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Evaluation of Pan-Immuno-Inflammation Value for In-Hospital Mortality in Acute Pulmonary Embolism Patients

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ABSTRACT

Background: Pan-immuno-inflammation value is a new and comprehensive index that reflects both the immune response and systemic inflammation in the body. **Objective:** The aim of this study was to investigate the prognostic relevance of pan-immuno-inflammation value in predicting in-hospital mortality in acute pulmonary embolism patients and to compare it with the well-known risk scoring system, pulmonay embolism severity index, which is commonly used for a short-term mortality prediction in such patients. **Methods:** In total, 373 acute pulmonary embolism patients diagnosed with contrast-enhanced computed tomography were included in the study. Detailed cardiac evaluation of each patient was performed and pulmonary embolism severity index and pan-immuno-inflammation value were calculated. **Results:** In total, 60 patients died during their hospital stay. The multivariable logistic regression analysis revealed that baseline heart rate, N-terminal pro–B-type natriuretic peptide, lactate dehydrogenase, pan-immuno-inflammation value, and pulmonary embolism severity index were independent risk factors for in-hospital mortality in acute pulmonay embolism patients. When comparing with pulmonary embolism severity index, pan-immuno-inflammation value was non-inferior in terms of predicting the survival status in patients with acute pulmonay embolism. **Conclusion:** In our study, we found that the PIV was statistically significant in predicting in-hospital mortality in acute pulmonay embolism patients and was non-inferior to the pulmonary embolism severity index. (REV INVEST CLIN. 2024;76(2):97-102)

Keywords: Pan-immuno-inflammation value. Acute pulmonary embolism. Pulmonary embolism severity index. In-hospital mortality.

INTRODUCTION

Acute pulmonary embolism (PE) is a sudden and potentially life-threatening condition that arises when an embolic substance, often a blood clot originating from the deep venous vessels in the legs or pelvis, obstructs one or more pulmonary arteries. This obstruction disrupts blood circulation, which can lead to increased pressure in the right ventricle of the heart. Among cardiovascular disorders, acute PE stands as the third leading cause of in-hospital mortality following acute myocardial infarction and stroke[1,2].

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Acute PE activates the pathophysiological cascade by inducing the virchow triad, which is consisting of stasis, hypercoagulability, and endothelial damage. However, inflammation also plays a significant role in the pathophysiology of thrombosis formation, even when not explicitly part of this triad. Moreover, inflammation triggers the aggregation of platelets in which activated platelets release polyphosphates, procoagulant microparticles, and proinflammatory mediators. Furthermore, inflammation can activate a series of biochemical reactions in the vascular endothelium that support thrombosis formation[3,4].

Pan-immuno-inflammation value (PIV) is a new, easily measurable, and comprehensive index that reflects both the immune response and systemic inflammation in the body. This index is obtained by calculating the neutrophil count × platelet count × monocyte/lymphocyte count. Previous studies showed that the PIV could be used to determine the prognosis or treatment response of patients with conditions such as cancer, auto-immune disease, and acute heart failure[5,6]. However, this index is not investigated in patients with acute PE. As the inflammation is closely related with the pathogenesis of acute PE, we consider that the PIV can be applied to estimate the prognosis in such patients. Thus, we aimed to examine the prognostic relevance of PIV in predicting in-hospital mortality in acute PE patients and to compare it with the well-known risk scoring system, PE severity index (PESI), which is commonly used for a short-term mortality prediction in such patients.

OBJECTIVES AND METHODS

Study population

A total of 373 patients diagnosed with acute PE at a tertiary hospital, between January 2017 and June 2023, were included in our study. The study, which was conducted retrospectively, involved reviewing the archival records of our center. The demographic characteristics, risk factors, physical examination findings, electrocardiograms, transthoracic echocardiography results, blood parameters, and treatment protocols of the patients at the time of admission to the hospital were recorded. The diagnosis of acute PE was confirmed in all patients using contrast-enhanced multidetector computed tomography. Patients who were under the age of 18, tested positive for COVID-19, and patients with autoimmune disease and end-stage malignancy were excluded from the study. The PESI score was determined for each patient enrolled in the study. All patients were treated in accordance with the most recent European society of cardiology guidelines. The PIV was calculated by multiplying the neutrophil count with platelet count and monocyte count, then dividing by lymphocyte count. PIV was calculated form the laboratory values obtained on admission in all patients.

Statistical analysis

R statistical software, version 4.1.2, from the Institute for statistics and mathematics in Vienna, Austria, was used. To determine if the data were normally distributed, the Kolmogorov–Smirnov test was used. Numbers and percentages were used to display the categorical data. To compare categorical variables between groups, Fisher's exact test or the two test were used, depending on the condition. For normal distributions, the continuous variables were presented as mean (standard deviation), and for non-normal distributions, median (interquartile range [IQR]). Comparing continuous variables between the groups was done using the independent Student's *t*-test and Mann–Whitney *U*-test. Utilizing univariable logistic regression analysis, the relationships between the variables and in-hospital mortality in patients with PE were assessed. Lasso penalized shrinkage was used to variables that were significantly identified in univariable logistic regression analysis to avoid overfitting by reducing variables. Finally, seven variables including baseline heart rate, N-terminal pro–B-type natriuretic peptide (NT-pro-BNP), serum lactate, lactate dehydrogenase (LDH), PIV, PESI score, and tissue plasminogen activator use were included in the multivariable model. Utilizing variance inflation factor (>3) and tolerance (0.1) values, multicollinearity was evaluated. The importance of variables in the multivariable model was ranked based on X^2 values. The receiver-operating characteristics (ROC) curve comparison was visualized to demonstrate the comparison of discriminative capabilities of the PIV and the PESI score for patients with in-hospital mortality. A 95% confidence interval (CI) and a 2-sided $p < 0.05$ were used for analyzing data. Patients were divided as high and low groups based on the median value of PIV. The Kaplan–Meier survival curve and De-Long

Table 1. Baseline characteristics, laboratory and echocardiographic findings of all patients

Variable	Survivors (n = 313)	Non-survivors (n = 60)	p-value
Age	69.0 (57.0-79.0)	79.0 (70.8-87.0)	< 0.001
Male gender	133 (42.5%)	26 (43.3%)	1.000
Hypertension	165 (52.7%)	30 (50.0%)	0.807
Diabetes mellitus	74 (23.6%)	15 (25.0%)	0.952
Cancer	60 (19.2%)	22 (36.7%)	0.005
Baseline saturation, %	94.0 (87.0-96.0)	87.5 (86.0-90.0)	< 0.001
Baseline heart rate, bpm	90.0 (80.0-105)	106 (88.0-120)	< 0.001
Systolic blood pressure, mmHg	124 (110-132)	114 (100-130)	0.006
D-dimer, mg/dL	2314 (1030-4000)	2574 (1980-4000)	0.099
Baseline troponin, ng/mL	26.0 (10.0-98.0)	50.5 (23.0-120)	0.002
NT-pro-BNP, pg/mL	276 (58.0-983)	784 (55.2-5166)	0.009
PIV	462 (151-917)	1300 (582-2534)	< 0.001
Serum lactate, mmol/L	1.66 (1.30-2.40)	2.32 (1.58-3.07)	0.001
LDH, units/L	379 (268-568)	568 (423-781)	< 0.001
HCO3, mEq/L	24.4 (22.8-28.1)	23.4 (20.8-28.3)	0.040
LVEF, %	60.0 (60.0-60.0)	60.0 (55.0-60.0)	0.023
TAPSE, mm	23.0 (20.0-24.0)	21.0 (17.0-23.0)	0.001
RV, mm	37.0 (34.0-42.0)	39.5 (34.0-45.0)	0.062
RA, mm	38.0 (25.0-49.0)	49.0 (26.5-50.0)	0.021
LAAP, mm	37.0 (34.0-41.0)	39.0 (35.0-43.0)	0.054
SPAP, mmHg	35.0 (28.0-45.0)	40.0 (30.0-50.0)	0.134
PESI score	94.0 (74.0-116)	132 (114-156)	< 0.001
t-PA use	13 (4.15%)	10 (16.7%)	0.001

BNP: brain natriuretic peptide; PIV: pan-immuno-inflammation value; LDH: lactate dehydrogenase; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricle; RA: right atrium; LAAP: left atrium anterior-posterior; SPAP: systolic pulmonary artery pressure; PESI: pulmonary embolism severity index; t-PA: tissue plasminogen activator.

test were employed to compare survival probabilities between high and low PIV groups.

RESULTS

Among 373 patients, 43% (159/373) were male. Of the patients, 16% (60/373) died during in-hospital follow-up. The research group was divided into two categories based on in-hospital survival status: Patients who died (non-survivor group) and those who did not die (survivor group).

Table 1 shows the comparison of patients' demographic characteristics, laboratory, and imaging results. Among demographic characteristics, advanced age, a history of congestive heart failure, and a history of cancer were significantly more common in the non-survivor group. Among initial vital signs, hypotension, tachycardia, and low oxygen saturation were

Table 2. Multivariable logistic regression for detecting the independent associations of variables with in-hospital mortality

Variable	OR	95% CI	p-value
Baseline heart rate	1.910	1.888-3.071	0.008
NT-pro BNP	1.094	1.019-1.175	0.012
Serum lactate	1.264	0.936-1.706	0.126
LDH	1.389	1.010-1.912	0.043
PIV	1.756	1.418-2.176	< 0.001
PESI score	3.626	2.149-6.116	< 0.001
t-PA use	2.203	0.687-7.066	0.184

BNP: brain natriuretic peptide; PIV: pan-immuno-inflammation value; PESI: pulmonary embolism severity index; t-PA: tissue plasminogen activator.

statistically significant in the non-survivor group. From the laboratory perspective, elevated NT-Pro BNP, troponin, hyperglycemia, elevated aspartate amino transaminase and alanine aminotransferase, high serum lactate and LDH, monocytosis, leukocytosis, low hemoglobin, lymphopenia, and low HCO_3 were statistically significant in the non-survivor group. Reduced tricuspid annular plane systolic excursion, enlarged right atrium, high PESI score, high PIV score, and longer in-hospital stays were statistically significant in the non-survivor group.

Table 2 presents a multivariable logistic regression analysis to determine the independent relationships between variables and in-hospital mortality. According to this analysis, baseline heart rate, NT-Pro-BNP, LDH, PIV (OR: 1.756, 95% CI: 1.418-2.176, p < 0.001), and PESI score (OR: 3.626, 95% CI: 2.149-6.116, p < 0.001) were independent risk factors for in-hospital mortality in acute PE patients.

The ROC analysis demonstrated an area under the curve of PESI score was 0.817 (p < 0.001) and it was 0.753 (p < 0.001) for the PIV score. While both scores were statistically significant in predicting in-hospital mortality, there was no statistically significant difference between them (p = 0.131) (Fig. 1). Patients with high PIV values had higher in-hospital mortality than patients with low PIV values as assessed in Kaplan–Meier curve (De-long test p < 0.001) (Fig. 2).

The rate of active cancer patients was not differentiated between survivor and non-survivor cancer patients (40/60 [66.7%] vs. 16/22 [72.7%], respectively, p = 0.799). Furthermore, PIV values were similar between active and non-active cancer patients (715 [249-1647] vs. 477 [264-1730], respectively, p = 0.498). Finally, there was no difference regarding PIV values between active and non-active cancer patients in non-survivor subpopulation (1544 [560-2671] vs. 1168 [379-2253], respectively, p = 0.658).

DISCUSSION

Previous studies indicated that the incidence rate of acute PE might range from 39 to 115 cases/100,000 individuals. Most deaths associated with acute PE could stem from complications linked to right-sided heart failure and lethal heart rhythm problems. In the United States, acute PE is estimated to be responsible for roughly 300,000 fatalities annually, and after being discharged from the hospital following an acute PE episode, 15% of such patients are readmitted within the initial 30 days. Thus, distinguishing between low-risk and high-risk patients in acute PE is crucial for tailoring treatment and predicting outcomes[7,8]. To aid in this distinction, several prognostic classification systems have been developed for acute PE patients. One of the most widely used is the PESI score, which is recommended to be used by recent guidelines. The PESI score incorporates 11 clinical predictor variables and effectively predicts the in-hospital mortality risk in acute PE patients[9,10]. In our study, when comparing with the PESI, the PIV was found to be non-inferior to it in predicting in-hospital mortality in acute PE patients.

Figure 1. ROC analysis of PESI and PIV score for in-hospital mortality in PE patients. PIV: pan-immuno-inflammation value; PE: pulmonary embolism; PESI: pulmonary embolism severity score.

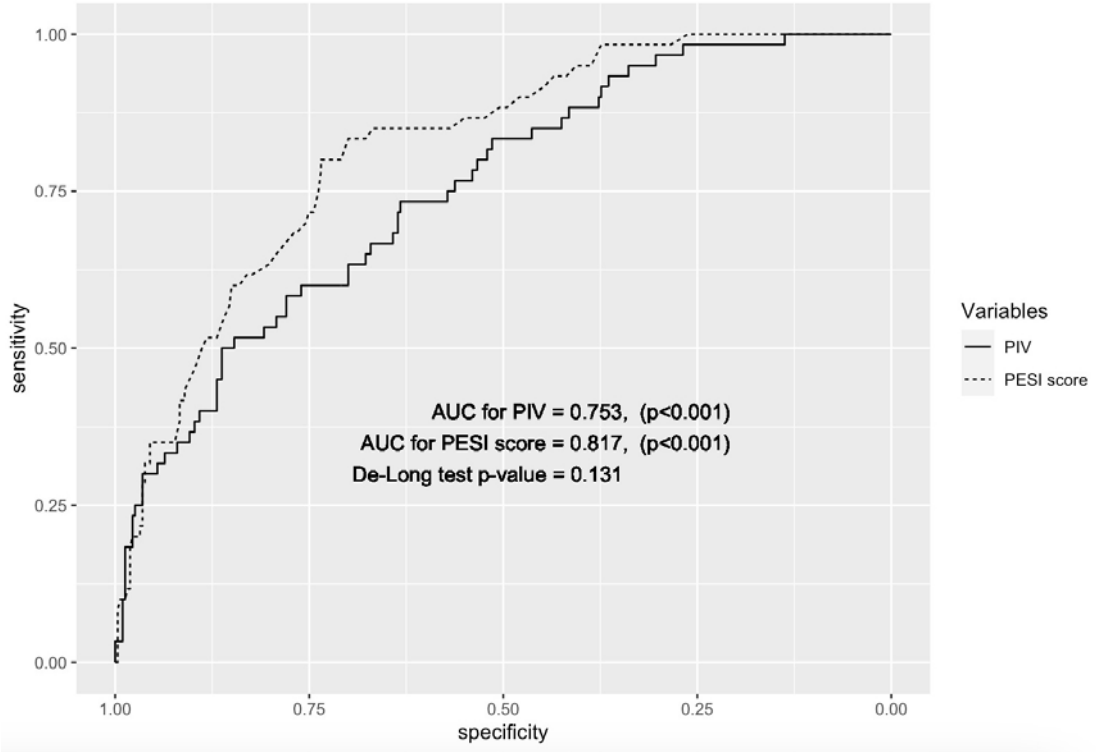
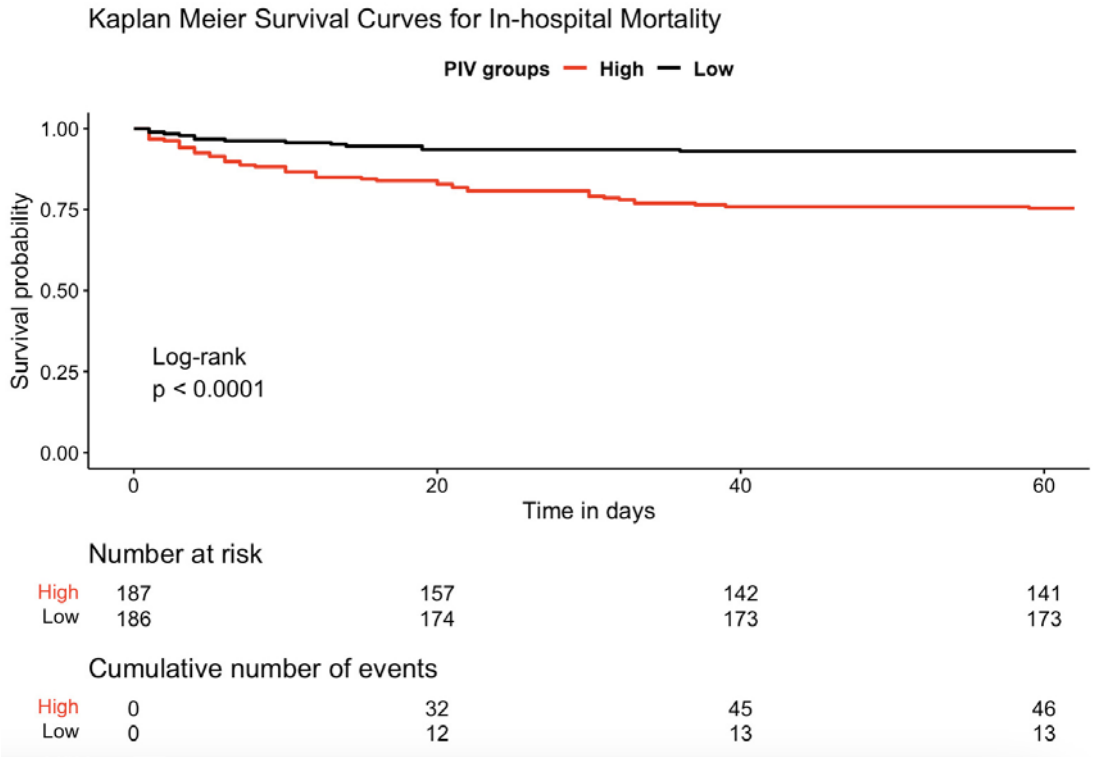


Figure 2. Kaplan Meier Survival Curves for high and low PIV groups. PIV: pan-immuno-inflammation value.



In the pathophysiology of acute PE, chronic inflammation plays a role, similar to its role in cancer. The increased occurrence of thrombotic events in cancer patients, like in the case of PE, is a result of this shared mechanism. A cancer diagnosis increases the risk of acute PE by four to seven times. Moreover, the presence of malignancy increases the risk of mortality in patients with acute PE[11,12]. In our study, we also found that a history of malignancy was statistically significant in predicting in-hospital mortality.

In 2020, Fuca et al. developed PIV as a prognostic biomarker for colorectal cancers. Subsequent studies have found it to be prognostically significant in several diseases including cancer, auto-immune disorder, and acute heart failure[13,14]. On the other hand, no prior study is investigated this index in predicting in-hospital mortality in acute PE patients. Our study found that PIV predicted in-hospital mortality in acute PE patients. Furthermore, we found that PIV was non-inferior to the recommended PESI score for short-term mortality prediction in PE patients. Our investigation's results have clinical relevance. It is critical to identify high-risk acute PE patients who might benefit from close follow-up and more aggressive treatment. Therefore, we consider that PIV, an easily calculable risk index, could be applied to determine the risk of in-hospital mortality in such patients. However, we also believe that our study's conclusions should be interpreted cautiously since some unmeasured confounders could affect the study's results.

Our study has some limitations. The main limitation of our study was that it was conducted retrospectively and in a single center. However, all consecutive patients were included in the study. Despite applying multivariate analysis in determining independent predictors of in-hospital mortality, there might be some unmeasured confounders. Unfortunately, the PIV was calculated based only on admission laboratory values. Thus, it would be important to determine whether a dynamic PIV is more valuable than a single PIV. Our research was a pilot study to determine the prognostic relevance of PIV in patients who are diagnosed with acute PE. Thus, further prospective and multicenter studies are needed to clarify the exact role of the PIV in predicting the in-hospital mortality in patients diagnosed with acute PE.

In conclusion, in our study, we found that PIV was statistically significant in predicting in-hospital mortality in acute PE patients. To the best of our knowledge, there is no study in the literature on this topic.

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