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*Original Article*

# Predictive value of NLR, PLR and MPVLR for recent major cardiovascular adverse events in elderly patients with heart failure

Zijuan Ren, Fei Xu, Zheng Wei

*Department of Cardiology, Suzhou Municipal Hospital of Anhui Province, Suzhou 234000, Anhui, China*

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**Abstract:** Objective: To evaluate the application value of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume to lymphocyte ratio (MPVLR) levels in identifying recent major cardiovascular adverse events (MACE) in elderly patients with heart failure (HF). Method: A total of 103 elderly HF patients admitted to Suzhou Hospital affiliated to Anhui Medical University from January 2022 to February 2025 were selected as the model group, and 74 patients from the same period served as the external validation group. All patients were followed up for 3 months after treatment. Patients were categorized into a MACE group and a non-MACE group based on the occurrence of MACE. Clinical data and levels of NLR, PLR, and MPVLR, were compared between the two groups. Multivariate logistic regression analysis was conducted to identify the independent risk factors for recent MACE. A forest plot was drawn using Graphpad Prism 8.0 software. Predictive models were evaluated using receiver operating characteristic (ROC) curves and calibration curves. Results: Patients in the MACE group were older and had a higher prevalence of diabetes compared to the non-MACE group. Levels of NLR, PLR, and MPVLR were significantly elevated in the MACE group. Multivariate logistic regression analysis identified NLR (*OR* = 7.928, *95 CI* 2.633-23.869), PLR (*OR* = 1.077, *95 CI* 1.038-1.117), MPVLR (*OR* = 1.688, *95 CI* 1.134-2.513) as risk factors for recent MACE in elderly HF patients (all $P < 0.05$). ROC curve analysis showed that the combined use of NLR, PLR, and MPVLR had superior predictive performance compared to individual indicators ($P < 0.05$). The predictive model demonstrated superior discriminative ability compared to individual indicators (AUC = 0.919), which was further validated in the external validation group (AUC = 0.810), indicating consistent predictive accuracy. Conclusion: Elevated levels of NLR, PLR, and MPVLR can serve as independent risk factors for assessing the risk of recent MACE in elderly HF patients. The combined predictive model demonstrates high accuracy and may assist in early risk stratification and personalized preventive strategies to reduce the risk of MACE.

**Keywords:** Elderly heart failure, major cardiovascular adverse events, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume to lymphocyte ratio

## Introduction

Heart failure (HF), as the terminal stage of various cardiovascular diseases, has emerged as a formidable challenge in global public health [1]. Epidemiological data indicate that the prevalence of HF among individuals aged ≥ 65 years ranges from 4% to 8%, increasing significantly with age [2]. Elderly HF patients often present with multiple comorbidities, leading to complex clinical conditions and an elevated risk of major adverse cardiovascular events (MACE), such as acute myocardial infarction and arrhythmias, which pose serious threats to patients' life and health [3]. Therefore, early identification of accessible biomarkers for predicting MACE in elderly HF patients is of paramount clinical importance for improving patient outcomes. The neutrophil to lymphocyte ratio (NLR) is a marker of systemic inflammation that reflects the inflammatory immune balance [4]. The platelet to lymphocyte ratio (PLR) reflects the relative relationship between platelet count and lymphocytes, and serves as another inflammatory marker [5]. The mean platelet volume-to-lymphocyte ratio (MPVLR) reflects platelet activation relative to immune function and has shown prognostic value in various diseases [6, 7].

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However, evidence regarding the prognostic utility of NLR, PLR, and MPVLR in predicting recent MACE in elderly HF patients remain limited. This study aims to investigate the association between NLR, PLR, MPVLR, and recent MACE in elderly HF patients, thereby identifying reliable prognostic markers to support early risk assessment and guide clinical management.

## Data and methods

### *General information*

A total of 103 elderly HF patients admitted to Suzhou Hospital affiliated to Anhui Medical University between January 2022 and February 2025 were retrospectively included as the model group. This group included 49 males and 54 females, aged 37-93 years, with an average age of (71.70±11.26) years. An additional 74 patients from the same period were selected as the external validation cohort, including 32 males and 42 females, aged 47-95 years, with a mean age of (74.58±9.41) years. There were no significant differences in the general data between the two groups ($P > 0.05$).

Inclusion criteria: (1) Met the diagnostic criteria of the *ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure* [8]; (2) No infectious diseases; (3) Complete clinical data and follow-up available; (4) Good treatment compliance and clear awareness. Exclusion criteria: (1) Presence of severe hepatic or renal dysfunction; (2) Malignant tumors; (3) Recent major trauma; (4) Recent use of medications (e.g., glucocorticoids) that could affect study parameters; (5) Combined coagulation dysfunction; (6) Autoimmune diseases; (7) Congenital heart disease. This study was approved by the Ethics Committee of Suzhou Hospital affiliated to Anhui Medical University.

### *Sample size calculation*

Based on the formula: $n = Z^2_{\alpha/2}\, p(1-p)/d^2$, where n is the estimated sample size, p the expected population proportion (assumed as 0.5), $Z\alpha/2$ the standard normal value corresponding to $\alpha = 0.05$ ($Z = 1.96$), and d the allowable error (0.1), the minimum sample size was calculated to be 97 cases. Considering clinical feasibility and to ensure robustness, a total of 177 cases were ultimately included, of whom 74 constituted the external validation cohort.

### *Methods*

Clinical data of all patients were systematically collected from the hospital information system, including gender, age, body mass index (BMI), education level, place of residence, history of underlying diseases, smoking and alcohol consumption history, New York Heart Association (NYHA) functional classification [9], echocardiographic parameters, blood pressure, and heart rate.

Laboratory parameters included platelet count, neutrophil count, lymphocyte count, mean platelet volume (MPv), total cholesterol, triglycerides, hemoglobin, serum sodium, potassium, calcium, phosphorus, and brain natriuretic peptide levels. On the first day after admission, 5 mL of fasting venous blood was collected from all patients. The samples were centrifuged at 3,000 r/min for 15 minutes, with a radius of 10 cm. The detecting equipment included a fully automatic biochemical analyzer (Shandong Boke Biotechnology Industry; Model: BK-1200; Registration No.: Luxie Zhuzhun 20192220157), a fully automatic blood cell analyzer (Shenzhen Mindray Biomedical; Model: BC-20s; Registration No.: Yue Xie Zhu Zhuzhun 20152220916), and a fully automatic chemiluminescence immunoassay analyzer (Shandong Boko Diagnostic Technology; Model: BKI1100; Registration No.: Luxie Zhuzhun 20202220932). Index calculation: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; MPVLR = average platelet volume/lymphocyte count.

All patients received standardized pharmacological treatment based on disease severity and guideline recommendations [10], including diuretics, β-blockers, aldosterone receptor antagonists, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and digitalis preparations.

All patients were followed up for 3 months after discharge. At baseline (discharge), a follow-up manual was issued, outlining key precautions and emergency contact information. Month 1: outpatient visit or telephone follow-up to assess symptoms, medication compliance, and MACE-related signs; Month 2: telephone follow-

up to detect MACE-related symptoms; Month 3: outpatient follow-up for cardiac function assessment and repeat laboratory testing if necessary. The follow-up was terminated upon the occurrence of a MACE or completion of the 3-month period, whichever came first.

MACE outcomes were defined as the occurrence of any of the following events during follow-up: acute myocardial infarction (based on ECG ST-T changes and elevated myocardial enzymes), acute heart failure (characterized by sudden dyspnea, NT-proBNP > 125 ng/L, and imaging-confirmed pulmonary congestion), readmission for worsening heart failure symptoms (resting chest pain lasting > 20 minutes with dynamic ECG changes but without elevated myocardial enzymes). Based on the follow-up results, patients were categorized into a MACE group and a non-MACE group.

*Statistical methods*

Statistical analysis was performed using SPSS 26.0 and R4.2.1. Categorical variables were expressed as frequencies and percentages [n (%)], and compared using the chi-square test. The Kolmogorov Smirnov (K-S) test was used to evaluate the normality of continuous variables. Normally distributed data were presented as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were conducted using the independent samples *t*-test.

Multivariate logistic regression analysis was used to identify independent risk factors associated with recent MACE in elderly HF patients. A forest plot was generated using Graphpad Prims 8.0 to visualize the regression results.

Receiver operating characteristic curve (ROC) was used to evaluate the predictive performance of risk factors for recent MACE in elderly HF patients, while calibration curve (Bootstrap method) was used to assess the agreement between predicted and observed values. A two-sided *P*-value < 0.05 was considered statistically significant. The test level was set at $\alpha = 0.05$.

## Results

*Recent MACE*

During the follow-up period, 40 patients (38.83%) in the model group experienced MACE, including 26 cases (25.24%) of worsening heart failure, 12 cases (11.65%) of heart failure readmission, 1 case (0.97%) of acute myocardial infarction, and 1 case (0.97%) of unstable angina pectoris. The remaining 63 patients (61.17%) did not experience MACE. Based on the follow-up outcomes, patients were categorized into a MACE group (40 cases) and a non-MACE group (63 cases).

*Comparison of baseline characteristics between the MACE and non-MACE groups*

No statistically significant differences were observed in baseline demographic or clinical characteristics between the two groups ($P > 0.05$). However, patients in the MACE group were older and had a higher prevalence of diabetes, as well as elevated levels of NLR, PLR, MPVLR compared to the non-MACE group ($P < 0.05$), as shown in **Table 1**.

*Analysis of factors associated with recent MACE in elderly HF patients*

With recent MACE as the dependent variable, and age, diabetes history, NLR, PLR, MPVLR as the independent variables, univariate logistic regression analysis showed that diabetes history, NLR, PLR, MPVLR were significantly associated with an increased risk of MACE in elderly HF patients ($P < 0.05$). Multivariate regression analysis further identified NLR, PLR, and MPVLR as independent risk factors for recent MACE (all $P < 0.05$) (**Table 2**).

Significant variables from the univariate analysis were visualized in a forest plot based on odds ratios (OR), as shown in **Figure 1**. Similarly, independent risk factors identified from the multivariate analysis are presented **Figure 2**. In these plots, squares represent *OR* values, where $OR < 1$ indicates a negative correlation with poor prognosis, and $OR > 1$ indicates a positive correlation with poor prognosis.

*Prognostic value of NLR, PLR, MPVLR for recent MACE in elderly HF patients*

ROC curve analysis showed that the combined detection of NLR, PLR, and MPVLR had a significantly higher area under the curve (AUC) for predicting recent MACE in elderly HF patients compared to each individual marker alone ($P < 0.05$) (**Table 3**; **Figure 3**).

**Table 1.** Comparison of general information between the two groups [($\bar{x} \pm s$), *n* (%)]

| Variable | MACE group (*n* = 40) | Non-MACE group (*n* = 63) | $\chi^2/t$ | *P* |
|---|---|---|---|---|
| Gender (Male/Female) | 22/18 | 27/36 | 1.446 | 0.229 |
| Age (years) | 76.22±10.03 | 71.03±9.72 | 2.657 | 0.009 |
| Body Mass Index (kg/m$^2$) | 22.82±2.43 | 22.65±2.3 | 0.358 | 0.721 |
| Educational attainment | | | 0.639 | 0.405 |
| High school and below | 37 (92.50) | 55 (87.30) | | |
| College and above | 3 (7.50) | 8 (12.70) | | |
| Place of residence | | | 0.397 | 0.528 |
| Urban | 31 (77.50) | 52 (82.54) | | |
| Rural | 9 (22.50) | 11 (17.46) | | |
| NYHA classification | | | 0.597 | 0.440 |
| Level III | 23 (57.50) | 41 (65.08) | | |
| Level IV | 17 (42.50) | 22 (34.92) | | |
| Left ventricular ejection fraction (%) | 56.17±4.73 | 55.42±4.68 | 0.789 | 0.432 |
| Left ventricular end diastolic diameter (mm) | 60.23±5.76 | 60.37±5.43 | 0.125 | 0.901 |
| Left ventricular end systolic diameter (mm) | 46.81±5.13 | 47.06±5.27 | 0.237 | 0.813 |
| History of hypertension | 25 (62.50) | 45 (71.43) | 0.896 | 0.344 |
| History of hyperlipidemia | 22 (55.00) | 22 (34.92) | 4.031 | 0.045 |
| History of diabetes | 24 (60.00) | 39 (61.90) | 0.037 | 0.847 |
| Smoking history | 27 (67.50) | 38 (60.32) | 0.542 | 0.462 |
| Alcohol consumption history | 11 (27.50) | 19 (30.16) | 0.084 | 0.772 |
| Systolic pressure (mmHg) | 137.52±10.38 | 136.08±10.04 | 0.609 | 0.544 |
| Diastolic pressure (mmHg) | 90.83±9.55 | 89.66±9.47 | 0.428 | 0.670 |
| Heart rate (beats/min) | 79.42±8.14 | 78.73±8.02 | 0.423 | 0.673 |
| Total cholesterol (mmol/L) | 4.73±0.82 | 4.57±0.65 | 1.098 | 0.275 |
| Triglyceride (mmol/L) | 1.24±0.23 | 1.26±0.22 | 0.442 | 0.660 |
| Hemoglobin (g/L) | 121.43±9.45 | 122.06±9.57 | 0.327 | 0.744 |
| Blood potassium (mmol/L) | 3.35±0.70 | 3.39±0.72 | 0.278 | 0.782 |
| Blood sodium (mmol/L) | 135.43±5.52 | 136.56±5.60 | 1.004 | 0.318 |
| Blood calcium (mmol/L) | 2.55±0.18 | 2.61±0.19 | 1.594 | 0.114 |
| Blood phosphorus (mmol/L) | 1.36±0.14 | 1.38±0.15 | 0.677 | 0.500 |
| BNP (ng/L) | 461.43±19.27 | 458.18±18.46 | 0.856 | 0.394 |
| NLR | 3.29±0.74 | 2.68±0.63 | 4.473 | < 0.001 |
| PLR | 156.68±20.24 | 139.57±19.13 | 4.325 | < 0.001 |
| MPVLR | 6.83±1.46 | 5.58±1.28 | 4.572 | < 0.001 |

Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio.

**Table 2.** Analysis of factors associated with recent MACE in elderly HF patients

| Factor | Univariate logistic regression analysis | | | Multivariate logistic regressions analysis | | |
|---|---|---|---|---|---|---|
| | *P* | *OR* | *95% CI* | *P* | *OR* | *95% CI* |
| Age | 0.900 | 1.032 | 0.995-1.070 | 0.540 | 1.016 | 0.966-1.069 |
| History of diabetes | 0.046 | 2.278 | 1.013-5.121 | 0.085 | 2.964 | 0.860-10.212 |
| NLR | < 0.001 | 5.482 | 2.515-11.946 | < 0.001 | 7.928 | 2.633-23.869 |
| PLR | < 0.001 | 1.066 | 1.037-1.096 | < 0.001 | 1.077 | 1.038-1.117 |
| MPVLR | 0.011 | 1.460 | 1.090-1.956 | 0.0010 | 1.688 | 1.134-2.513 |

Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio.

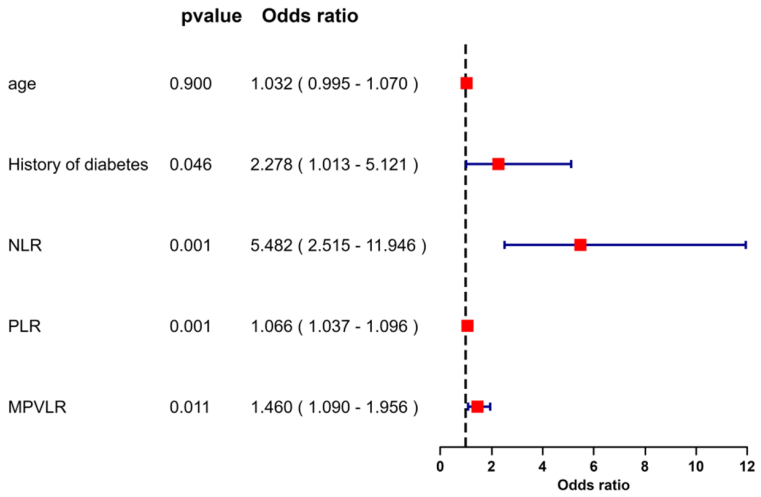


**Figure 1.** Forest plot of significant variables identified in univariate logistic regression analysis. Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio.

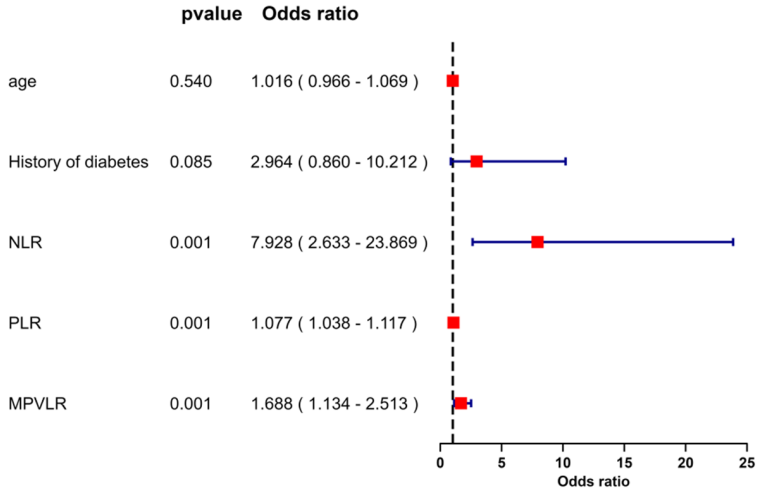


**Figure 2.** Forest plot of significant variables identified in multivariate logistic regression analysis. Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio.

*Comparison of clinical data between model group and external validation group*

No significant differences were observed in general data between the model group and the external validation group ($P > 0.05$), indicating good consistency and comparability between the two cohorts, as shown in **Table 4**.

*Nomogram and model evaluation for predicting recent MACE risk in elderly HF patients*

A nomogram was constructed based on multivariate logistic regression analysis to predict the short-term risk of MACE in elderly HF patients. The nomogram incorporated three independent predictors: NLR, PLR, and MPVLR. Among these, MPVLR had the greatest weight in the scoring system, indicating its important role in risk prediction (**Figure 4**).

The ROC curve of the model group showed an AUC value of 0.912, indicating excellent discriminative ability for predicting recent MACE risk (**Figure 5A**). Calibration was assessed using the bootstrap method with 1,000 resamples. The gray line represents the model's predicted probability, while the black line indicates the actual observed outcomes. The calibration curve demonstrated a high degree of agreement between predicted and observed values (**Figure 5B**). The goodness of fit test showed a *P* value of 0.179, indicating good model fit. The average absolute error the calibration was 0.016, indicating high prediction accuracy.

The external validation group also showed good discriminative performance, with an AUC value of 0.810 (**Figure 5C**), consistent with the results from the model group. The calibration curve again demonstrated good concordance between predicted and actual outcomes (**Figure 5D**). The goodness of fit test showed a *P* value of 0.391, indicating good fitting, and the average absolute error was 0.052, further verifying the model's predictive accuracy and reliability in an independent cohort.

## Discussion

Previous investigations [11, 12] have demonstrated that medications including β-blockers and angiotensin-converting enzyme inhibitors can significantly ameliorate ventricular remodeling and enhance cardiac function in HF

**Table 3.** Predictive value of NLR, PLR, MPVLR and their combination for recent MACE in elderly HF patients

| Index | AUC | Standard Error | 95% *CI* | *P* | Cut-off | Youden index | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|
| NLR | 0.774* | 0.048 | 0.681-0.851 | < 0.001 | > 2.848 | 0.349 | 72.50 | 71.43 |
| PLR | 0.806* | 0.043 | 0.716-0.877 | < 0.001 | > 147.714 | 0.473 | 77.50 | 69.84 |
| MPVLR | 0.673* | 0.058 | 0.574-0.762 | 0.003 | > 6.722 | 0.369 | 57.50 | 79.37 |
| Combined detection | 0.919 | 0.028 | 0.864-0.974 | < 0.001 | | 0.628 | 85.00 | 84.13 |

Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio. *$P < 0.05$, compared with combined detection.

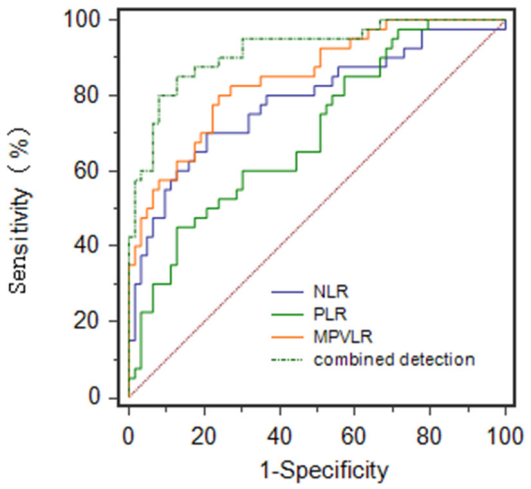


**Figure 3.** ROC curves illustrating the prognostic value of NLR, PLR, and MPVLR for recent MACE in elderly HF patients. Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio; MACE: Major adverse cardiovascular events; HF: Heart failure.

patients. Nevertheless, a considerable proportion of patients still develop MACE. The underlying mechanisms of MACE remain incompletely elucidated. Current evidence suggests that MACE is driven by complex interplay of multiple pathophysiological processes, encompassing activation of inflammatory cascades, dysregulation of the neuroendocrine system, heightened programmed cell death, and alterations in hemodynamic parameters [13]. In clinical practice, risk assessment for MACE in HF patients primarily relies on echocardiographic parameters and symptom-based assessments. However, these approaches are associated with notable limitations. Echocardiographic measurements are subject to operator variability, while symptom-based evaluations are often subjective and influenced by external factors [14]. Inflammation has been implicated in promoting myocardial cell apoptosis and fibrosis, which contributes to myocardial remodeling, HF progression, and elevated risk of MACE [15, 16]. This study analyzed the associations between NLR, PLR, and MPVLR levels with recent MACE occurrence, and evaluated their prognostic significance. The findings offer novel insights and evidence for clinical assessment of disease conditions.

NLR is a key indicator of systemic inflammation. Under physiological homeostasis, neutrophil and lymphocyte counts remain relatively stable. However, upon the onset of an inflammatory response, a surge in neutrophil production coupled with a concurrent decline in lymphocytes leads to an elevation in NLR [17]. Platelets, upon activation, release a plethora of inflammatory mediators, including platelet-derived growth factor and transforming growth factor-β. These mediators recruit and activate immune cells to amplify the inflammatory cascade [18]. Elevated PLR levels may reflect a persistent inflammatory response and platelet activation, thus promoting cardiac remodeling and deterioration of cardiac function [19]. An increase in MPV is recognized as a marker of enhanced platelet activation, associated with greater adhesion, aggregation, and secretion capacity [20]. MPVLR is an emerging biomarker that integrates platelet activation and systemic inflammatory status, offering prognostic value in thromboinflammatory conditions [21].

The results of this study showed that the age of the MACE group was older than that of the non-MACE group, along with significantly elevated levels of NLR, PLR, and MPVLR compared to the non-MACE group. The analysis suggests that age-related structural and functional cardiac changes, such as myocardial cell atrophy

**Table 4.** Comparison of baseline characteristics between the model group and external validation group [($\bar{x}$ ± s), *n* (%)]

| Variable | Model Group (*n* = 103) | Validation group (*n* = 74) | $\chi^2/t$ | *P* |
|---|---|---|---|---|
| Gender (Male/Female) | 49/54 | 32/42 | 0.325 | 0.568 |
| Age (years) | 71.70±11.26 | 74.58±9.41 | 1.795 | 0.074 |
| Body Mass Index (kg/m$^2$) | 22.73±2.36 | 22.42±2.17 | 0.891 | 0.374 |
| Educational attainment | | | 0.331 | 0.565 |
| High school and below | 92 (89.32) | 64 (86.49) | | |
| College and above | 11 (10.68) | 10 (13.51) | | |
| Place of residence | | | 0.298 | 0.585 |
| Urban | 83 (80.58) | 62 (83.78) | | |
| Rural | 20 (19.42) | 12 (16.22) | | |
| NYHA classification | | | 0.292 | 0.589 |
| Level III | 64 (62.13) | 43 (58.11) | | |
| Level IV | 39 (37.86) | 31 (41.89) | | |
| Left ventricular ejection fraction (%) | 55.76±4.79 | 55.30±4.51 | 0.646 | 0.519 |
| Left ventricular end diastolic diameter (mm) | 60.31±5.63 | 60.48±5.52 | 0.199 | 0.842 |
| Left ventricular end systolic diameter (mm) | 46.94±5.19 | 46.62±5.04 | 0.409 | 0.683 |
| History of hypertension | 70 (67.96) | 52 (70.27) | 0.107 | 0.7434 |
| History of hyperlipidemia | 44 (42.72) | 28 (37.84) | 0.425 | 0.514 |
| History of diabetes | 63 (61.16) | 41 (55.41) | 0.598 | 0.443 |
| Smoking history | 65 (63.11) | 42 (56.76) | 0.726 | 0.394 |
| Alcohol consumption history | 30 (29.13) | 18 (24.32) | 0.502 | 0.478 |
| Systolic pressure (mmHg) | 137.26±10.15 | 136.42±10.19 | 0.542 | 0.588 |
| Diastolic pressure (mmHg) | 90.02±9.31 | 88.52±9.36 | 1.055 | 0293 |
| Heart rate (beats/min) | 79.06±8.09 | 79.19±8.13 | 0.105 | 0.916 |
| Total cholesterol (mmol/L) | 4.65±0.76 | 4.54±0.66 | 1.003 | 0.317 |
| Triglyceride (mmol/L) | 1.25±0.23 | 1.24±0.25 | 0.275 | 0.784 |
| Hemoglobin (g/L) | 121.73±9.50 | 122.42±9.63 | 0.474 | 0.636 |
| Blood potassium (mmol/L) | 3.36±0.73 | 3.31±0.72 | 0.452 | 0.652 |
| Blood sodium (mmol/L) | 135.83±5.44 | 136.43±5.58 | 0.716 | 0.475 |
| Blood calcium (mmol/L) | 2.58±0.19 | 2.63±0.18 | 1.765 | 0.079 |
| Blood phosphorus (mmol/L) | 1.37±0.15 | 1.35±0.17 | 0.827 | 0.409 |
| BNP (ng/L) | 460.59±18.93 | 459.32±18.67 | 0.443 | 0.658 |
| NLR | 2.83±0.75 | 2.71±0.69 | 4.085 | 0.279 |
| PLR | 146.83±22.87 | 145.37±20.46 | 0.437 | 0.662 |
| MPVLR | 6.12±1.46 | 6.09±1.36 | 0.139 | 0.890 |

Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio.

and fibrosis, reduce cardiac reserve and increase vulnerability to adverse events. Chronic hyperglycemia in diabetic patients can damage endothelial cells, accelerate the progression of atherosclerosis, and promote plaque instability. It also induces myocardial metabolic disturbances, diminishing the myocardium's tolerance to ischemia and hypoxia, thereby increasing the incidence of MACE. Heart failure induces a chronic inflammatory and hypercoagulable state, leading to impaired cardiac pumping function and insufficient perfusion of tissues and organs. This activates the renin-angiotensin-aldosterone system and the sympathetic nervous system, promoting the release of pro-inflammatory cytokines such as IL-6. Neutrophils surge under the chemotactic influence of these cytokines, while lymphocytes decrease, resulting in elevated NLR. Persistent inflammation stimulates megakaryo-

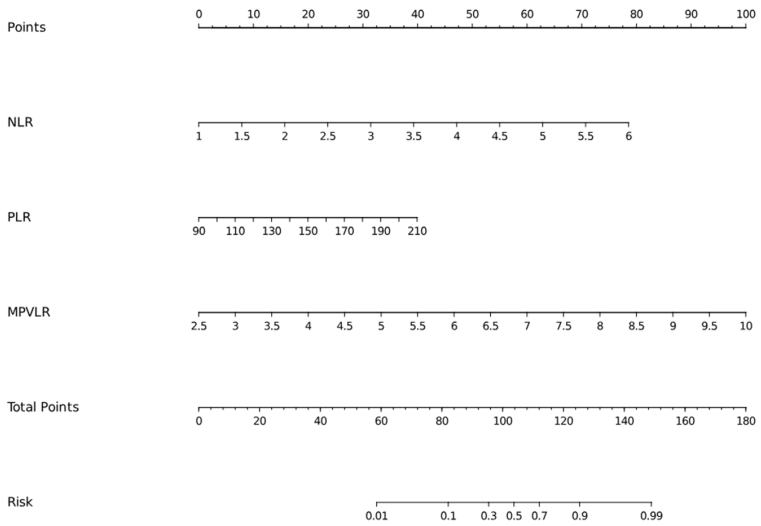


**Figure 4.** Nomogram for predicting the risk of recent MACE in elderly HF patients based on logistic regression analysis. Note: NLR: neutrophil to lymphocyte ratio; PLR: ratio of platelets to lymphocytes; MPVLR: Mean platelet volume to lymphocyte ratio; MACE: Major adverse cardiovascular events; HF: Heart failure.

cyte proliferation in the bone marrow, enhancing platelet production and activation. Activated platelets further amplify inflammation through cytokine release, contributing to elevated PLR. Inflammation and neuroendocrine activation promote the release of larger and newly generated platelets from the bone marrow, which have stronger adhesion and aggregation abilities, making them more prone to thrombosis. The decrease in lymphocytes further weakens the body's immune defense, and the level of MPVLR increases. Gao et al. [22] proposed that NLR and PLR levels were higher in patients with cardiovascular disease complicated with MACE than those without MACE, suggesting that NLR and PLR can be used as potential indicators to assess the risk of MACE. Li et al. [23] reported that patients with higher PLR levels have a higher risk of MACE and recommended its use in identifying high-risk individuals due to its simplicity and accessibility. Similarly, Yang et al. [24] observed a positive association between elevated NLR and MACE incidence in HF patients. The above results are similar to those of this study.

Mechanistically, MACE- related deterioration in cardiac function triggers a systemic stress responses, elevating pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines promote neutrophil proliferation and lymphocyte suppression, increasing NLR. The inflammatory microenvironment activates the PI3K-AKT signaling pathway in bone marrow megakaryocytes, accelerating platelet production. Expression of surface molecules such as P-selectin on activated platelets facilitates further immune cell recruitment, forming a vicious cycle of inflammation and platelet activation. Inflammatory conditions additionally shift hematopoietic stem cell differentiation toward the megakaryocytic lineage, promoting the release of more newly formed, larger, and more active platelets into the bloodstream. Combined with lymphocyte immune suppression, this leads to an increase in MPVLR levels. The changes in the levels of NLR, PLR, and MPVLR jointly reflect the inflammation and coagulation status of the body, suggesting that they can serve as potential indicators for evaluating the risk of MACE.

Multivariate regression analysis identified NLR, PLR and MPVLR as risk factors for recent MACE in elderly HF patients. Further ROC curve analysis showed that the AUC of the combined detection of NLR, PLR and MPVLR for recent MACE in elderly HF patients was higher than that of any single detection, indicating superior discriminatory ability. An elevated NLR reflects enhanced systemic inflammation, in which neutrophils release reactive oxygen species and proteases that directly impair vascular endothelial function and promote the instability of atherosclerotic plaques. Concurrent lymphopenia compromises anti-inflammatory and immune regulatory ability, facilitating myocardial remodeling and microcirculation dysfunction, thereby increasing MACE risk. Similarly, a high PLR reflects the synergistic effect of platelet activation and inflammatory response. Enhanced platelet aggregation contributes to a prothrombotic state, while reduced lymphocyte levels further weaken immune regulation, creating a vicious cycle of thrombosis and inflammation, ultimately contributing to MACE. Elevated MPV suggests a higher platelet activi-

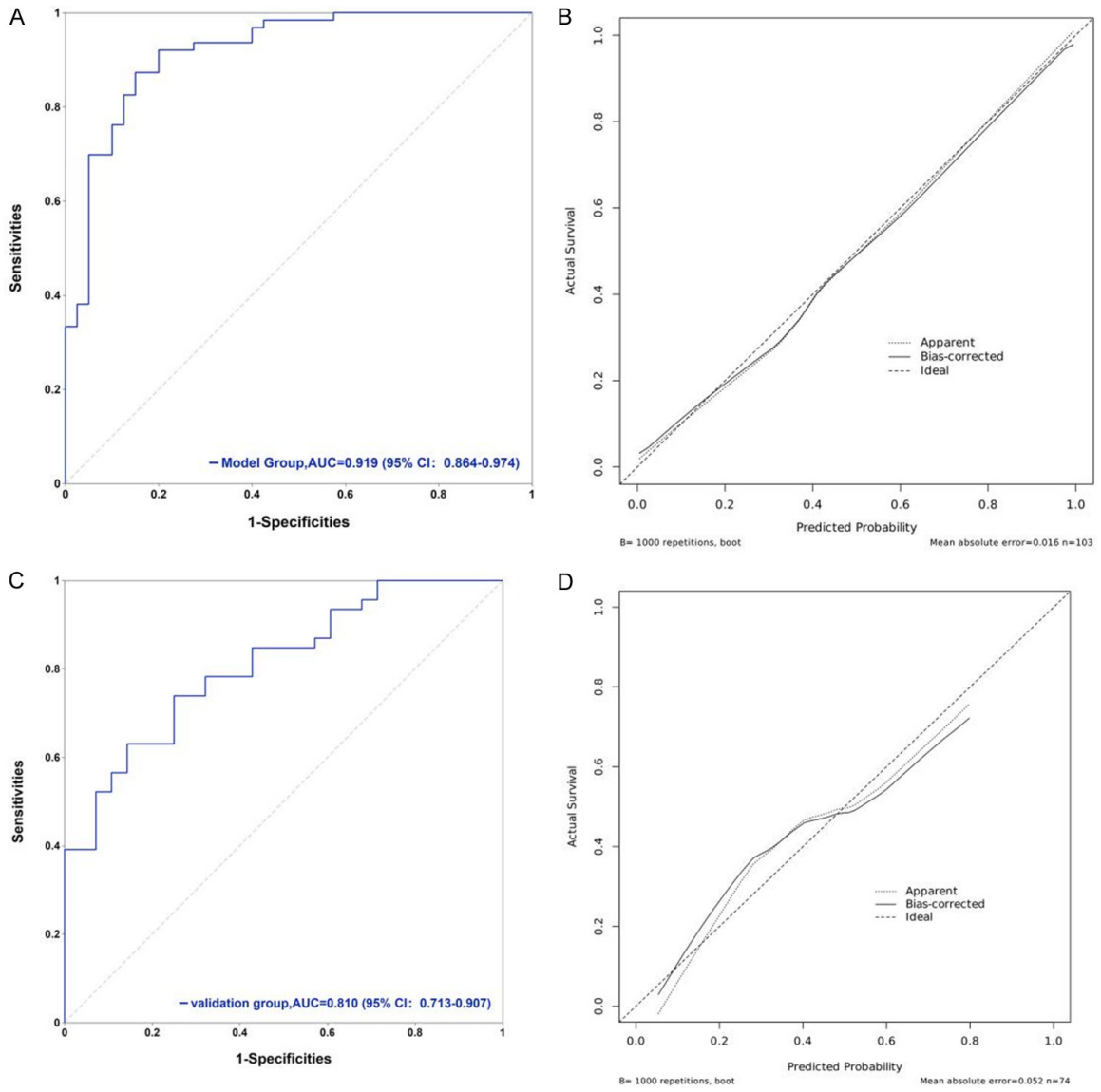


**Figure 5.** ROC curves and calibration curves for the model group and validation group. Note: (A) ROC curve of model group; (B) Calibration curve of model group; (C) ROC curve of the external validation group; (D) Calibration curve of the external validation group.

ty, and the associated release of pro-inflammatory mediators such as P-selectin aggravates endothelial injury and promotes plaque rupture. The reduction in lymphocytes aggravates the immune imbalance and increases the risk of MACE. Together, the simultaneous elevation of NLR, PLR, and MPVLR reflects a pathological milieu characterized by inflammation, thrombosis, and immune dysregulation, which collectively drives myocardial ischemia, thrombosis, and heart failure progression. Compared with a single-index analysis, their combined detection demonstrated higher accuracy. Wang et al. [25] reported that PLR is independently associated with MACE. Liu et al. [26] found that NLR can serve as an effective indicator for predicting MACE in elderly HF patients, but its predictive power is limited when detected alone. Similarly, Angkananard et al. [27] proposed that the combined prediction of NLR and MPVLR yielded an AUC of 0.77 for predicting MACE, which was lower than their combined detection. This suggests that NLR and MPVLR can be combined with PLR as an effective evaluation indicator for MACE. Compared with these prior findings, this study elucidates the mechanistic relevance of

inflammation-coagulation-immune interaction: elevated NLR reflects neutrophil damage and immune imbalance, an increase in PLR reflects the synergy between platelet coagulation and inflammation, and an increase in MPVLR indicates high platelet activity that disrupts plaque stability. The combined detection of multiple indicators can simultaneously reflect multidimensional pathological features such as inflammation infiltration, thrombosis, and immune disorders, providing a reliable basis for evaluating the risk of MACE.

A nomogram-based predictive model for MACE was developed based on NLR, PLR, and MPVLR, and achieved an AUC of 0.919, indicating excellent predictive performance. The external validation group further confirmed its high discrimination. The consistency of predictive factors between the external validation group and the model group indicates that the model can be used for different patient populations, providing strong support for its clinical application. In clinical practice, routine assessment of NLR, PLR and MPVLR levels in elderly HF patients can facilitate early identification of those at high risk for MACE. For patients with elevated markers, treatment regimens should be promptly optimized, incorporating anti-inflammatory, antiplatelet, and other supportive therapies. Intensified monitoring and personalized intervention strategies - including closer follow-up and comprehensive risk management - may effectively reduce MACE incidence and improve prognosis.

Still, there are some limitations in this study. First, the sample size of this study is relatively small, which may affect the generalizability of the findings. Second, the short follow-up time precluded analysis of long-term prognostic outcomes. Additionally, the model did not incorporate other potentially relevant variables (e.g., biomarkers, imaging parameters, socioeconomic factors) that might influence prognosis. Future studies should include larger, multi-center cohorts with extended follow-up durations and expanded multivariate analyses to further validate the diagnostic and prognostic utility of NLR, PLR, and MPVLR in elderly HF patients.

In summary, NLR, PLR, MPVLR are closely associated with the occurrence of recent MACE in elderly HF patients. The combined detection of these three biomarkers demonstrates high predictive value and can effectively aid in the early identification of high-risk individuals.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Zijuan Ren, Department of Cardiology, Suzhou Municipal Hospital of Anhui Province, Suzhou 234000, Anhui, China. E-mail: renzijuan137@163.com

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