International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 7, No. 3, 2024

Prognostic Value of the Pan-Immune-Inflammation Value (PIV) in ARDS Patients: A Retrospective Study on MIMIC-IV database

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Abstract: (ARDS) is a severe and life-threatening condition characterized by acute lung injury and hypoxemic respiratory failure. Despite significant advances in critical care, ARDS continues to have a high incidence and mortality rate worldwide. The pathophysiology of ARDS is complex, primarily involving a complicated interplay between inflammation, immune response, and endothelial damage, leading to impaired gas exchange and respiratory distress. Therefore, identifying reliable biomarkers that can accurately predict patient outcomes is crucial for developing patient management strategies. Recent studies have highlighted the importance of systemic inflammation in the progression and outcomes of ARDS. The Pan-Immune-Inflammation Value (PIV), an emerging biomarker, integrates multiple immune and inflammation parameters, including neutrophil count, monocyte count, lymphocyte count, and platelet count. Research has shown that PIV is associated with the severity of inflammation and can predict the prognosis of various critical illnesses, including sepsis and cardiovascular diseases. Given the role of inflammation in ARDS and the potential use of PIV to assess and predict levels of inflammation, this retrospective study aims to evaluate the prognostic value of PIV in patients with ARDS. By analyzing patient data from the MIMIC-IV database, this study seeks to determine whether PIV can serve as an independent predictor of mortality and clinical outcomes in ARDS patients, thereby providing clinical guidance to improve patient outcomes.

Keywords: Acute Respiratory Distress Syndrome (ARDS); Mortality; Pan-Immune-Inflammation Value.

1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is characterized by acute respiratory failure due to diffuse pulmonary inflammation and edema, primarily manifesting as severe hypoxemia, diffuse pulmonary edema, and decreased lung compliance [1]. Despite significant advancements in modern critical care techniques and supportive therapies, the mortality rate of ARDS remains high, and most survivors of ARDS, even if they recover normal or near-normal lung function, often experience long-term physical and psychological sequelae [2].

ARDS can be triggered by various factors, including both infectious and non-infectious causes. These triggers can cause direct lung injury through localized inflammation or indirectly damage lung tissue through systemic inflammation and injury mediators. Sepsis is the most common cause of ARDS, with a complex pathophysiology involving multiple and interacting mechanisms of pulmonary and systemic injury, inflammation, and coagulation. Both localized and systemic acute inflammation are prominent features of ARDS[3].Due to the heterogeneity and complex pathophysiological mechanisms of ARDS, targeted therapeutic options remain limited, and there is an urgent need for reliable biomarkers to better predict patient outcomes.

The Pan-Immune-Inflammation Value (PIV) is a novel composite index that integrates the counts of neutrophils, platelets, monocytes, and lymphocytes, reflecting both the inflammatory and immune status of patients[4-6].Initially, PIV was used to study the relationship between the inflammatory response and immune status in cancer patients and their prognosis[7].With further research, PIV has shown promising potential in prognostic assessment across various conditions, including cardiovascular diseases, malignancies, and acute kidney injury[8-12].In patients with ARDS, dysregulated inflammation and immune responses are critical factors in disease progression and high mortality[3].Previous studies have demonstrated the roles of platelets, lymphocytes, neutrophils, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio[13, 14].Therefore, as an indicator that comprehensively reflects inflammation and immune status, PIV may have significant clinical value in predicting the prognosis of ARDS patients. However, research on the application of PIV in ARDS patients is still relatively limited. This study aims to explore the prognostic value of PIV in ARDS patients, particularly its predictive ability for 28-day mortality, to provide new insights and approaches for the clinical management and treatment of ARDS.

2. Methods

2.1. Data Source

Data Extraction: Data were extracted from MIMIC-IV version 2.2. The MIMIC-IV database includes patients admitted to the intensive care units (ICU) at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. Developed by the MIT Laboratory for Computational Physiology, the comprehensive, high-quality MIMIC-IV database contains health records for over 190,000 ICU patients from 2008 to 2016, including demographic information, laboratory results, vital signs, and medications. To gain access to the database, the authors completed the Human Research Participant Protection course (Certification Number: 58063775). This retrospective cohort study aims to investigate the relationship between PIV and the risk of mortality in critically ill septic patients.

2.2. Inclusion Criteria

The MIMIC-IV database records a total of 73,181 adult ICU admissions. Study participants were required to meet the Berlin Definition criteria. Exclusion criteria were as follows: 1. Exclude patients who were not admitted to the ICU for the first time. 2. Exclude patients with an ICU stay of less than 2 days. 3. Exclude patients with missing or abnormal platelet, neutrophil, lymphocyte, or monocyte counts within the first 24 hours after admission. The flowchart of this study is presented in FIGURE 1.

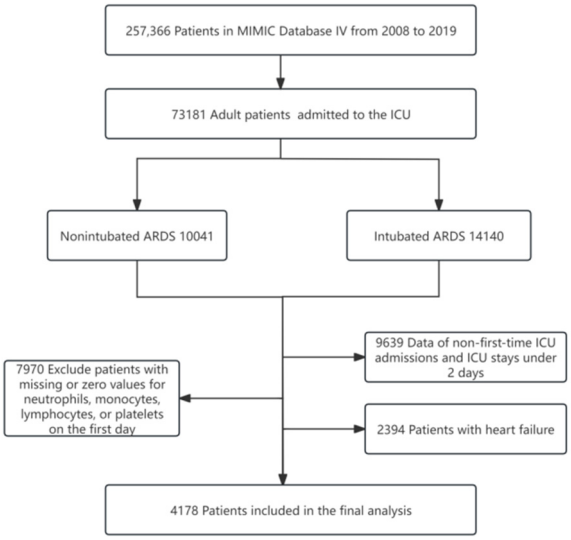

Figure 1. Flow chart showing patient screening and inclusiong

2.3. Extraction of Data

Using SQL, the study extracted examination results within the first 24 hours after ICU admission from the MIMIC-IV database, collecting the following patient data: Basic Information: age, gender; Vital Signs: heart rate, mean blood pressure, respiratory rate, temperature, oxygen saturation; Comorbidities: congestive heart failure, myocardial infarction, hypertension, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, Charlson comorbidity index; Laboratory Indicators: white blood cell count, hemoglobin, platelet count, total bilirubin, albumin, anion gap, blood urea nitrogen, serum creatinine, glucose, lactate; Scores: SOFA score, Simplified Acute Physiology Score (SAPS); Organ Support: vasopressors, invasive ventilation, continuous renal replacement therapy (CRRT).

2.4. Definition and Endpoint

The PIV calculation formula is: (neutrophil count (×10^9/L) × platelet count (×10^9/L) × monocyte count (×10^9/L)) ÷ lymphocyte count (×10^9/L). The primary endpoint is 28-day mortality, with survival information extracted from the MIMIC-IV database.

2.5. Statistical Analysis

Patients' baseline characteristics were stratified by the median PIV. Categorical variables were expressed as frequencies or percentages and compared using the chi-square test. Continuous variables were summarized as means and standard deviations, and differences in continuous measures were tested using the Kruskal-Wallis H test.

We used restricted cubic splines (RCS) with four knots corresponding to the 5th, 35th, 65th, and 95th percentiles to explore the relationship between PIV and mortality in critically ill septic patients. Kaplan-Meier survival curves were used to estimate patient survival, and differences between curves were compared using the log-rank test. The Cox proportional hazards model was employed to assess the relationship between PIV and 28-day mortality, with results presented as hazard ratios and 95% confidence intervals. Three different models were developed: Model 1 linked PIV to mortality using univariate Cox regression; Model 2 adjusted for age, gender, heart rate, mean blood pressure, respiratory rate, temperature, oxygen saturation, vasopressin use, invasive ventilation, continuous renal replacement therapy (CRRT), and liver disease; Model 3 further adjusted for blood glucose, chronic pulmonary disease, diabetes, renal disease, hypertension, hemoglobin, anion gap, blood urea nitrogen, creatinine, lactate, and malignancy. Missing values for all variables were less than 20%, and multiple imputation was used to estimate missing data.

The primary endpoint analysis was also conducted in several subgroups, including age, gender, myocardial infarction, hypertension, diabetes, chronic kidney disease, COPD, Charlson comorbidity index, and SAPS II score. All analyses were conducted using R, with a p-value less than 0.05 considered statistically significant. All tests were two-sided.

Considering differences in baseline characteristics, we conducted propensity score matching (PSM) on the patient data, matching patients in a 1:1 ratio using a propensity score logit SD caliper width of 0.05. Matching quality was evaluated using standardized mean differences.

3. Results

3.1. Baseline Characteristics

According to the inclusion and exclusion criteria, 4,178 ARDS patients met the criteria for this study from the MIMIC-IV database, including 2,513 males (60.1%) and 1,665 females (39.9%). Patients were divided into two groups based on the median PIV (Q1: ≤ 872.47, Q2: > 872.47). Table 1 summarizes the comprehensive data of vital signs, laboratory parameters, and comorbidities for each cohort. Patients with higher PIV values were more likely to be male, have a history of COPD and malignancy, and had higher levels of white blood cells, platelets, anion gap, BUN, and serum creatinine, as well as lower oxygen saturation levels. Additionally, patients with higher PIV were more likely to have a higher SAPS II score and to receive vasopressors and CRRT.

3.2. Restricted Cubic Splines Analysis

We used RCS to analyze and visualize the relationship between PIV and mortality in ARDS patients (FIGURE 2). After adjusting for all variables, we found a nonlinear association between PIV and 28-day mortality (nonlinear $P < 0.001$). For the J-shaped relationship between SII and 28-day mortality, breakpoint analysis showed that PIV was significantly positively correlated with 28-day mortality in patients when PIV > 872.47. Based on the RCS results, we categorized patients into Q1 (Low risk) and Q2 (High risk) based on the value of 872.47.

3.3. Kaplan-Meier Analysis

The Kaplan-Meier curves, grouped according to the RCS results, are shown in the Figure 3. The survival rate of the Q1 group was higher than that of the Q2 group ($P < 0.001$).

Table 1. Baseline characteristics

Variables	Systemic immune-inflammation index		P value
	Q1	Q2	
N	2090	2088	
PIV	≤872.47	> 872.47	
age	63.5 (15.2)	61.6 (16.3)	<0.001
gender:			0.017
F	795 (38.0%)	870 (41.7%)	
M	1295 (62.0%)	1218 (58.3%)	
Vital signs			
Heart rate, beats/min	105 (20.9)	111 (22.0)	<0.001
Mean blood pressure, mmHg	106 (28.8)	109 (32.0)	0.001
Respiratory rate, breaths/min	28.1 (6.62)	29.5 (6.70)	<0.001
Temperature, ℃	37.6 (0.85)	37.7 (0.93)	0.024
SPO2, %	99.7 (0.87)	99.6 (1.01)	<0.001
Comorbidities, n (%)			
Myocardial infarction	310 (14.8%)	277 (13.3%)	0.145
COPD	481 (23.0%)	581 (27.8%)	<0.001
Diabetes mellitus	585 (28.0%)	554 (26.5%)	0.29
Chronic kidney disease	313 (15.0%)	282 (13.5%)	0.174
Hypertension	1358 (65.0%)	1276 (61.1%)	0.01
Severe liver disease	232 (11.1%)	138 (6.6%)	<0.001
Malignant cancer	194 (9.3%)	276 (13.2%)	<0.001
Scoring			
Charlson comorbidity index	4.38 (2.53)	4.21 (2.72)	0.042
SAPS II	41.6 (13.8)	43.3 (14.9)	<0.001
Laboratory parameters			
White blood cell, -10^9/L	12.6 (5.88)	19.8 (8.98)	<0.001
Neutrophils, -10^9/L	7.62 (3.98)	15.3 (7.18)	<0.001
Lymphocytes, -10^9/L	1.66 (1.17)	1.26 (0.93)	<0.001
Monocytes, -10^9/L	0.42 (0.29)	0.93 (0.63)	<0.001
Hemoglobin, g/dL	11.7 (2.09)	12.0 (2.31)	<0.001
Platelets, -10^9/L	178 (81.1)	273 (131)	<0.001
Anion gap	16.1 (5.39)	17.9 (5.44)	<0.001
BUN, mg/dL	25.8 (18.8)	30.5 (23.5)	<0.001
Serum creatinine, mg/dL	1.49 (1.46)	1.72 (2.36)	<0.001
Serum glucose, mg/dL	191 (80.2)	198 (91.5)	0.021
Curing, n (%)			
Vasopressor	317 (15.2%)	411 (19.7%)	<0.001
Invasive ventilation	2047 (97.9%)	2040 (97.7%)	0.593
CRRT	174 (8.3%)	222 (10.6%)	0.011
Mortality, n (%)			
28-day	321 (15.4)	532 (25.5)	<0.001
90-day	426 (20.4)	678 (32.5)	<0.001

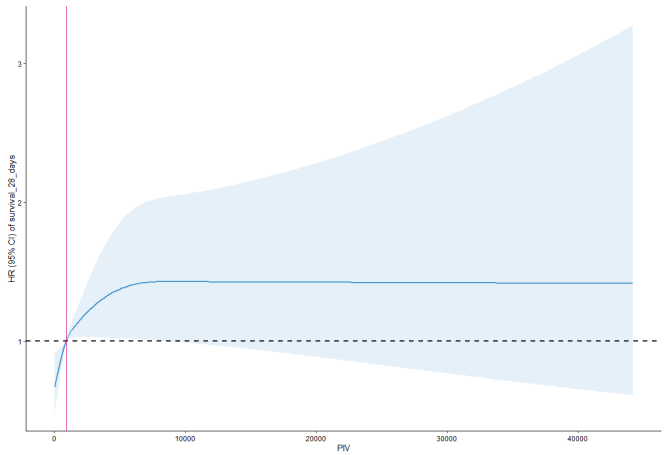

Figure 2. Restricted cubic spline for the association between PIV and mortality.

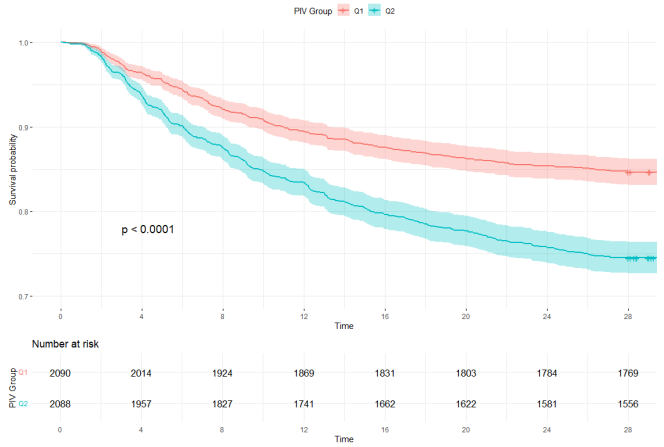

Figure 3. Kaplan–Meier survival curve for mortality according to PIV.

3.4. Cox Regression Analysis

Among all enrolled patients, the 28-day mortality rate was 853 (18.1%). We used Cox regression models to evaluate the relationship between PIV and the risk of 28-day mortality (Table 2). Using the Q1 group as a reference, a higher PIV (Q2 group) was associated with an increased risk of 28-day mortality (Model 1: 1.77 (1.54-2.03); Model 2: 1.68 (1.46-1.93); Model 3: 1.56 (1.36-1.80)).

Table 2. Multivariable Cox regression analysis for 28-day mortality

Variable	Event, n (%)	Model 1		Model 2		Model 3	
		HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
PIV							
Q1	321 (15.4)	1	Reference	1	Reference	1	Reference
Q2	532 (25.5)	1.77(1.54-2.03)	< 0.001	1.68 (1.46 - 1.93)	< 0.001	1.56 (1.36 - 1.80)	<0.001
Covariates				1.02 (1.02 - 1.03)	<0.001	1.02 (1.01 - 1.02)	<0.001
Age				1.02 (1.02 - 1.03)	< 0.001	1.02 (1.02, 1.03)	< 0.001
Gender				0.92 (0.80 - 1.05)	0.205	0.92 (0.80 - 1.06)	0.226
Heart rate				1.01 (1.00 - 1.01)	<0.001	1.01 (1.00 - 1.01)	0.002
Mean blood pressure				1.00 (1.00, 1.00)	0.225	1.00 (1.00 - 1.00)	0.238
Respiratory rate				1.01 (1.00 - 1.02)	0.025	1.01 (1.00 - 1.02)	0.291
Temperature				0.77 (0.71 - 0.83)	< 0.001	0.79 (0.73 - 0.86)	<0.001
SPO2				0.96 (0.90 - 1.01)	0.101	0.95 (0.90 - 1.01)	0.084
Myocardial infarction				0.93 (0.76 - 1.13)	0.462	0.95 (0.78 - 1.16)	0.597
Severe liver disease				2.29 (1.89 - 2.77)	<0.001	1.83 (1.49 - 2.25)	< 0.001
Vasopressor				2.66 (2.27 - 3.11)	< 0.001	2.36 (2.00 - 2.78)	< 0.001
Invasive ventilation				1.14 (0.69 - 1.88)	0.611	1.09 (0.66 - 1.80)	0.742
CRRT				1.21 (0.99 - 1.47)	0.057	1.11 (0.90 - 1.38)	0.338
Serum glucose						1.00 (1.00 - 1.00)	0.476
Hemoglobin						1.00 (0.96 - 1.03)	0.824
Anion gap						1.03 (1.01 - 1.05)	< 0.001
BUN						1.01 (1.00 - 1.01)	< 0.001
Serum creatinine						0.91 (0.86 - 0.97)	0.007
Serum lactate						1.01 (0.99 - 1.04)	0.307
Congestive heart failure						0.87 (0.77-0.98)	0.02
COPD						1.11 (0.95 - 1.29)	0.191
Diabetes mellitus						0.85 (0.71 - 1.01)	0.066
Chronic kidney disease						0.86 (0.70 - 1.06)	0.164
Hypertension						0.84 (0.72 - 0.98)	0.023
Malignant cancer						1.53 (1.28 - 1.82)	< 0.001

3.5. Subgroup Analyses

Table 3. Subgroup analysis of the association between SII and 28-day mortality

Variables	n	Fully adjusted HR (95%CI)		P for interaction
		Q1	Q2	
Age (years)				0.007
≤ 65		Ref	1.32 (1.08-1.63)	
> 65		Ref	1.74 (1.42-2.13)	
Gender				0.627
Male		Ref	1.53 (1.27-1.85)	
Female		Ref	1.58 (1.27-1.98)	
Myocardial infarction				0.726
No		Ref	1.54 (1.32-1.80)	
Yes		Ref	1.57 (1.04 - 2.39)	
Hypertension				0.015
No		Ref	1.21 (0.97-1.51)	
Yes		Ref	1.80 (1.49-2.18)	
Diabetes mellitus				0.3
No		Ref	1.18 (1.03-1.36)	
Yes		Ref	1.22 (0.99-1.50)	
Chronic kidney disease				0.926
No		Ref	1.55 (1.32-1.80)	
Yes		Ref	1.61 (1.08-2.38)	
COPD				0.088
No		Ref	1.45 (1.23-1.71)	
Yes		Ref	1.97 (1.45-2.64)	
Severe liver disease				0.017
No		Ref	1.56 (1.33-1.82)	
Yes		Ref	1.55 (1.08 - 2.23)	
Malignant cancer				0.308
No		Ref	1.60 (1.36-1.88)	
Yes		Ref	1.28 (0.917-1.785)	
Charlson comorbidity index				0.092
≤ 2		Ref	1.18 (0.80 - 1.72)	
> 2		Ref	1.65 (1.41-1.93)	
SAPS II				0.017
≤ 40		Ref	1.88 (1.38-2.55)	
> 40		Ref	1.22 (1.00-1.47)	

To further explore the relationship between PIV and 28-day mortality in ARDS patients, we conducted subgroup analyses based on age, gender, myocardial infarction, hypertension, diabetes, chronic kidney disease, COPD, severe liver disease, malignancy, as well as CCI and SAPS II scores (Table 3). In the fully adjusted model, the primary endpoint showed a similar trend in most subgroups; however, significant interactions were observed in age (P for interaction = 0.007), hypertension (P for interaction = 0.015), and severe liver disease (P for interaction = 0.017).

3.6. Propensity Score Matching Analysis

PSM was used to further understand the relationship between PIV and prognosis in patients with Acute Respiratory Distress Syndrome (ARDS). This analysis ensured a balanced distribution of baseline patient characteristics across different PIV cohorts, effectively reducing potential biases. After performing PSM on the two cohorts and using Cox regression analysis for 28-day mortality, a high PIV was clearly identified as an independent factor associated with an increased risk of 28-day mortality in critically ill septic patients (1.43 (1.21-1.68)).

4. Discussion

In this cohort study of 4,178 patients with Acute Respiratory Distress Syndrome (ARDS) from the MIMIC database, our analysis showed that high levels of PIV have a J-shaped relationship with 28-day mortality, indicating that elevated PIV is closely associated with increased 28-day all-cause mortality in ARDS patients. Even after adjusting for multiple variables, PIV remained a significant predictor of 28-day all-cause mortality in ARDS patients. Our study extends the predictive scope of PIV, which is a cost-effective and readily available biomarker obtainable from routine blood tests, aiding clinicians in developing treatment plans for ARDS patients.

In recent years, various indices have been proposed to predict inflammatory and immune status, such as NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), and SII (systemic immune-inflammation index) [15-17].These indices reflect the inflammatory response and immune status to some extent but often focus on a single aspect and fail to comprehensively integrate information from multiple facets of inflammation and immune status. In contrast, PIV integrates the values of NLR, PLR, and SII, offering a more comprehensive reflection of the patient's overall immune status, inflammation levels, and coagulation status.

The high sensitivity and specificity of PIV allow it to demonstrate excellent predictive capabilities across various disease contexts[7].PIV was initially used to predict the prognosis of patients with metastatic colorectal cancer , and subsequent studies have demonstrated its predictive value in breast cancer, metastatic melanoma, small cell lung cancer, metastatic renal cell carcinoma, and other cancers [18-21].Some studies have even shown that PIV has a role in aiding the diagnosis of ANCA-associated vasculitis and hypoxic-ischemic encephalopathy in infants[22, 23].Sepsis is one of the most common causes of ARDS, and previous studies have explored the role of PIV in sepsis, with findings consistent with our results[6, 24].Therefore, PIV not only has predictive value in oncology but also shows significant predictive potential in acute conditions such as ARDS and sepsis.

However, the calculation of PIV directly uses the patient's blood cell counts. Patients with severe liver disease often experience splenomegaly, leading to decreased platelet and white blood cell counts[25].Many malignancies and immunodeficiency syndromes are also associated with altered white blood cell and platelet counts[26-30].Neutropenia and thrombocytopenia are common in the ICU[31-33],potentially affecting the calculation and interpretation of PIV. Additionally, our study found a significant interaction between severe liver disease and PIV, suggesting that PIV may not accurately reflect the condition of certain critically ill patients. This highlights the need for caution when using PIV in clinical practice. Moreover, our study used only blood tests from the day of admission to calculate PIV, lacking dynamic data on PIV changes during hospitalization, limiting our understanding of the progression of the patient's condition over time. Since data in the MIMIC database are solely from Beth Israel Deaconess Medical Center in the United States, this single-center data may not fully represent patient characteristics and treatments in other regions or countries, limiting the generalizability of the results. Therefore, when using PIV as a predictive indicator, these potential influencing factors must be considered, along with clinical judgment, to comprehensively assess the patient's condition.

5. Conclusion

Based on our study, PIV can be used as an independent factor to predict the prognosis of patients with Acute Respiratory Distress Syndrome (ARDS). This biomarker is cost-effective and accessible, as it can be obtained through routine blood tests, making it suitable for widespread use in clinical practice. Although the predictive ability of PIV has been preliminarily validated, further research is needed to clarify its specific performance in different patient populations and clinical settings, thereby optimizing its practical application in ARDS prognosis assessment.

Acknowledgments

We thank Hu Hai for his support of our work.

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