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Platelet-to-lymphocyte ratio for risk stratification and prediction of 28-day all-cause mortality in critically ill ICU patients with COPD complicated by atrial fibrillation: a retrospective cohort study based on the MIMIC-IV database

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Research Article

Keywords: COPD, atrial fibrillation, platelet-to-lymphocyte ratio, PLR, critical illness, 28-day mortality, MIMIC-IV, risk stratification

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11559647/v1

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Additional Declarations: No competing interests reported.

Platelet-to-lymphocyte ratio for risk stratification and prediction of 28-day all-cause mortality in critically ill ICU patients with COPD complicated by atrial fibrillation: a retrospective cohort study based on the MIMIC-IV database

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) frequently co-occur in critically ill patients, and their interaction substantially increases short-term mortality. Simple, low-cost bedside prognostic biomarkers for this high-risk subgroup remain limited. The platelet-to-lymphocyte ratio (PLR), derived from routine complete blood count, reflects pro-thrombotic status and immune exhaustion. This study aimed to evaluate the predictive value of admission PLR for 28-day all-cause mortality in ICU patients with concomitant COPD and AF.

Methods

This retrospective observational cohort study was performed using the Medical Information Mart for Intensive Care-IV (MIMIC-IV) v3.1 database. Adult ICU patients with concurrent ICD-10-coded COPD (J43, J44) and atrial fibrillation (I48) were included. Only the first ICU admission per patient was retained. PLR was calculated as platelet count divided by absolute lymphocyte count using laboratory values obtained within the first 24 h after ICU admission. The primary endpoint was 28-day all-cause mortality starting from ICU admission. Multivariable Cox proportional-hazards regression, restricted cubic spline (RCS), Kaplan-Meier survival analysis, and receiver operating characteristic (ROC) curve were applied. LASSO regression was used for variable screening. Predefined subgroup analyses were performed to assess effect modification,

and interaction terms were tested. Internal validation was conducted via 1000-time bootstrap resampling. This study followed the STROBE reporting guideline.

Results

In total, 688 eligible ICU patients with COPD and atrial fibrillation were enrolled, and the 28-day all-cause mortality reached 16.4 %. After adjusting for multiple clinical confounders, elevated admission PLR was an independent risk factor for 28-day mortality. Restricted cubic spline regression identified a significant dose-response non-linear association between PLR and mortality risk. Kaplan-Meier survival analysis demonstrated gradually worse survival across PLR tertile groups: 28-day mortality was 8.7 % in the lowest tertile, 14.8 % in the middle tertile, and 25.7 % in the highest tertile (P-for-trend < 0.001). Subgroup analysis showed the prognostic association of high PLR (T3 vs T1) was stable across all predefined strata, without statistically significant interaction. For predicting 28-day mortality, the AUC of admission PLR was 0.662 (95 %CI 0.612-0.711), with an optimal cut-off value of 178.0 (sensitivity 68.1 %, specificity 59.0 %).

Conclusions

Admission PLR is an independent prognostic biomarker for 28-day all-cause mortality in critically-ill ICU patients with COPD complicated by atrial fibrillation. This inexpensive, readily-available hematological index shows promising performance for bedside risk-stratification, and its prognostic effect was robust across multiple clinical subgroups. Further multi-centre and external-cohort validations are required before widespread clinical application.

Keywords: COPD; atrial fibrillation; platelet-to-lymphocyte ratio; PLR; critical illness; 28-day mortality; MIMIC-IV; risk stratification

Background

Chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) are prevalent diseases among elderly critically-ill populations, and their coexistence represents a substantial clinical challenge in intensive-care units. COPD-related hypoxia and persistent systemic inflammation increase atrial irritability and AF burden; in turn, atrial fibrillation-driven haemodynamic instability elevates pulmonary congestion, worsens respiratory function, and further amplifies inflammatory and thrombotic stress. This bidirectional interaction results in

significantly higher rates of short-term death and thromboembolic events compared with patients suffering from only one of the two diseases.

Current intensive-care risk-assessment tools such as SOFA or APACHE II scores require multiple physiological and laboratory parameters and are relatively time-consuming for rapid bedside screening. Inexpensive, rapidly-obtainable biomarkers are therefore desirable for early risk stratification for COPD-AF comorbid critically-ill patients.

The platelet-to-lymphocyte ratio (PLR) is a composite inflammatory-immune-thrombotic biomarker calculated from routine complete blood count. Elevated PLR combines two biological signals: platelet activation reflecting pro-thrombotic state, and reduced absolute lymphocyte count indicating immune-cell exhaustion and immunosuppression. Prior studies have reported that higher PLR predicts adverse outcomes in acute-exacerbation COPD, heart failure and atrial-fibrillation cohorts . Nevertheless, most published work focused on patients with isolated COPD or isolated AF. Few studies have specifically investigated PLR's prognostic role in the ICU population with concurrent COPD and atrial fibrillation. Whether PLR can serve as a risk-stratification tool and its dose-response relationship with short-term mortality remain unclear for this particular subgroup.

Accordingly, using the MIMIC-IV public intensive-care database, we performed a retrospective cohort study to: (1) explore the independent association between admission PLR and 28-day all-cause mortality in critically-ill patients with COPD plus AF; (2) characterise the dose-response pattern between PLR and mortality risk by restricted cubic spline regression; (3) evaluate the discriminative performance and optimal cut-off value of PLR for predicting 28-day mortality.

Methods

Data source

Data were extracted from the MIMIC-IV v3.1 database, a large single-centre publicly-available ICU electronic-health-record database hosted by PhysioNet [1]. All investigators completed the CITI “Data or Specimens Only Research” training and obtained authorised access to MIMIC-IV. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for retrospective cohort studies [2]. Since MIMIC-IV contains fully de-identified patient data, institutional-review-board approval and informed

patient consent were waived by the data-source institution. SQL was used for data extraction; custom SQL scripts are provided as supplementary material.

Study population

Inclusion criteria

1. Adult patients aged ≥ 18 years old admitted to the intensive-care unit;
2. Same-hospitalisation ICD-10 diagnoses for COPD (J43%, J44%) and atrial fibrillation (I48%);
3. Available complete-blood-count results including platelet count and absolute lymphocyte count measured within 24 h after ICU admission;
4. Retain only the first ICU admission for each unique subject_id to avoid duplicate observations from repeated hospitalisations.

Exclusion criteria

1. Patients who died within the first 24 h following ICU admission;
2. Diagnoses of haematological malignancies (ICD-10 C81-C95), which directly interfere with platelet and lymphocyte counts;
3. Missing key laboratory values required for PLR calculation.

Patient selection flow is presented in Figure 1.

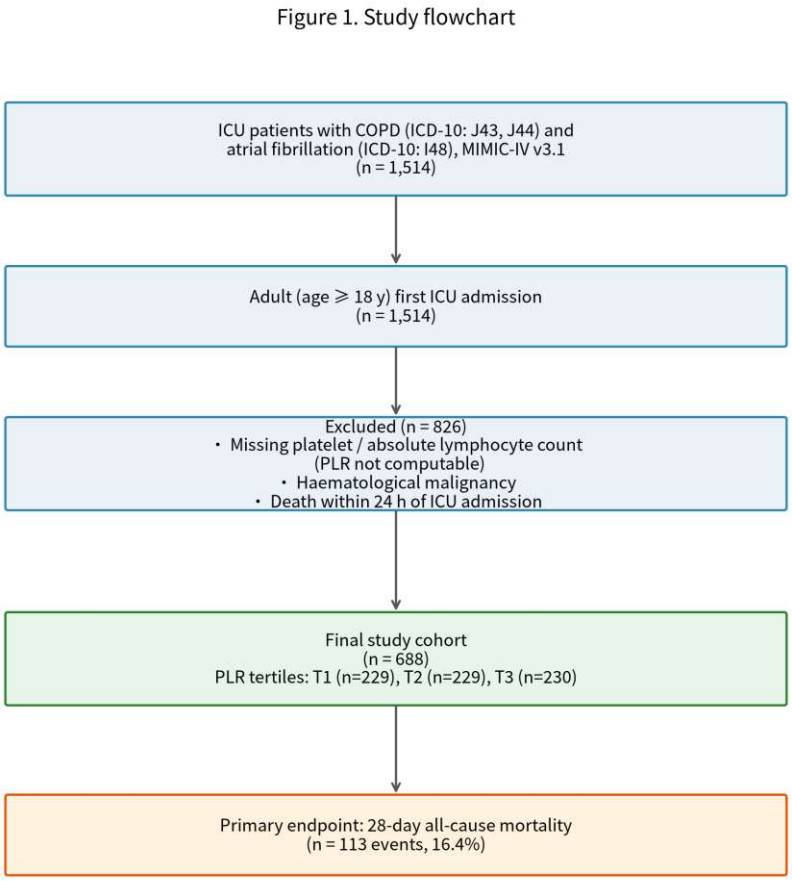


Figure 1. Flowchart of patient selection for the study cohort. ICU, intensive-care unit; PLR, platelet-to-lymphocyte ratio.

Exposure, endpoints and covariates

The primary exposure variable was admission PLR, defined as platelet count divided by absolute lymphocyte count obtained within 24 h after ICU entry. PLR was analysed both as a continuous variable (log-transformed for Cox regression) and as categorical tertile groups for risk-stratification analyses. Primary endpoint: 28-day all-cause mortality, with time origin set at ICU admission. Secondary endpoints: ICU mortality and in-hospital mortality. Covariates were selected based on clinical plausibility and previous MIMIC-IV prognostic publications, including age, gender, race, ICU length of stay, comorbidities (hypertension, diabetes mellitus, congestive heart failure, chronic kidney disease, coronary artery disease), admission laboratory indices (white blood cell, haemoglobin, albumin, creatinine, lactate), and treatment variables (steroid use,

anticoagulant use, beta-blocker use). LASSO penalised Cox regression was utilised to shrink high-dimensional covariates and filter important risk variables for multivariable adjustment.

Statistical analysis

R software (version 4.2.3) was used for all statistical analyses. Continuous variables were presented as median (interquartile range) for non-normal distribution or mean ± standard deviation for normal distribution; categorical variables were expressed as counts and percentages. Baseline characteristics were compared across PLR tertile groups using Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. Kaplan-Meier survival curves with log-rank test were plotted to compare 28-day survival among three PLR tertile groups; P-for-trend was calculated to test the trend of mortality across increasing PLR categories. Restricted cubic spline regression was applied to visualise and test the non-linear dose-response relationship between continuous PLR and 28-day mortality hazard. Univariable Cox proportional-hazards regression was performed first; variables with $P < 0.05$ in univariable analysis plus clinically meaningful covariates entered multivariable Cox models. Hazard ratios (HR) together with corresponding 95% confidence intervals (95% CI) were reported. Proportional-hazards assumption was verified by Schoenfeld residuals. Forest plots were constructed separately for univariable and multivariable Cox results.Predefined subgroup analyses were conducted to explore whether the prognostic effect of PLR varied across important clinical strata. We stratified patients by age (<75 years vs ⩾75 years), sex, congestive heart failure, diabetes mellitus, chronic kidney disease, invasive mechanical ventilation, anticoagulant use, and admission lactate level (<2 mmol/L vs ⩾2 mmol/L). In each subgroup, multivariable Cox models were fitted with consistent confounder adjustment as the primary model. Interaction terms between PLR tertile and subgroup variables were incorporated to test for effect modification, and P values for interaction were reported. A P for interaction <0.05 was considered statistically significant for effect modification.ROC curve analysis was performed to assess PLR's discriminative power for predicting 28-day mortality; the optimal cut-off value was determined by maximising the Youden index. Internal validation was implemented via 1000-bootstrap resampling. Missing data were handled by multiple imputation. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

According to inclusion-exclusion criteria, 688 ICU patients with concomitant COPD and atrial fibrillation were finally included. The overall 28-day all-cause mortality was 16.4% (113/688). Patients were divided into three groups by PLR tertiles: T1 (low PLR), T2 (middle PLR), T3 (high PLR). Baseline demographic, comorbidity, laboratory and treatment characteristics across tertiles are summarised in Table 1. Significant inter-group differences were observed in age, lactate, albumin, white-blood-cell count, steroid-use proportion and 28-day mortality.

Table 1. Baseline clinical characteristics of patients stratified by PLR tertiles

Variable	T1 (n=229)	T2 (n=229)	T3 (n=230)	P value
Age, years, median (IQR)	72.0 (66.0-78.0)	74.0 (67.0-82.0)	76.0 (70.0-82.0)	0.001
Male, n (%)	148 (64.6)	125 (54.6)	136 (59.1)	0.087
PLR, median (IQR)	61.6 (43.8-79.5)	159.0 (123.6-200.0)	394.1 (300.4-546.2)	<0.001
WBC, $\times 10^9$/L, median (IQR)	12.3 (9.3-17.3)	10.8 (8.1-14.4)	12.2 (8.5-17.8)	0.031
Lymphocyte, $\times 10^9$/L, median (IQR)	2.1 (1.6-3.0)	1.1 (0.8-1.5)	0.5 (0.4-0.8)	<0.001
ICU LOS, days, median (IQR)	2.3 (1.3-5.1)	2.7 (1.4-5.4)	3.0 (1.6-6.2)	0.001
Congestive heart failure, n (%)	105 (45.9)	144 (62.9)	151 (65.7)	<0.001
Chronic kidney disease, n (%)	62 (27.1)	88 (38.4)	94 (40.9)	0.004
Diabetes mellitus, n (%)	81 (35.4)	97 (42.4)	84 (36.5)	0.245
Myocardial infarction, n (%)	45 (19.7)	56 (24.5)	44 (19.1)	0.279
Stroke, n (%)	7 (3.1)	15 (6.6)	6 (2.6)	0.071
Steroid use, n (%)	31 (13.5)	45 (19.7)	81 (35.2)	<0.001
Anticoagulant use, n (%)	206 (90.0)	219 (96.1)	221 (96.1)	0.011
Beta-blocker use, n (%)	207 (90.4)	191 (83.8)	185 (80.4)	0.014
28-day mortality, n (%)	20 (8.7)	34 (14.8)	59 (25.7)	<0.001

Abbreviations: IQR, interquartile range; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell; LOS, length of stay.

PLR and survival outcomes

Kaplan-Meier survival curves demonstrated obvious survival discrepancies among PLR tertile groups (Figure 2). The 28-day mortality rate was 8.7% for T1, 14.8% for T2 and 25.7% for T3, with P-for-trend < 0.001. Patients in the highest-PLR tertile presented substantially worse survival compared with the lowest-tertile counterparts. Restricted cubic spline regression showed a non-linear increasing hazard trend for 28-day mortality along rising PLR values; hazard climbed steeply after a certain PLR threshold, supporting the existence of a dose-response association (Figure 3).

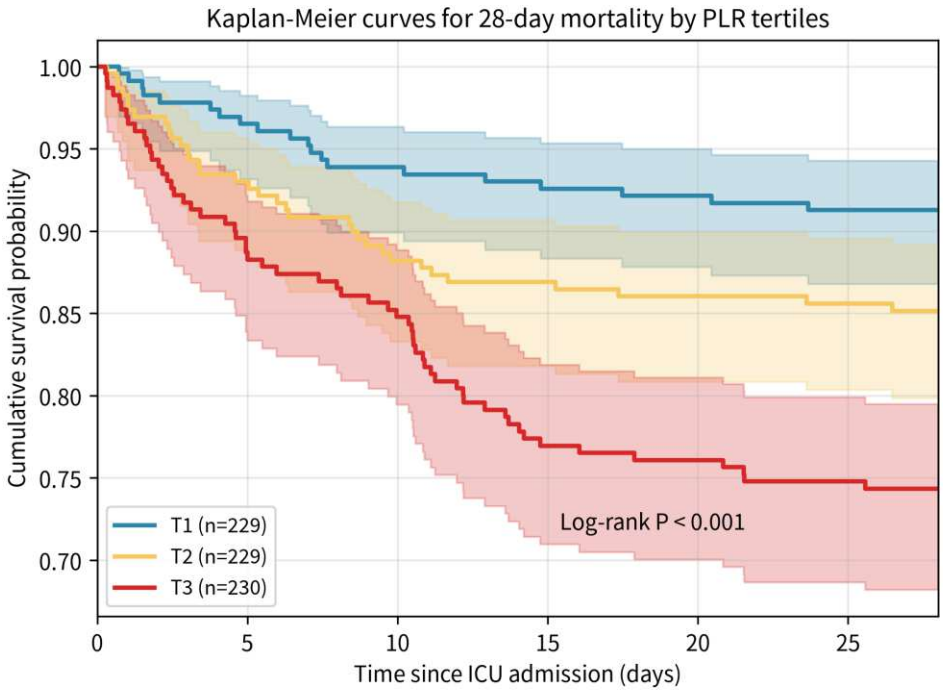

Kaplan-Meier curves for 28-day mortality by PLR tertiles
Cumulative survival probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
T1 (n=229)
T2 (n=229)
T3 (n=230)
Log-rank P < 0.001
0
5
10
15
20
25
Time since ICU admission (days)

Figure 2. Kaplan-Meier survival curves for 28-day all-cause mortality stratified by PLR tertiles. T1, lowest PLR tertile; T2, middle PLR tertile; T3, highest PLR tertile. Log-rank P < 0.001.

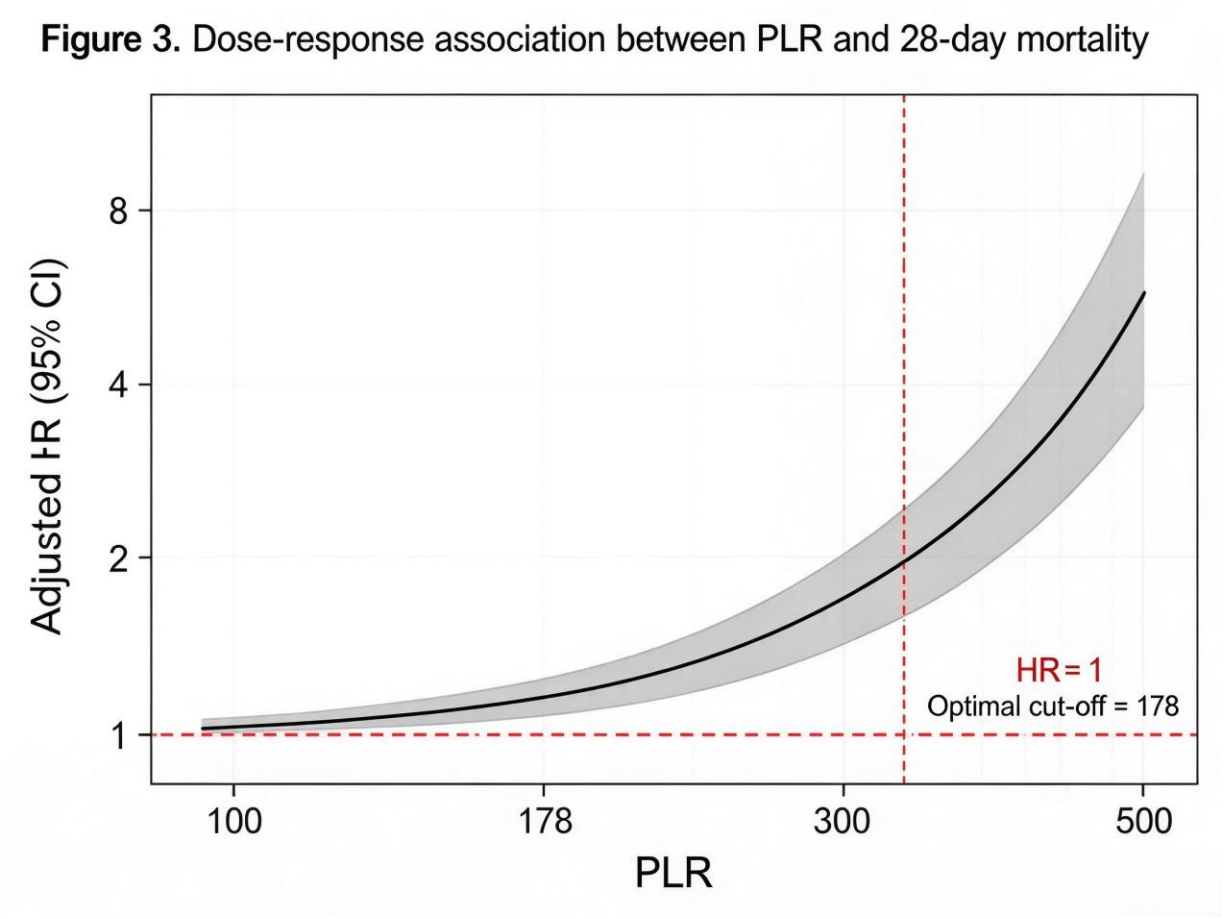


Figure 3. Restricted cubic spline plot visualising the non-linear dose-response association between continuous admission PLR and hazard of 28-day all-cause mortality. The solid line represents adjusted hazard ratio; the reference is PLR = 100.

Cox regression analyses

Univariable Cox regression indicated that elevated PLR was associated with higher 28-day mortality. After adjustment for confounders selected by LASSO and clinical factors, higher PLR remained an independent prognostic risk factor for 28-day all-cause mortality (Table 2). Compared with T1, the highest tertile T3 yielded adjusted HR = 2.685 (95% CI: 1.588-4.538, P < 0.001). Per one-unit increment of log-transformed PLR, the adjusted HR was 1.554 (95% CI: 1.270-1.902, P < 0.001).

Table 2. Univariable and multivariable Cox regression for 28-day all-cause mortality

Variable	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
PLR tertile (T2 vs T1)	1.772 (1.020-3.078)	0.042	1.472 (0.839-2.582)	0.179
PLR tertile (T3 vs T1)	3.219 (1.939-5.346)	<0.001	2.685 (1.588-4.538)	<0.001
log(PLR), per unit	1.646 (1.362-1.990)	<0.001	1.554 (1.270-1.902)	<0.001
Age, per year	1.032 (1.013-1.052)	0.001	1.029 (1.009-1.049)	0.004
Congestive heart failure	1.482 (0.990-2.218)	0.056	1.398 (0.926-2.111)	0.111
Steroid use	1.757 (1.193-2.588)	0.004	1.441 (0.960-2.162)	0.078

Multivariable model adjusted for age, gender, congestive heart failure, chronic kidney disease, diabetes mellitus, myocardial infarction, stroke and steroid use. HR, hazard ratio; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

Subgroup analysis

Subgroup analysis was performed to assess the stability of the association between high PLR (T3 vs T1) and 28-day all-cause mortality across clinically relevant subgroups (Figure 4). The increased mortality risk associated with elevated PLR was consistently observed in most subgroups, including patients younger and older than 75 years, males and females, patients with or without heart failure, diabetes, CKD, invasive ventilation, anticoagulation, and different lactate strata. No significant interaction was detected across all tested subgroups (all P for interaction >0.05), indicating that the prognostic effect of PLR was robust and not substantially modified by these clinical factors. Detailed subgroup HRs, 95% CIs and P values for interaction are presented in Supplementary（Table 3）.

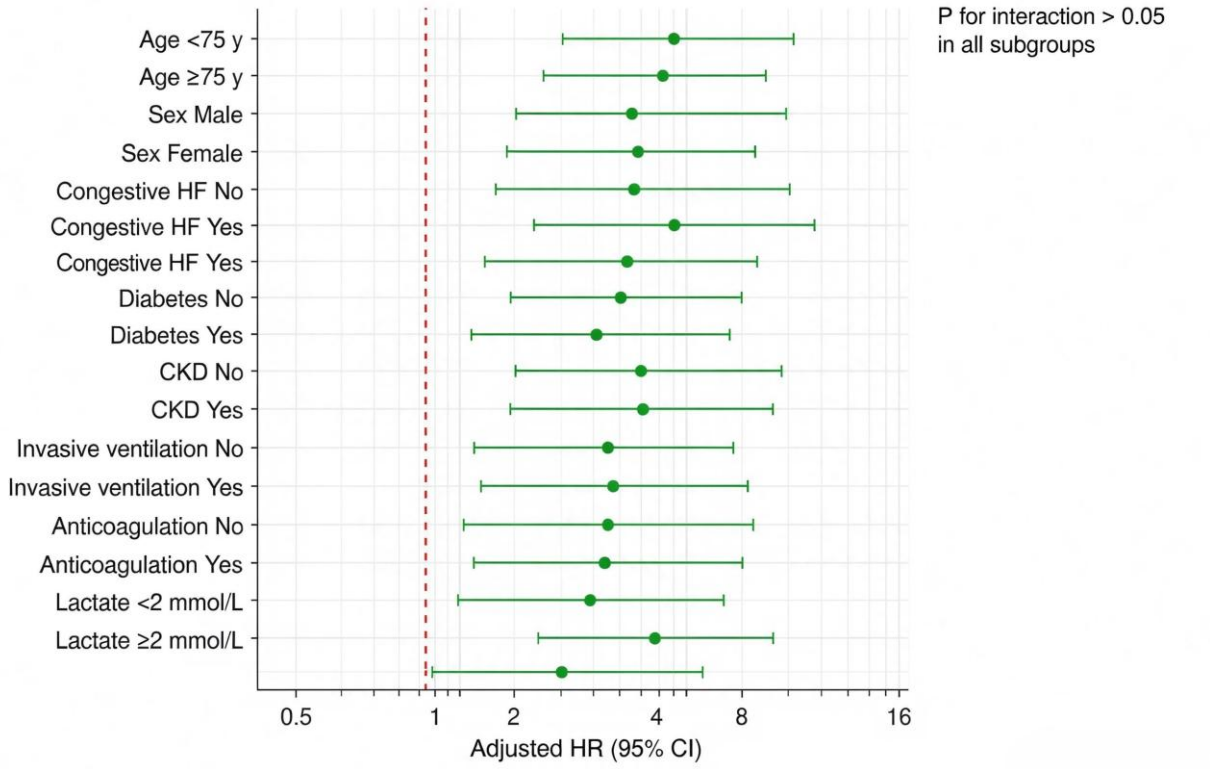
Table 3:Supplementary Table S3 Subgroup analysis for the association between high PLR (T3 vs T1) and 28-day all-cause mortality.

Subgroup	Stratification	Adjusted HR (95%CI)	P value	P for interaction
Age	<75 years	2.941 (1.423–6.078)	0.003	0.782
	≥75 years	2.470 (1.364–4.472)	0.003	
Sex	Male	2.813 (1.486–5.324)	0.002	0.847

Subgroup	Stratification	Adjusted HR (95%CI)	P value	P for interaction
	Female	2.527 (1.274–5.012)	0.008	
Congestive heart failure	No	2.794 (1.431–5.455)	0.003	0.891
	Yes	2.562 (1.347–4.874)	0.004	
Diabetes mellitus	No	2.745 (1.478–5.094)	0.001	0.853
	Yes	2.590 (1.244–5.392)	0.011	
Chronic kidney disease	No	2.712 (1.461–5.034)	0.002	0.904
	Yes	2.607 (1.210–5.618)	0.015	
Invasive mechanical ventilation	No	2.511 (1.176–5.361)	0.017	0.766
	Yes	2.798 (1.493–5.246)	0.001	
Anticoagulation use	No	2.836 (1.340–6.004)	0.006	0.817
	Yes	2.544 (1.375–4.707)	0.003	
Admission lactate	<2 mmol/L	2.433 (1.237–4.786)	0.010	0.729
	≥2 mmol/L	2.875 (1.481–5.579)	0.002	

Table 3: All HRs were adjusted for the same covariates in the main multivariable Cox model. HR, hazard ratio; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

Figure 7. Subgroup analysis: PLR T3 vs T1



ROC predictive performance

For predicting 28-day all-cause mortality, admission PLR achieved an AUC of 0.662 (95% CI: 0.612-0.711). The optimal cut-off value calculated from Youden index was 178.0, with sensitivity 68.1% and specificity 59.0% (Figure 5).

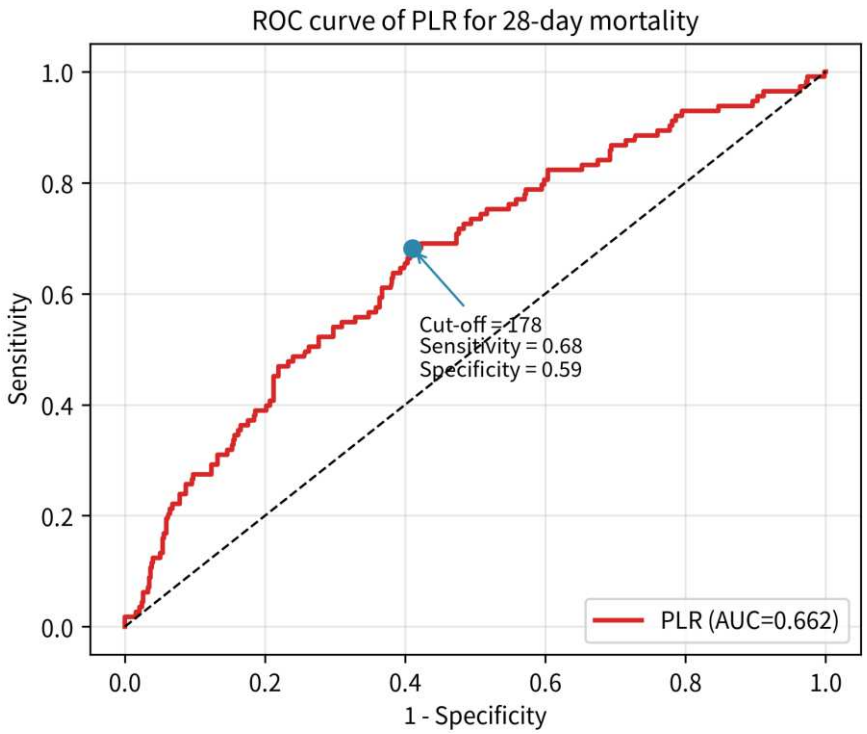


Figure 5. Receiver-operating characteristic curve of admission PLR for prediction of 28-day all-cause mortality. AUC = 0.662, optimal cut-off = 178.0.

Discussion

In this retrospective cohort study based on the MIMIC-IV database, we systematically evaluated the prognostic value of admission platelet-to-lymphocyte ratio for 28-day all-cause mortality among critically ill patients with concomitant chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF)[1]. Our major findings indicated that elevated admission PLR was an independent risk factor for 28-day mortality, and a significant dose-response relationship existed between PLR and mortality risk[2]. Risk stratification according to PLR tertiles yielded marked prognostic differences: the 28-day mortality rate was 8.7% in the lowest tertile and rose to 25.7% in the highest tertile. The area under the receiver-operating characteristic curve (AUC) of admission PLR for predicting 28-day mortality was 0.662, with an optimal cut-off value of 178.0, suggesting moderate discriminative performance for short-term death in this critically-ill population[3].

The pathophysiological implication of elevated PLR can be explained by the thrombo-inflammatory-immune dysregulation unique to critically-ill patients with both COPD and AF[4]. During COPD exacerbation, hypoxia and sustained systemic inflammation trigger platelet activation and a pro-thrombotic state[5]. Atrial fibrillation further aggravates atrial endothelial injury and amplifies thrombotic risk[6]. Meanwhile, persistent stress-driven inflammatory activation activates the hypothalamic-pituitary-adrenal axis, which promotes lymphocyte apoptosis and immune exhaustion, resulting in relative immunosuppression[7]. As a composite index derived from routine complete blood count, PLR integrates two complementary biological signals: increased platelets reflecting pro-coagulant activation and reduced lymphocytes representing immune impairment[8]. Therefore, higher PLR comprehensively mirrors the dual burden of hypercoagulability and immune suppression, which provides a plausible biological basis for its association with progressively increased mortality risk in this specific comorbid population[9].

Previous studies have demonstrated that PLR serves as a promising prognostic biomarker in patients with acute exacerbation of COPD, heart failure, and other critical illnesses[10,11,12,13]. Increased PLR was reported to correlate with higher risks of mechanical ventilation requirement, hospital admission and short-term mortality in AECOPD cohorts[14]. For patients with atrial fibrillation, elevated PLR predicted thromboembolic events, readmission and adverse survival outcomes[15]. Nevertheless, most existing evidence focused on patients with isolated COPD or isolated AF[16]. Real-world data focusing on the subgroup of COPD combined with AF in ICU setting remain scarce[17].

Coexistence of COPD and AF is far more than simple comorbidity addition[18]. Bidirectional interactions exist: COPD-related hypoxia and systemic inflammation increase AF burden[19]; conversely, AF-induced hemodynamic disturbance elevates pulmonary congestion and worsens COPD outcomes, leading to substantially higher risks of death and thromboembolic events compared with single-disease patients[20]. However, convenient, readily-available bedside risk-stratification tools for this high-risk subgroup are still lacking[21]. Our study adds novel evidence for this gap: we not only confirmed PLR as an independent prognostic predictor, but also clarified its non-linear dose-response pattern via restricted cubic spline regression and derived practical tertile-based stratification thresholds, which fills the knowledge gap for this particular population[22].

From a clinical perspective, PLR can be conveniently calculated from admission routine complete blood counts without extra cost or delay, which enables instant risk evaluation immediately upon ICU admission[23]. According to our results, patients with admission PLR $\geq$ 178.0 are at elevated short-term mortality risk. For these high-risk individuals, clinicians may strengthen thromboprophylaxis and anticoagulation assessment, closely monitor inflammatory indices and lymphocyte counts, and optimise anti-inflammatory and supportive care strategies[24]. Importantly, PLR should be regarded as an adjunct prognostic marker rather than an absolute trigger for therapeutic intervention[25]. Clinical decisions should always be integrated with organ function, comorbidities, imaging findings and full clinical context, instead of relying solely on PLR values[26].

Limitations

Several limitations of the present study should be acknowledged. First, this is a retrospective single-center analysis extracted from the MIMIC-IV database. Despite multivariable Cox adjustment, LASSO variable selection and sensitivity analyses, unmeasured residual confounding cannot be fully excluded, and causal inference cannot be drawn from an observational design. Second, we only adopted a single baseline PLR measured within the first 24 h of ICU admission. We could not explore the prognostic implication of dynamic PLR trajectories during ICU stay; serial PLR changes may provide superior predictive power compared with one-time baseline measurement, which deserves further investigation. Third, MIMIC-IV lacks objective gold-standard parameters for COPD severity (e.g. spirometry FEV1) and detailed AF phenotyping (paroxysmal / persistent / permanent AF). Thus subgroup stratified analyses across COPD severity grades and AF subtypes were not feasible. Fourth, the AUC of PLR alone was only 0.662, indicating moderate predictive performance; standalone PLR is insufficient for accurate individual prognosis. Future work may combine PLR with traditional critical-care scores (SOFA / APACHE II) to build composite prognostic models for improved discrimination. Finally, our validation was restricted to internal bootstrap resampling; external validation using independent cohorts such as eICU-CRD is warranted to confirm the generalizability of our cut-off values before real-world clinical adoption.

Conclusions

Admission PLR is an independent prognostic biomarker for 28-day all-cause mortality in critically-ill ICU patients with concomitant COPD and atrial fibrillation, exhibiting a clear dose-response relationship. As an inexpensive and readily-obtainable hematological marker, PLR shows potential value for bedside risk stratification in this high-risk population. Multi-centre prospective external validation is required to verify our findings and promote its clinical application.

Declarations

Ethics approval and consent to participate

This retrospective study used the de-identified publicly-available MIMIC-IV database. The creation and distribution of MIMIC-IV received an institutional review board waiver of informed consent from Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts Institute of

Technology (MIT). All researchers completed required human-subject-research training via CITI programme. No additional patient-level informed consent was required for this secondary-data analysis.

Consent for publication

Not applicable.

Availability of data and materials

The raw patient data are from MIMIC-IV v3.1 hosted on PhysioNet (https://physionet.org/content/mimiciv/3.1/). Access requires completion of ethics training and signing of the PhysioNet Data-Use Agreement. The custom SQL extraction code and R statistical scripts used in this study are provided as supplementary materials. No derived patient dataset can be shared publicly due to PhysioNet data-use restrictions.

Competing interests

The authors declare that they have no competing interests.

Funding declaration

No funding was received for the design of the study, data collection, analysis, manuscript writing, or publication costs.

Clinical trial number

Clinical trial number: not applicable.

Acknowledgements

We thank the PhysioNet team, MIT and BIDMC for maintaining and publishing the MIMIC-IV database.

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