV added APACHE-II,and(6) PIV added SOFA.ROC-curve analysis showed that the combined model incorporating PIV, SOFA and APACHE-II achieved the highest AUC (0.7849, 95% CI 72.47%–84.52%), indicating superior predictive accuracy for in-hospital mortality in patients with acute pancreatitis.These analyses are presented in Fig. 4 and Table 3. We conclude that PIV provides meaningful incremental predictive value beyond both SOFA and APACHE-II for early risk stratification in critically ill patients with acute pancreatitis.

Discussion

To the best of our knowledge, this is the first study to evaluate the relationship between PIV and adverse outcomes in critically ill patients with AP, with a particular focus on

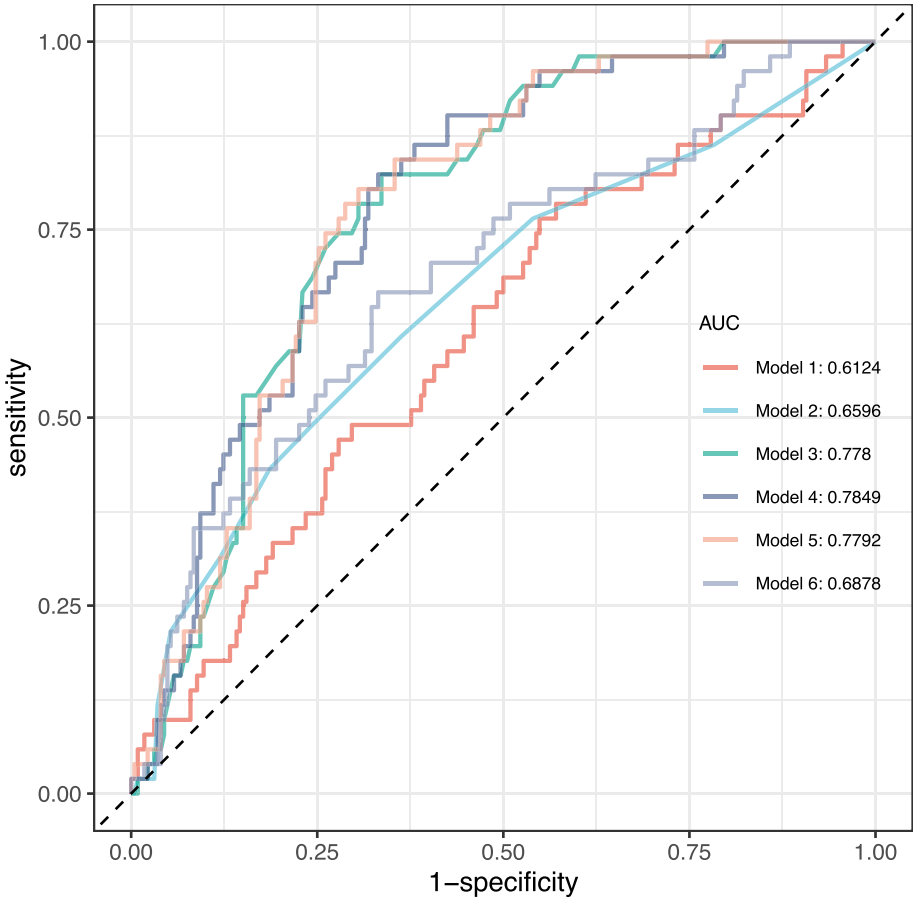

Fig. 4 Receiver operator characteristic curves assessing the predictive capability of the PIV for in-hospital mortality.Model 1:PIV,Model 2:SOFA,Model 3:APACHE-II,Model 4:PIV + SOFA + APACHE-II,Model 5:PIV + APACHE-II,Model 6:PIV + SOFA

Table 3 Information of ROC curves in Figure S1

Model name	95%CI	AUC	threshold	specificity	sensitivity
PIV	52.72%–69.77%	0.6124	0.17	0.45	0.76
SOFA	57.25%–74.66%	0.6596	0.2	0.76	0.49
APACHE-II	71.75%–83.85%	0.7780	0.17	0.66	0.82
PIV + SOFA + APACHE-II	72.47%–84.52%	0.7849	0.16	0.67	0.82
PIV + APACHE-II	71.91%–83.93%	0.7792	0.18	0.69	0.8
PIV + SOFA	60.5%–77.07%	0.6878	0.17	0.67	0.67

in-hospital mortality. We found that an elevated $\log_2$-PIV was associated with increased risks for both in-hospital and 90-day mortality. After adjusting for multiple laboratory parameters and comorbidities, a high $\log_2$-PIV remained significantly associated with in-hospital mortality; however, the association with 90-day mortality was attenuated and became nonsignificant in the fully adjusted model. Restricted cubic spline analysis further revealed a linear relationship between $\log_2$-PIV and in-hospital mortality (P for non-linearity = 0.868). In addition, the subgroup analyses detected no significant interactions across various comorbidities or intervention strata, indicating that the prognostic value of PIV is consistent across diverse clinical contexts.Although $\log_2$-PIV remained an independent predictor of in-hospital mortality across all four models, its association with 28-day and 90-day mortality became non-significant in the fully adjusted model (Model 3). This discrepancy may reflect the fact that early, intensive-care–driven factors (reflected by SOFA, hemoglobin, RDW and total bilirubin) capture much of the short-term prognostic information, thereby diluting the longer-term signal of PIV. Additionally, unmeasured post-discharge events (e.g., recurrent pancreatitis, new infections, or re-hospitalizations) that strongly influence 90-day death could not be captured in the MIMIC-IV database. Finally,,the modest sample size (277 patients and 69 ninety-day events) limited statistical power for detecting smaller but clinically relevant effect sizes beyond the acute phase. These considerations suggest that

while PIV is a robust early-warning biomarker, its utility for longer-term risk stratification may require supplementation with post-ICU clinical data or alternative biomarkers.The clinical relevance of PIV is further supported by absolute risk differences: a 13.8-percentage-point higher in-hospital mortality risk in the highest versus lowest $\log_2$-PIV tertile translates to 14 additional deaths per 100 patients. Even incremental increases in PIV (e.g., a single doubling) confer a 3–5 percentage-point higher absolute risk, which is meaningful for bedside risk stratification. These data confirm that PIV can identify high-risk patients who may benefit from intensified monitoring or targeted anti-inflammatory interventions.Collectively, our results support the potential utility of PIV as a novel biomarker for risk stratification and therapeutic decision-making in critically ill patients with AP.

PIV is a systemic inflammatory biomarker derived from a complete blood count that integrates neutrophil, monocyte, lymphocyte, and platelet counts, thereby providing a more comprehensive assessment of global inflammation. An accumulating body of research has investigated the relationship between PIV and mortality in patients with various critical illnesses. In a prospective cohort study of septic shock, APACHE II scores were significantly lower in the low-PIV group than in the high-PIV group, and median survival was markedly longer in the low-PIV group (28 days [interquartile range (IQR) 15.25–40.76 days] [vs.] 16 days [IQR 9.46–22.55 days]), indicating that PIV may serve as a reliable prognostic indicator in septic shock [22]. Another retrospective cohort study evaluating the relationship between PIV and short- and long-term mortality in patients with sepsis demonstrated that elevated PIV was closely associated with increased 28-day and 90-day mortalities [14]. Mardan et al. [23] further demonstrated that PIV was strongly associated with all-cause mortality in patients with rheumatoid arthritis; survival probability declined markedly across ascending PIV quartiles, establishing PIV as an important and independent predictor of death. A retrospective cohort study examining preoperative PIV in patients undergoing surgery for acute Stanford type A aortic dissection (ATAAD) [24] reported that individuals in the high-PIV group experienced significantly higher incidences of severe postoperative complications, including acute kidney injury, acute hepatic injury, and gastrointestinal bleeding, and markedly elevated in-hospital mortality. These findings indicate that an elevated admission PIV is an independent predictor of postoperative death in patients with ATAAD. These results underscore the prognostic utility of the preoperative inflammatory state, emphasizing that even aggressive therapeutic strategies must be tailored to and potentially tempered by this readily quantifiable systemic burden. Huang et al. [25] demonstrated that elevated admission PIV was closely linked to both short- and long-term all-cause mortality in patients with non-traumatic subarachnoid hemorrhage, establishing it as an independent determinant of death in this population.

To the best of our knowledge, the present study is the first to validate the relationship between PIV and mortality in critically ill patients with AP. We found that higher PIV was associated with an increased risk for in-hospital and 90-day mortality, consistent with previous reports. Importantly, after adjusting for multiple confounders, elevated PIV remained independently associated with increased in-hospital mortality. These findings support the potential clinical utility of PIV as a prognostic biomarker in AP, inform the development of tailored therapeutic strategies, and underscore the need for further investigation of its role as a therapeutic target in critically ill patients with AP.

AP is characterized by pancreatic inflammation, edema, and necrosis, accompanied by inflammatory injury in remote organs [26]. The clinical spectrum of the disease is highly heterogeneous, ranging from mild, self-limited pancreatic involvement to profound multiorgan failure and death [27]. In the early phases of AP, neutrophils and monocytes are rapidly recruited to the inflamed pancreas. Once infiltrated, neutrophils amplify pancreatic injury by releasing proinflammatory mediators and generating reactive oxygen species, thereby exacerbating local inflammation and tissue damage [28]. Experimental studies have confirmed that AP is characterized by pronounced neutrophil infiltration within the pancreatic parenchyma, and depletion of neutrophils using anti-neutrophil serum markedly attenuates pancreatic injury and the severity of associated lung injury, thereby ameliorating both local and systemic inflammatory responses [29, 30].

Moreover, Gui et al. [31] experimentally demonstrated that the early phase of severe AP is characterized by extensive microthrombosis, microvascular failure, and marked platelet activation events, which constitute a critical step toward pancreatic necrosis. Their study further revealed that high-dose vitamin C attenuates pancreatic necrosis by downregulating the CXCL12/CXCR4 axis, thereby suppressing platelet activation. However, the precise mechanism through which lymphocytopenia influences the course of AP remains unclear. Nevertheless, compelling evidence indicates that early lymphocyte depletion in acute necrotizing pancreatitis is closely linked to the subsequent development of infected pancreatic necrosis [32]. As a novel composite biomarker integrating neutrophil, monocyte, lymphocyte, and platelet counts, the PIV directly mirrors the magnitude of the inflammatory response in patients with AP.Any intervention that favourably alters these cell populations(e.g., limiting neutrophil recruitment, curbing platelet activation, or restoring lymphocyte counts) would be expected

to lower PIV and, potentially, improve prognosis.thereby demonstrating substantial clinical utility in everyday practice.

The present study is the first to leverage information from the MIMIC-IV v3.1 database to comprehensively delineate the associations between PIV and in-hospital mortality and 90-day mortality. Its principal strength lies in the use of a rigorously validated region-wide electronic medical record system that prospectively captures all diagnoses, hospitalizations, and laboratory parameters. This high-quality dataset effectively circumvents the selection and recall biases common in conventional observational studies and permits precise adjustment for potential confounders. Multidimensional sensitivity analyses further bolstered the credibility of our findings and provided robust internal validation.

This study, however, also had several limitations. First, the PIV calculation requires all four hematologic parameters; 655 admissions were excluded because any one of them was missing. This necessary exclusion, together with the retrospective design, may have produced a non-representative sample and further limits the generalizability of our results to the wider population of critically ill patients with acute pancreatitis.Moreover,the modest sample size may have curtailed statistical power and limited our ability to explore potential interactions, thereby tempering the generalizability of the subgroup analyses; as such, the results should be interpreted cautiously. However, the baseline characteristics of the excluded cohort (age, sex, crude mortality) are comparable to the included group (Supplementary Table S4), suggesting that the main limitation is feasibility (missing data) rather than systematic selection bias. Future multicentre studies with richer laboratory coverage are needed to validate PIV across the full spectrum of acute pancreatitis. Second, despite extensive adjustment for known confounders, residual unmeasured factors, such as immunocompromised states (e.g., HIV infection or hematological malignancies) that can directly affect blood cell counts and, thus PIV, cannot be fully excluded. Third, because the MIMIC database predominantly houses data from residents of the United States and other specific ethnic populations, the external validity of our findings for other racial groups or geographical areas requires further confirmation. Third,the present study is restricted to admission values; we cannot determine whether rising or falling PIV during hospitalisation predicts outcome trajectories. Repeated CBC sampling and time-updated modelling are required to test this dynamic hypothesis. Finally, given the single-center retrospective design of this study, well-designed multicenter prospective studies aimed at corroborating our findings are warranted.

Conclusions

In conclusion, this study demonstrated that PIV was independently associated with in-hospital mortality in patients diagnosed with AP, whereas its association with 90-day mortality was not statistically significant. These findings underscore the clinical utility of PIV as a simple and reliable biomarker for risk stratification and therapeutic decision making. It can promptly identify high-risk patients and guide targeted interventions to improve patient outcomes. Future investigations with larger and more diverse cohorts to validate these findings and explore potential therapeutic strategies aimed at modulating PIV to enhance patient prognosis are warranted.

Abbreviations

PIV	The pan-immune-inflammation value
AP	Acute pancreatitis
MIMIC-IV	Medical Information Mart for Intensive Care-IV
ICU	Intensive care unit
WBC	White blood cell count
RDW	Red cell distribution width
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
PaO_2	Partial pressure of oxygen
APTT	Activated partial thromboplastin time
INR	International normalized ratio
PT	Prothrombin time
SOFA	Sequential Organ Failure Assessment
SAPS II	Simplified Acute Physiology Score II

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04521-7.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

The authors would like to thank the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center for the MIMIC-IV database.

Authors' contributions

HWJ designed and supervised the study. ZF collected the data. HWJ and ZF conducted the data analysis. HWJ and ZF analyzed and interpreted the result. HWJ and ZF drafted the manuscript, HWJ revised and polished the manuscript. All authors approved the submitted version.

Funding

None.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: The Medical Information Mart for Intensive Care IV (MIMIC-IV) database at **https://physionet.org/content/mimiciv/3.1/**.

Declarations

Ethics approval and consent to participate

The studies involving humans were approved by the Institutional Review Board at the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed

consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 October 2025 / Accepted: 27 November 2025
Published online: 05 January 2026

References

1. Xiao AY, Tan MLY, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1:45–55. https://doi.org/10.1016/S2468-1253(16)30004-8.
2. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: a review. JAMA. 2021;325:382–90. https://doi.org/10.1001/jama.2020.20317.
3. Yadav D, Lowenfels AB. The Epidemiology of Pancreatitis and Pancreatic Cancer. Gastroenterology. 2013;144:1252–61. https://doi.org/10.1053/j.gastro.2013.01.068.
4. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. Lancet. 2020;396:726–34. https://doi.org/10.1016/S0140-6736(20)31310-6.
5. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019;68:1044–51. https://doi.org/10.1136/gutjnl-2017-314657.
6. Yang CJ, Chen J, Phillips ARJ, Windsor JA, Petrov MS. Predictors of severe and critical acute pancreatitis: a systematic review. Dig Liver Dis. 2014;46:446–51. https://doi.org/10.1016/j.dld.2014.01.158.
7. Bang JY, Wilcox CM, Arnoletti JP, Varadarajulu S. Superiority of endoscopic interventions over minimally invasive surgery for infected necrotizing pancreatitis: meta-analysis of randomized trials. Dig Endosc. 2020;32:298–308. https://doi.org/10.1111/den.13470.
8. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57:1698–703. https://doi.org/10.1136/gut.2008.152702.
9. Forsmark CE, Baillie J, AGA Institute Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA institute technical review on acute pancreatitis. Gastroenterology. 2007;132:2022–44. https://doi.org/10.1053/j.gastro.2007.03.065.
10. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet Lond Engl. 1989;2:201–5. https://doi.org/10.1016/s0140-6736(89)90381-4.
11. Trikudanathan G, Yazici C, Evans Phillips A, Forsmark CE. Diagnosis and management of acute pancreatitis. Gastroenterology. 2024;167:673–88. https://doi.org/10.1053/j.gastro.2024.02.052.
12. Roxvall L, Bengtson A, Sennerby L, Heideman M. Activation of the complement cascade by trypsin. Biol Chem Hoppe-Seyler. 1991;372:273–8. https://doi.org/10.1515/bchm3.1991.372.1.273.
13. Uehara S, Honjyo K, Furukawa S, Hirayama A, Sakamoto W. Role of the kallikrein-kinin system in human pancreatitis. Adv Exp Med Biol. 1989;247B:643–8. https://doi.org/10.1007/978-1-4615-9546-5_106.
14. Xu H-B, Xu Y-H, He Y, Lin X-H, Suo Z, Shu H, et al. Association between admission pan-immune-inflammation value and short-term mortality in septic patients: a retrospective cohort study. Sci Rep. 2024;14:15205. https://doi.org/10.1038/s41598-024-66142-6.
15. Giri M, Puri A, Chen Y, Liu Y, Guo S. Association between pan-immune-inflammation value and in-hospital mortality in critically ill patients with chronic obstructive pulmonary disease: an observational study. Respir Med. 2025;245:108213. https://doi.org/10.1016/j.rmed.2025.108213.
16. Murat B, Murat S, Altınbas ME, Yalvac HE, Durmaz FE, Mert KU, et al. Association of pan immune-inflammation value with long term outcomes of acute decompensated heart failure. Arq Bras Cardiol. 2024;121:e20230817. https://doi.org/10.36660/abc.20230817.
17. Bilgin M, Akkaya E, Dokuyucu R. Inflammatory and metabolic predictors of mortality in pulmonary thromboembolism: a focus on the triglyceride-glucose index and pan-immune inflammation value. J Clin Med. 2024;13:6008. https://doi.org/10.3390/jcm13196008.
18. Zhao W, Liao Q, Feng Y, Du F, Liang Z, Chen X, et al. Association of pan-immune inflammation value with mortality in patients with pulmonary embolism: a cohort study. Sci Rep. 2025;15:6571. https://doi.org/10.1038/s41598-025-90951-y.
19. Liu Y, Liu J, Liu L, Cao S, Jin T, Chen L, et al. Association of systemic inflammatory response index and pan-immune-inflammation-value with long-term adverse cardiovascular events in ST-segment elevation myocardial infarction patients after primary percutaneous coronary intervention. J Inflamm Res. 2023;16:3437–54. https://doi.org/10.2147/JIR.S421491.
20. Johnson AEW, Bulgarelli L, Shen L, Gayles A, Shammout A, Horng S, et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data. 2023;10:1. https://doi.org/10.1038/s41597-022-01899-x.
21. Austin PC, White IR, Lee DS, Van Buuren S. Missing data in clinical research: a tutorial on multiple imputation. Can J Cardiol. 2021;37:1322–31. https://doi.org/10.1016/j.cjca.2020.11.010.
22. Turan YB. The prognostic importance of the pan-immune-inflammation value in patients with septic shock. BMC Infect Dis. 2024;24:69. https://doi.org/10.1186/s12879-023-08963-w.
23. Mardan M, Zheng H, Xu Q, Song S, Lu Z, Deng H, et al. Comprehensive analysis of pan-immune inflammation and all-cause mortality in rheumatoid arthritis: a database-driven approach, 1999–2018. Front Immunol. 2025;16:1549955. https://doi.org/10.3389/fimmu.2025.1549955.
24. Yu X, Chen Y, Peng Y, Chen L, Lin Y. The Pan-immune inflammation value at admission predicts postoperative in-hospital mortality in patients with acute type A aortic dissection. J Inflamm Res. 2024;17:5223–34. https://doi.org/10.2147/JIR.S468017.
25. Huang Y-W, Zhang Y, Li Z-P, Yin X-S. Association between a four-parameter inflammatory index and all-cause mortality in critical ill patients with non-traumatic subarachnoid hemorrhage: a retrospective analysis of the MIMIC-IV database (2012–2019). Front Immunol. 2023;14:1235266. https://doi.org/10.3389/fimmu.2023.1235266.
26. Pandol SJ, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. Gastroenterology. 2007;132:1127–51. https://doi.org/10.1053/j.gastro.2007.01.055.
27. Habtezion A, Gukovskaya AS, Pandol SJ. Acute pancreatitis: a multifaceted set of organelle and cellular interactions. Gastroenterology. 2019;156:1941–50. https://doi.org/10.1053/j.gastro.2018.11.082.
28. Tsuji N, Watanabe N, Okamoto T, Niitsu Y. Specific interaction of pancreatic elastase and leucocytes to produce oxygen radicals and its implication in pancreatitis. Gut. 1994;35:1659–64. https://doi.org/10.1136/gut.35.11.1659.
29. Frossard JL, Saluja A, Bhagat L, Lee HS, Bhatia M, Hofbauer B, et al. The role of intercellular adhesion molecule 1 and neutrophils in acute pancreatitis and pancreatitis-associated lung injury. Gastroenterology. 1999;116:694–701. https://doi.org/10.1016/s0016-5085(99)70192-7.
30. Gukovskaya AS, Vaquero E, Zaninovic V, Gorelick FS, Lusis AJ, Brennan M-L, et al. Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. Gastroenterology. 2002;122:974–84. https://doi.org/10.1053/gast.2002.32409.
31. Gui M, Huang J, Sheng H, Chen Y, Yang Z, Ma L, et al. High-dose vitamin C alleviates pancreatic necrosis by inhibiting platelet activation through the CXCL12/CXCR4 pathway in severe acute pancreatitis. J Inflamm Res. 2023;16:2865–77. https://doi.org/10.2147/JIR.S415974.
32. Cai T, Mao W, Liu M, Zhou J, Wang X, Zhou J, et al. Early mean absolute lymphocyte count in acute necrotizing pancreatitis is associated with infected pancreatic necrosis. Int Immunopharmacol. 2023;117:109883. https://doi.org/10.1016/j.intimp.2023.109883.

Publisher's Note