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Innovative Inflammatory Burden Index for identification of high mortality risk in patients with pulmonary embolism: a large retrospective cohort study

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ABSTRACT

Background The prognostic significance of systemic inflammation in pulmonary embolism (PE) remains unclear. This study aimed to evaluate the predictive value of a novel Inflammatory Burden Index (IBI) for long-term mortality in patients with acute PE.

Methods A total of 1642 patients with acute PE were retrospectively analysed. The optimal cut-off for IBI was determined using maximally selected rank statistics. The association between high IBI and all-cause mortality was assessed using multivariable Cox proportional hazards models. The predictive performance of IBI and its individual components was compared using time-dependent receiver operating characteristic (ROC) curves. Variable importance for mortality prediction was further evaluated using random survival forest (RSF) analysis.

Results During a median follow-up of 41.2 months, 262 patients (16.0%) died. High IBI was independently associated with increased risk of all-cause mortality (adjusted HR 2.33, 95% CI 1.78 to 3.04; p<0.001). Time-dependent ROC analysis demonstrated that IBI provided superior prognostic accuracy for mortality, with area under the curve (AUC) values of 0.73, 0.74 and 0.75 at 1, 3 and 5 years, respectively, which were higher than those of C-reactive protein, neutrophil count and lymphocyte count. Addition of IBI to the basic clinical model significantly improved the AUC at all time points. RSF analysis confirmed that IBI was the most important inflammatory predictor of long-term mortality.

Conclusions The IBI is a robust and independent predictor of long-term mortality in patients with acute PE and offers incremental prognostic value beyond conventional risk factors. Incorporating IBI into clinical risk stratification may improve patient management and outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although some individual inflammatory biomarkers, such as C-reactive protein (CRP), neutrophil count and lymphocyte count, are associated with the poor prognosis of acute pulmonary embolism (PE), no comprehensive inflammatory index has been proven to be applicable for predicting the long-term mortality of acute PE at present.

WHAT THIS STUDY ADDS

⇒ This study introduces the Inflammatory Burden Index (IBI), a novel composite marker integrating CRP, neutrophil count and lymphocyte count, as a robust predictor of long-term all-cause mortality in acute PE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the potential of the IBI as a valuable tool for comprehensive risk assessment in acute PE.

⇒ Future research should validate IBI in diverse populations and explore its dynamic changes over time.

⇒ Policymakers are encouraged to consider including IBI in standardised protocols to optimise resource allocation and improve patient care.

INTRODUCTION

Pulmonary embolism (PE), together with deep vein thrombosis (DVT), represents the two principal manifestations of venous thromboembolism (VTE).[1] PE remains a major cause of cardiovascular mortality, contributing to about 100 000 deaths annually in the USA.[2] PE is the third leading cause of death from cardiopulmonary disease, following acute myocardial infarction and stroke, with an overall mortality rate of 15–20%.[3] Despite advances in diagnostic technologies, therapeutic options and the implementation of multidisciplinary care models such as PE response teams (PERTs), recent data indicate that PE-related mortality has been increasing over the past decade.[4]

In the diagnostic workup and risk assessment of patients with confirmed or suspected PE, tools such as the PE Severity Index (PESI), echocardiography, lower extremity venous Doppler ultrasonography and CT pulmonary angiography (CTPA) are commonly employed alongside clinical judgement and vital signs.[5 6] However, these modalities often have limited positive predictive value and impose substantial healthcare costs. The long-term prognosis

of acute PE remains an area of concern. A large retrospective cohort study involving 872 hospitalised patients with a first episode of acute PE found that over a median follow-up period of 25 months, 58.3% of patients died.[7] The mortality risk persists well beyond the acute phase.

Current studies on the pathology of PE have demonstrated that inflammation, primarily mediated by neutrophils (NEU) and macrophages, occurs within the pulmonary arteries and the right ventricle.[8] In recent years, several novel inflammatory markers derived from routine blood counts have gained attention for their association with PE. Among these, the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR) and lymphocyte–monocyte ratio (LMR) have been identified as significant indicators of systemic inflammation related to PE.[9] Notably, NLR has emerged as a particularly valuable marker; it not only serves as an independent predictor of in-hospital mortality in patients with acute PE but also aids in clinical risk stratification.[10] Disturbances in inflammatory and coagulation processes can lead to haematological changes, which are measurable through blood cell indices. Emerging research highlights the significance of routinely obtained complete blood count–derived parameters as valuable tools for assessing risk in patients with VTE.

The Inflammatory Burden Index (IBI) is a novel composite marker that integrates C-reactive protein (CRP), NEU count and lymphocyte (LYM) count to capture both the magnitude of systemic inflammation and the balance between proinflammatory and regulatory immune responses.[11] Unlike single-parameter indices, IBI offers a broader assessment of inflammatory status. The IBI reflects both the magnitude of the inflammatory burden and the balance between proinflammatory and regulatory immune mechanisms. Recent studies have demonstrated the utility of the IBI in predicting clinical outcomes in a variety of diseases characterised by inflammatory processes, including cardiovascular diseases, infections and malignancies. For instance, in a large multicentre prospective study of patients with non-small cell lung cancer, IBI showed the highest predictive accuracy among systemic inflammation biomarkers for overall survival.[12] Moreover, a recent study found that higher IBI was significantly and linearly associated with an increased prevalence of gallstones among 2598 adults.[13]

Given that inflammation contributes to both the severity and prognosis of PE, IBI has the potential to serve as a useful biomarker for risk stratification and outcome prediction in this population. However, to our knowledge, no large-scale studies have evaluated the association between IBI and mortality risk in patients with acute PE. Therefore, the aim of the present study was to investigate the association between IBI and adverse outcomes in patients with acute PE. By analysing a representative cohort, this study sought to determine whether IBI could serve as a practical and informative inflammatory marker to improve prognostic assessment in acute PE.

METHODS

Study population

This investigation employed a retrospective cohort design to evaluate adult patients with a diagnosis of acute PE admitted to the First Affiliated Hospital of Ningbo University from January 2017 to January 2024. The diagnosis of PE was established in all patients via CTPA, ensuring a consistent and objective confirmation across the cohort.

Eligible participants were required to meet the following criteria: (1) age 18 years or older; and (2) diagnosis of acute PE confirmed by CTPA. Exclusion criteria comprised: (1) absence of baseline inflammatory biomarker measurements within 24 hours of hospital admission; (2) the presence of active cancer, defined as a malignancy diagnosed within the past 6 months, undergoing current anticancer treatment, or with evidence of recurrence or metastasis at admission; (3) severe hepatic or renal impairment, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) exceeding five times the upper limit of normal, or estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m^2; (4) evidence of sepsis or systemic infection at presentation; and (5) incomplete follow-up information. A detailed flowchart of the inclusion and exclusion process is provided in online supplemental figure S1.

After applying these inclusion and exclusion criteria, a total of 1642 patients constituted the final study population. The primary outcome of interest was all-cause mortality. Outcome ascertainment was conducted in January 2025 using both electronic medical record review and structured telephone interviews with patients' families, and all endpoint events were adjudicated by qualified clinical personnel. This study was conducted in accordance with the Declaration of Helsinki and was registered in the Chinese Clinical Trial Registry (ChiCTR2400084036, https://www.chictr.org.cn/).

Data collection

Comprehensive clinical data for all eligible participants were systematically retrieved from the hospital's electronic medical record system. Baseline characteristics collected at the time of admission encompassed demographic information (age, sex), as well as length of hospital stay. Detailed medical histories were documented, including the presence of hypertension, diabetes mellitus, coronary artery disease, heart failure, history of malignancy, prior fractures and DVT.

Vital sign measurements and physical examination findings, such as mean heart rate, systolic and diastolic blood pressure, and body mass index (BMI), were obtained on admission. Within 24 hours of hospitalisation, arterial blood gas analyses were performed, recording parameters such as arterial pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), serum bicarbonate (HCO_3^-) and lactate concentration.

Routine laboratory assessments included serum creatinine, blood urea nitrogen (BUN), ALT, AST, D-dimer, cardiac troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP). Cardiac structure and function were assessed by transthoracic echocardiography, with parameters including left ventricular end-systolic diameter (LVDs), left ventricular end-diastolic diameter (LVDd), left atrial diameter (LA), left ventricular ejection fraction (LVEF), and pulmonary artery systolic pressure (PASP).

The anatomical location of the PE was determined via CTPA and categorised as involving the main pulmonary artery, main branch, upper or lower lobes, bilateral distribution or small branches. Information on therapeutic interventions prior to and during hospitalisation, including the use of thrombolytic agents, anticoagulants and diuretics, was also systematically recorded. All data were collected and verified independently by two trained investigators to ensure accuracy and completeness.

Calculation of IBI

The IBI is a validated composite marker that integrates CRP, NEU count and LYM count to reflect systemic inflammation. The IBI has been previously established and its prognostic significance for adverse clinical outcomes has been confirmed in several high-quality studies.[11 14] In this study, IBI was calculated using the following formula:

IBI= CRP (mg/L) × [Neutrophil count (10^9/L)/ Lymphocyte count (10^9/L)]

For each patient, CRP, NEU and LYM values were obtained from peripheral blood samples collected within 24 hours of hospital admission. All laboratory tests were conducted in the central clinical laboratory according to standardised protocols. Implausible or extreme values were reviewed and excluded as appropriate.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean±SD or median with IQR, and categorical variables as frequencies and percentages. For between-group comparisons, the Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The χ^2 test or Fisher's exact test was applied for categorical variables. Missing values for covariates were less than 10% for all variables and were imputed using multiple imputation by chained equations with the 'mice' package. Collinearity among covariates was assessed by calculating variance inflation factors (VIF), with all VIF values less than 5, indicating no significant multicollinearity (online supplemental table S1).

For survival analyses, the optimal IBI cut-off was estimated using maximally selected rank statistics as implemented in the 'survminer' package. This procedure scans all observed IBI values and identifies the threshold that maximises the standardised log-rank statistic for time-to-event separation, while controlling for multiple testing inherent to the cut-point search. To prevent spurious splits, the search was constrained to cut-points that yielded sufficiently sized groups (pre-specified minimum proportion per group), and the selected cut-off was then fixed and carried forward for Kaplan-Meier estimation and Cox modelling. Other clinically relevant variables were stratified using established clinical cut-offs or median splits, as appropriate. For continuous analyses, variables with skewed distributions were natural log (ln) transformed prior to modelling. Kaplan-Meier curves were generated to estimate survival probabilities, and group differences were assessed using the log-rank test with the 'jskm' packages.

To identify candidate variables for the multivariable Cox proportional hazards model, univariate Cox regression was performed for each variable, and those with $p<0.05$ were included in the subsequent multivariate analysis using a stepwise forward selection procedure. Multivariable Cox models were used to estimate HRs and 95% CIs for all-cause mortality. The proportional hazards assumption for the Cox models was tested using Schoenfeld residuals with the 'survival' package, and no significant violations were detected. Potential non-linear associations between log-transformed IBI and mortality risk were examined using restricted cubic spline (RCS) analysis with the 'rms' package. Non-linearity was assessed by comparing the model containing only the linear term to the model including both linear and spline terms using a likelihood ratio test.

Time-dependent receiver operating characteristic (ROC) curves and area under the curve (AUC) at 1, 3 and 5 years were calculated with the 'timeROC' package to evaluate and compare the discriminatory performance of IBI and its individual components (CRP, NEU count, LYM count). The incremental prognostic value of IBI was assessed by comparing the predictive performance of a basic clinical model (including age, sex, systolic blood pressure, heart rate, cancer, heart failure, DVT, lactate, creatinine, D-dimer and NT-proBNP) with and without the addition of IBI.

Correlation analyses between IBI and its components were performed using Spearman correlation coefficients. The prognostic importance of IBI and its components was further evaluated using random survival forest (RSF) analysis with the 'randomForestSRC' package. Variable importance was quantified using both permutation-based variable importance (VIMP), where a higher value indicates a greater impact on prediction accuracy, and minimal depth, where a lower value suggests greater variable importance. The RSF model was constructed with 1000 trees and default settings unless otherwise specified, and the stability of variable rankings was confirmed by repeated runs.

Subgroup analyses were conducted to evaluate the association between high IBI and all-cause mortality across clinically relevant strata, with adjustment for established covariates in each model and formal tests of

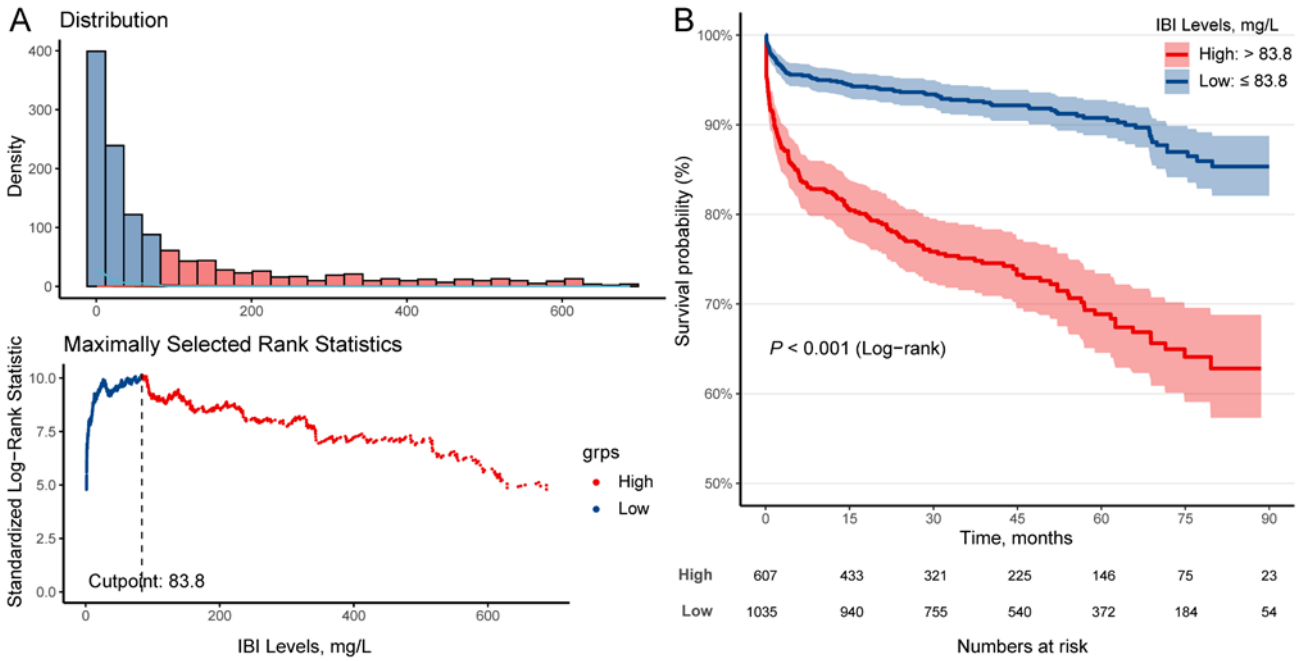

Figure 1 Distribution, stratification and survival analysis by Inflammatory Burden Index (IBI). (A) Distribution of the IBI and determination of the optimal cut-off value for group classification. (B) Kaplan-Meier survival curves for all-cause mortality by the IBI group.

interaction to assess effect modification. To assess the robustness of the association between the IBI and all-cause mortality, we conducted two sensitivity analyses. First, a fully adjusted Cox proportional hazards model was constructed, in which IBI and all key clinical covariates with a p value <0.05 in univariate analysis were forcibly included, regardless of statistical significance in the final model. Second, we examined the association between IBI and all-cause mortality by categorising IBI into quartiles and tertiles, rather than relying solely on a binary cut-off. All statistical analyses were performed using R software (V.4.2.2, R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value <0.05 was considered statistically significant.

RESULTS

IBI stratification and baseline characteristics

As illustrated in figure 1A, the distribution of the IBI in patients with PE was notably right-skewed, with most values clustered at the lower end of the scale. Using the optimal cut-off determined by maximally selected rank statistics, patients were divided into a low IBI group (IBI ≤83.8 mg/L, n=1035) and a high IBI group (IBI >83.8 mg/L, n=607).

Baseline characteristics according to the IBI group are summarised in online supplemental table S2. The mean age was similar between groups (54.4±12.8 years overall), but the proportion of males was significantly higher in the high IBI group than in the low IBI group (59.8% vs 45.3%, p<0.001). Patients in the high IBI group also had a longer median hospital stay (14 (9–20) vs 10 (7–16) days, p<0.001). There were no significant differences in the prevalence of hypertension, diabetes mellitus, coronary heart disease, heart failure or cancer. However, a history of fracture was more common in the high IBI group (10.9% vs 5.2%, p<0.001). At admission, patients with high IBI exhibited a higher average heart rate, lower systolic and diastolic blood pressures and lower BMI (all p<0.001).

Laboratory analyses revealed that the high IBI group had significantly higher levels of serum creatinine, BUN, ALT, AST, D-dimer, troponin T and NT-proBNP (all p<0.01). Echocardiographic parameters showed that patients in the high IBI group had larger left ventricular end-systolic and end-diastolic diameters, larger left atrial diameter, lower left ventricular ejection fraction and higher pulmonary artery systolic pressure (all p<0.05). Regarding CTPA findings, the high IBI group was more likely to have emboli in the main branches and lower lobes (p<0.001 for both) and more likely to have received thrombolytic therapy or diuretics during hospitalisation (p=0.015 and p<0.001, respectively).

Association between IBI levels and all-cause mortality among patients with PE

During a median follow-up of 41.2 months (IQR 22.7–67.1 months), a total of 262 patients (16.0%) died from all causes. As depicted in figure 1B, Kaplan-Meier analysis revealed that patients in the high IBI group had a substantially lower probability of survival compared with those in the low IBI group throughout the follow-up period (log-rank p<0.001).

Table 1 presents the results of univariate and multivariate Cox regression analyses for all-cause mortality

Table 1 Univariate and multivariate stepwise Cox regression analysis for all-cause mortality in patients with pulmonary embolism

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	1.10 (1.08 to 1.11)	<0.001	1.09 (1.08 to 1.11)	<0.001
Male, %	1.58 (1.23 to 2.02)	<0.001		
Length of hospital stay, days	1.01 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001
Hypertension, %	1.82 (1.42 to 2.33)	<0.001		
DM, %	1.49 (1.05 to 2.11)	0.026		
CHD, %	2.21 (1.63 to 3.00)	<0.001		
Heart failure, %	4.02 (2.64 to 6.13)	<0.001	2.04 (1.30 to 3.19)	0.002
History of fracture, %	1.53 (1.02 to 2.29)	0.040		
Deep vein thrombosis, %	2.63 (1.85 to 3.74)	<0.001	2.54 (1.78 to 3.64)	<0.001
Average heart rate, bpm	1.01 (1.00 to 1.02)	0.002		
Systolic BP, mm Hg	0.99 (0.98 to 0.99)	<0.001	0.99 (0.98 to 0.99)	0.029
Diastolic BP, mm Hg	0.96 (0.95 to 0.97)	<0.001		
BMI, kg/m^2	0.94 (0.91 to 0.97)	<0.001		
PaO_2, mm Hg	0.99 (0.98 to 0.99)	0.005		
Lactate, mmol/L	1.12 (1.07 to 1.18)	<0.001	1.11 (1.03 to 1.19)	0.005
Ln serum creatinine, µmol/L	8.51 (6.69 to 10.82)	<0.001	3.45 (2.36 to 5.04)	<0.001
BUN, mmol/L	1.19 (1.17 to 1.21)	<0.001	1.09 (1.06 to 1.12)	<0.001
Ln ALT, U/L	1.47 (1.29 to 1.68)	<0.001		
Ln AST, U/L	1.77 (1.57 to 2.00)	<0.001	1.46 (1.26 to 1.70)	<0.001
Ln D-dimer, ng/mL	1.42 (1.29 to 1.57)	<0.001	1.21 (1.08 to 1.35)	0.001
Ln cTnT, ng/mL	1.27 (1.19 to 1.36)	<0.001		
Ln NT-proBNP, ng/L	1.89 (1.71 to 2.09)	<0.001	1.25 (1.12 to 1.41)	<0.001
LVEF, %	0.90 (0.89 to 0.91)	<0.001		
PASP, mm Hg	1.04 (1.03 to 1.05)	<0.001		
Main pulmonary artery, %	2.13 (1.61 to 2.82)	<0.001		
High IBI levels, %	3.51 (2.73 to 4.51)	<0.001	2.33 (1.78 to 3.04)	<0.001

Variables with p<0.05 in univariate analysis were entered into the multivariate Cox proportional hazards model using a stepwise forward selection approach. Continuous variables with non-normal distributions were transformed using the natural logarithm (Ln) prior to analysis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CHD, coronary heart disease; cTnI, cardiac troponin I; D-dimer, D-dimer; DM, diabetes mellitus; IBI, Inflammatory Burden Index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PaO_2, partial pressure of oxygen; PASP, pulmonary artery systolic pressure.

in patients with PE. In univariate analysis, numerous factors—including older age, male sex, longer hospital stay, history of hypertension, diabetes mellitus, coronary heart disease, heart failure, DVT, higher heart rate, lower blood pressures, lower BMI, impaired oxygenation, elevated lactate and several laboratory and echocardiographic abnormalities—were all significantly associated with increased risk of mortality (all p<0.05). Notably, patients with high IBI levels had a more than threefold higher risk of death compared with those with low IBI (HR 3.51, 95% CI 2.73 to 4.51, p<0.001).

In the multivariate model, after stepwise adjustment for significant covariates, high IBI remained an independent predictor of all-cause mortality (HR 2.33, 95% CI 1.78 to 3.04, p<0.001). Other independent risk factors included older age, longer hospital stay, presence of heart failure or DVT, higher lactate, increased serum creatinine, BUN, AST, D-dimer, NT-proBNP and lower systolic blood pressure.

RCS analysis demonstrated a linear association between log-transformed IBI levels and the risk of all-cause mortality (P for non-linearity=0.218; online supplemental figure S2). The hazard of mortality increased steadily with higher IBI levels, indicating no significant evidence of a non-linear relationship across the observed range.

In addition to the IBI, we conducted separate analyses to evaluate the prognostic significance of individual

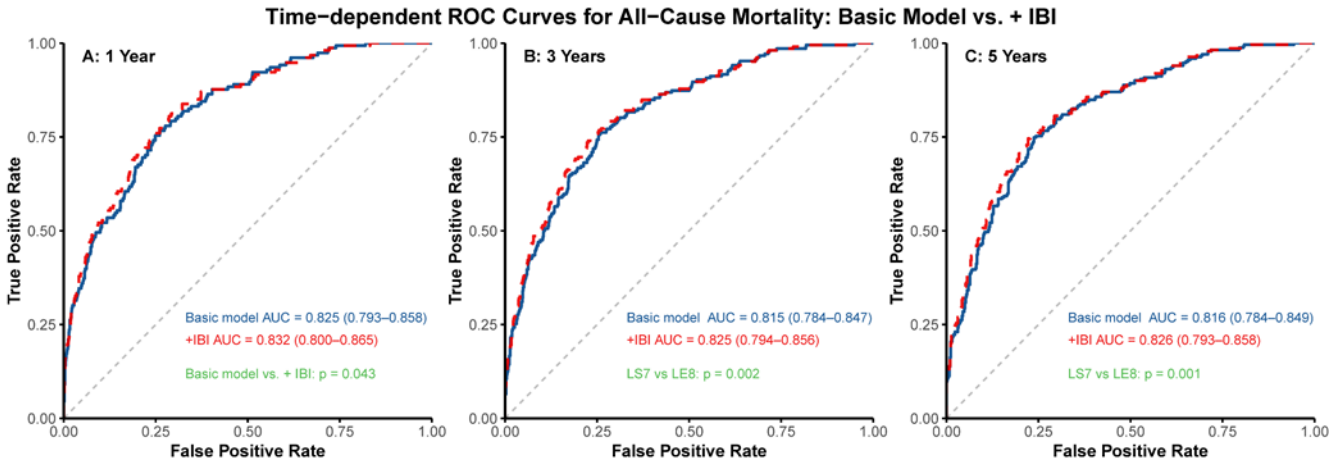

Figure 2 Incremental prognostic value of IBI in risk prediction models. Time-dependent area under the curve (AUC) comparison between the basic clinical model and the basic model plus IBI for predicting all-cause mortality at 1 year (A), 3 years (B) and 5 years (C). The basic model includes age, length of hospital stay, systolic blood pressure, heart failure, deep vein thrombosis, lactate, serum creatinine, blood urea nitrogen, aspartate aminotransferase, D-dimer and NT-proBNP. IBI, Inflammatory Burden Index; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic.

inflammatory markers, including CRP, NEU and LYM. As shown in online supplemental table S3, higher CRP levels were strongly associated with increased mortality risk in both univariate and multivariate models. Elevated NEU and reduced LYM levels also demonstrated significant associations, though to a lesser extent. These results suggest that the IBI provides a composite inflammatory burden score, while individual components, particularly CRP, retain independent prognostic value.

Time-dependent ROC analysis of IBI and its components for mortality prediction

Time-dependent ROC analysis was performed to evaluate and compare the predictive accuracy of the IBI and its individual components—CRP, NEU and LYM—for all-cause mortality in patients with PE (online supplemental figure S3). Across 1-year, 3-year and 5-year follow-up periods, IBI demonstrated consistently superior discriminatory power, with AUC values of 0.73 (95% CI 0.69 to 0.76), 0.74 (0.70 to 0.77) and 0.75 (0.71 to 0.79), respectively. These AUCs were significantly higher than those of CRP, NEU and LYM at each corresponding time point (all p<0.05), indicating that IBI provided more robust mortality risk stratification than any single biomarker.

Further, addition of IBI to the basic clinical risk model resulted in significant improvements in time-dependent AUC for all-cause mortality at 1, 3 and 5 years, as illustrated in figure 2 (from 0.825 to 0.832 at 1 year, p=0.043; from 0.815 to 0.825 at 3 years, p=0.002; from 0.816 to 0.828 at 5 years, p=0.001). These findings highlight the incremental prognostic value of IBI beyond traditional risk factors and support its clinical utility for dynamic mortality risk assessment in patients with PE.

Correlation and random survival forest analysis of IBI and its components

Spearman correlation analysis revealed that IBI was highly correlated with CRP (r=0.95) and moderately correlated with NEU count (r=0.58), while showing a negative correlation with LYM count (r=−0.45) (figure 3A). The intercorrelations among the components were generally modest, supporting the complementary information captured by the composite IBI.

In the RSF model, IBI consistently demonstrated the highest variable importance for predicting all-cause mortality compared with its individual components (figure 3B,C). Both minimal depth and permutation importance measures ranked IBI as the most influential predictor, far surpassing CRP, NEU count and LYM count.

Stratified analyses and sensitivity analyses

Stratified analyses demonstrated that the association between high IBI and increased all-cause mortality was consistent across a range of clinically relevant subgroups, including age, length of hospital stay, systolic blood pressure, lactate, creatinine, BUN, AST, D-dimer, NT-proBNP, heart failure and DVT (online supplemental figure S4). No significant interactions were observed between high IBI and any subgroup (all P for interaction >0.05), indicating that the prognostic effect of IBI was robust across diverse patient populations. The elevated risk persisted regardless of baseline risk profiles. However, findings from subgroups with smaller sample sizes should be interpreted with caution due to limited statistical power.

In the first sensitivity analysis, IBI remained significantly associated with long-term all-cause mortality in the fully adjusted Cox model, which forcibly included clinically relevant variables. The HR for high IBI was 2.29 (95%

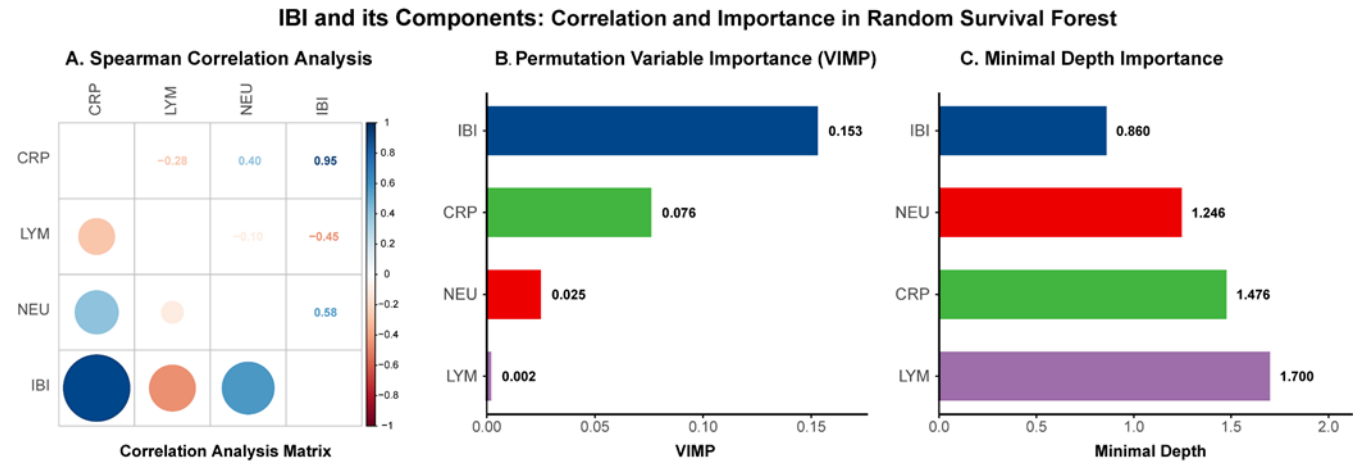

Figure 3 Correlation and random survival forest analysis of Inflammatory Burden Index (IBI) and its components. (A) Spearman correlation matrix between the IBI and its individual components. (B) Variable importance scores (VIMP) for IBI, C-reactive protein (CRP), neutrophil count (NEU) and lymphocyte (LYM) count obtained from random survival forest analysis; higher VIMP indicates greater contribution to mortality prediction. (C) Minimal depth values for IBI and its components derived from random survival forest analysis; lower minimal depth indicates greater variable importance.

CI 1.72 to 3.04) (online supplemental table S1). In the second sensitivity analysis, a stepwise increase in mortality risk was observed with higher IBI categories. Compared with the lowest quartile, participants in the highest quartile of IBI had a multivariable-adjusted HR of 4.54 (95% CI 2.71 to 7.62; P for trend <0.001). Similar trends were observed across tertiles, with the highest tertile showing a significantly elevated risk (HR 3.39, 95% CI 2.27 to 5.04; P for trend <0.001) (online supplemental table S4). These findings support a dose-dependent relationship between IBI and mortality risk in patients with acute PE.

DISCUSSION

In this study, we assessed the association between a novel IBI and long-term mortality among 1642 patients with acute PE. We demonstrated that a novel IBI was a strong and independent predictor of long-term all-cause mortality in patients with acute PE. While prior studies have individually examined markers such as CRP, NEU count and LYM count, our results showed that IBI provided superior prognostic value. The consistent performance of IBI across 1-year, 3-year and 5-year time points and its prominence in the RSF model suggested that it captured a broader and more clinically meaningful inflammatory signal than single markers. Our analysis confirmed that high IBI levels were strongly associated with increased long-term mortality in PE patients. Over a median follow-up of more than 3 years, patients in the highest IBI category had over twice the risk of death compared with those with low IBI. Time-dependent ROC curve analysis demonstrated that IBI consistently yielded higher AUC values than CRP, NEU count or LYM count alone at 1-year, 3-year and 5-year intervals.

According to previous studies, IBI was correlated with poor survival outcomes in various diseases. A recent large-scale cohort analysis using data from the National Health and Nutrition Examination Survey provided further evidence that elevated IBI is independently associated with increased risk of all-cause mortality in the general population aged over 45 years.[15] Zhai *et al* found that a stable, positive and nonlinear correlation between the IBI and both the prevalence of rheumatoid arthritis (RA) and RA-related all-cause mortality.[16] The study further highlighted a J-shaped association between IBI and mortality in RA.[16] Zhu *et al* explored the relationship between the IBI and both the prevalence of chronic inflammatory airway diseases (CIAD) and mortality outcomes in affected individuals, including asthma, chronic bronchitis and chronic obstructive pulmonary disease (COPD).[14] Among 27 495 adults, higher IBI quartiles were positively associated with increased prevalence of total CIAD, asthma, chronic bronchitis and COPD after multivariable adjustment.[14] Compared with the lowest quartile, the highest IBI quartile was linked to a significantly greater risk of all-cause mortality (HR 2.227) and respiratory mortality (HR 2.748).[14] A recent analysis of 1828 patients with sepsis from the MIMIC-IV database demonstrated that elevated log-transformed IBI (LnIBI) levels were independently associated with increased mortality at 28 days, during ICU stay and over the course of hospitalisation, even after adjustment for multiple confounders.[17]

Given the established role of inflammation in the pathophysiology and prognosis of acute PE, several studies have investigated individual inflammatory markers for their prognostic utility. In a prospective study of 56 patients with acute PE followed up for 36 months, CRP levels were significantly associated with right ventricular dysfunction and increased mortality.[18] Patients with CRP >48 mg/L had higher mortality, and CRP showed moderate predictive accuracy (sensitivity 72.7%, specificity 61.9%) for PE-related death.[18] Marta *et al* observed

that elevated CRP levels were significantly associated with the presence of right ventricular dysfunction, and higher CRP was linked to increased PE-related 30-day mortality in a cohort of 633 haemodynamically stable patients with acute PE.[19] While CRP was not independently associated with 30-day all-cause mortality in multivariable analysis, patients in higher CRP quartiles showed a stepwise increase in adjusted odds of death.[19] A retrospective study of 101 patients with postoperative acute PE identified the NLR and serum albumin as independent predictors of 30-day mortality.[20] Multivariate analysis revealed that each one-unit increase in NLR raised the risk of death by 17.1% (OR 1.171).[20] Ma *et al* also found that each unit increase in NLR was associated with a 13% rise in mortality risk (OR 1.13; 95% CI 1.04 to 1.23), with an AUC of 0.79, which showed good discriminatory ability.[21] In a retrospective study of 359 patients with confirmed acute PE, elevated NLR at admission was independently associated with 30-day mortality.[22] An NLR cut-off of >9.2 was associated with a 3.6-fold increased hazard of death (HR 3.60; 95% CI 1.44 to 9.18).[22] Peng *et al* found that elevated admission NEU counts were significantly and independently associated with intermediate-risk and high-risk acute PE (OR 1.239; 95% CI 1.055 to 1.455; p=0.009).[23] NEU levels correlated positively with the PE severity index, high-sensitivity CRP, D-dimer and Pulmonary Artery Obstruction Index.[23] IBI is derived by combining CRP and the NLR. CRP reflects the degree of systemic inflammation, whereas NLR serves as an indicator of immune response balance. By integrating these two components, the IBI offers a more comprehensive measure of both inflammation and immune dysregulation, potentially providing greater prognostic utility. Our findings support this notion, demonstrating that IBI outperforms its individual components in predicting long-term mortality, likely due to its ability to capture the multifaceted nature of thrombo-inflammation in acute PE.

Systemic inflammation is increasingly recognised as a key modulator of thrombotic risk, vascular dysfunction and long-term morbidity in a variety of clinical contexts. In the setting of PE, inflammation is not only a driver of initial thrombus formation but also contributes to endothelial injury, right ventricular strain and potential chronic sequelae. Emerging evidence indicates that NEU play an active role in the pathophysiology of thrombosis. Experimental studies have confirmed their involvement in venous thrombus formation, and clinical data show that patients with pulmonary thromboembolism frequently present with endothelial dysfunction.[24] Through the release of oxygen radicals, activated leucocytes induce endothelial injury, thereby enhancing inflammatory responses and promoting thrombus propagation in PE.[25] Furthermore, NLR has been linked to massive embolism in PE.[26] Experimental models of PE have shown distinct temporal patterns of inflammatory cell infiltration. Lymphopenia may reflect stress-induced corticosteroid release, redistribution of LYM to lymphoid organs or apoptosis triggered by systemic inflammation. Reduced LYM counts can signal impaired adaptive immunity, which may predispose to secondary infections and poorer recovery.[27] Against this background, IBI integrates systemic inflammatory load with immune disequilibrium, thereby indexing the interaction across the 'inflammation–coagulation–endothelial injury' axis more directly than single markers. This mechanistic linkage provides a parsimonious explanation for IBI's superior prognostic performance compared with its individual components.

Inflammation is a highly dynamic and evolving process, future studies in acute PE should track changes in IBI over time. A single baseline value may not fully capture the fluctuations in systemic inflammatory burden that occur during the acute phase and recovery period of PE. NEU accumulate within the pulmonary arterial wall, peaking around day 2 and returning to baseline by day 8, whereas macrophage infiltration peaks on day 1 and normalises by day 4. Immunohistological analyses further demonstrate that NEU infiltrate the right ventricular wall within 6–18 hours after PE onset, with resolution occurring between day 4 and day 7.[28] Furthermore, previous analysis also demonstrated NEU infiltration within 6 to 18 hours after onset, with resolution occurring between day 4 and the end of the first week.[28 29] Tracking IBI longitudinally could help identify patients with persistent or escalating inflammatory activity, which may signal ongoing thrombus propagation, endothelial injury or heightened risk of chronic complications such as chronic thromboembolic pulmonary hypertension. In acute PE, sustained inflammatory activity may be a manifestation of pre-existing comorbidities. Even when PE is accurately diagnosed and managed, most deaths within the first year are attributable to underlying disorders rather than to the embolic event itself, such as malignancy, chronic lung disease, heart failure or severe infections.[30] In the present study, the strong association between elevated IBI and long-term mortality may partly reflect the cumulative inflammatory burden arising from these coexisting conditions.

To our knowledge, our study is the first to evaluate the prognostic role of IBI in acute PE and demonstrated that its predictive performance exceeds that of its individual components. Existing PE risk stratification predominantly indexes clinical status and right-ventricular dysfunction at presentation, using instruments such as the simplified PE Severity Index and imaging assessments. These frameworks are clinically valuable, yet they offer limited resolution of systemic inflammatory activity. Within this landscape, IBI serves as an inflammation-oriented biomarker that is conceptually complementary to established clinical models, such as PESI, sPESI and ESC risk categories,[31–33] capturing residual risk that may not be fully reflected by haemodynamic status or comorbidity burden. In practice, incorporating IBI alongside PESI/sPESI could refine risk within ostensibly similar strata by identifying patients with a heightened inflammatory burden who may remain vulnerable after the

acute phase. Our results suggest that integrating IBI into routine PE assessment could identify individuals who have a high inflammatory burden and are at greater risk of adverse outcomes. Future studies should include head-to-head comparisons and incremental value analyses and evaluate external generalisability to determine how best to embed IBI within existing PESI/sPESI or ESC-based pathways.

Several limitations should be acknowledged in this study. First, the retrospective design limited our ability to assess a causal association between the IBI and the mortality risk among individuals with acute PE. Although we adjusted for multiple covariates in our multivariable models, unmeasured or incompletely captured factors—such as low-grade inflammation, autoimmune disease or subclinical infection—may still have influenced baseline CRP and blood counts, potentially introducing residual confounding. In addition, detailed prescribing records were not available in our retrospective database, precluding adjustment for the potential confounding effects of medications that may influence systemic inflammation or mortality risk. These include hormonal therapies (hormonal contraception), anti-inflammatory or immunomodulatory agents (corticosteroids or biologic therapies), antithrombotic treatments (anticoagulants and antiplatelet agents) and cardiovascular medications (statins or beta-blockers). The absence of these data may have resulted in residual confounding, and this limitation should be considered when interpreting the observed association between IBI and long-term mortality. Third, while the optimal IBI cut-off value (83.8 mg/L) was identified using statistically robust methods, it has not yet been externally validated or clinically optimised. Therefore, caution is warranted when applying this threshold in other settings, and validation in independent, multicentre cohorts will be essential to determine its clinical applicability and reproducibility. Finally, a full ESC risk–stratified analysis was not feasible due to incomplete and non-standardised data on key components, including haemodynamic status, sPESI, right ventricular dysfunction and cardiac biomarkers. Prospective studies with harmonised data collection are needed to assess the added value of IBI within ESC-defined risk categories.

CONCLUSION

In summary, this study demonstrates that the IBI, a composite marker incorporating CRP, NEU and LYM counts, is a robust and independent predictor of long-term mortality in patients with acute PE. IBI outperformed traditional inflammatory biomarkers in prognostic accuracy and provided significant incremental value when added to conventional clinical risk models. These findings highlight the clinical utility of IBI for risk stratification and underscore the importance of integrating inflammatory profiling into the management of patients with PE.

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