Research Square

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Prognostic value of neutrophil-to-lymphocyte ratio combined with platelet-to-lymphocyte ratio, serum creatinine and NT-proBNP in HFpEF patients with qi deficiency and blood stasis syndrome

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Research Article

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Abstract

Objective

To evaluate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), serum creatinine and N-terminal pro-B-type natriuretic peptide (NT-proBNP), alone and in combination, in patients with heart failure with preserved ejection fraction (HFpEF) and qi deficiency and blood stasis syndrome.

Methods

This observational study included 154 patients with HFpEF and qi deficiency and blood stasis syndrome who were admitted between January 2023 and January 2025. Patients were classified into a MACE group (n = 51) and a non-MACE group (n = 103) according to whether major adverse cardiovascular events (MACE), defined as cardiovascular death, readmission for heart failure or acute myocardial infarction, occurred during 1 year of follow-up. Baseline clinical characteristics and laboratory indicators were compared between groups. Binary logistic regression was used to identify prognostic factors, and receiver operating characteristic (ROC) curve analysis was used to assess predictive performance.

Results

During follow-up, 51 of 154 patients developed MACE, corresponding to an incidence of 33.1%. The MACE group had higher traditional Chinese medicine syndrome scores, serum creatinine, NT-proBNP, NLR and PLR than the non-MACE group. In multivariable logistic regression, NLR was independently associated with MACE (OR, 1.322; 95% CI, 1.141–1.532; P < 0.001). The combined model incorporating NLR, PLR, serum creatinine and NT-proBNP showed better discrimination than any single indicator (AUC, 0.799; 95% CI, 0.701–0.898; P < 0.001), with a sensitivity of 0.719 and a specificity of 0.876 at the optimal cut-off.

Conclusion

NLR is an independent prognostic indicator for MACE in patients with HFpEF and qi deficiency and blood stasis syndrome. A combined model based on NLR, PLR, serum creatinine and NT-proBNP may improve early identification of high-risk patients and support individualized integrated Chinese and Western medical management.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all heart failure cases. Its prevalence continues to increase with population ageing, and its prognosis remains poor, with

a 1-year readmission rate of approximately 30–40% [1–2]. Chronic heart failure represents the terminal stage of many cardiovascular diseases and is a major contributor to cardiovascular mortality [1–2].

In traditional Chinese medicine (TCM), the core pathogenesis of HFpEF is often interpreted as qi deficiency and blood stasis. Qi deficiency weakens the driving force of circulation, whereas blood stasis obstructs the vessels and collaterals. These processes may interact and aggravate cardiac dysfunction [3]. Current prognostic assessment in HFpEF still lacks sufficiently specific indicators. Conventional biomarkers, including BNP and NT-proBNP, are affected by age, renal function and other clinical factors [4], highlighting the need for additional prognostic markers.

The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are accessible indicators of inflammation and immune imbalance. Both have been associated with adverse outcomes in cardiovascular diseases, including coronary heart disease and heart failure [5–6]. Elevated values may reflect intensified inflammatory activity, which can contribute to HFpEF progression through myocardial fibrosis, oxidative stress and endothelial dysfunction [7].

Identifying factors associated with MACE in patients with HFpEF and constructing a clinically usable prediction model may help clinicians stratify risk, intervene earlier and reduce adverse outcomes. Evidence remains limited regarding the combined prognostic value of NLR, PLR, serum creatinine and NT-proBNP in patients with HFpEF and qi deficiency and blood stasis syndrome. Therefore, this study analyzed the association between these indicators and MACE in 154 patients, aiming to provide a basis for prognostic assessment that integrates TCM syndrome differentiation with Western medical biomarkers.

2. Materials and methods

2.1 Study population

A total of 154 patients with HFpEF and qi deficiency and blood stasis syndrome who were hospitalized in the Department of Cardiology of our hospital, including the coronary heart disease intensive care unit, from January 2023 to January 2025 were enrolled.

The inclusion criteria were as follows: (1) fulfillment of Western medical diagnostic criteria for HFpEF [8], defined as left ventricular ejection fraction (LVEF) > = 50%, symptoms or signs of heart failure, and evidence of left ventricular diastolic dysfunction; (2) fulfillment of the TCM diagnostic criteria for qi deficiency and blood stasis syndrome [9], including main symptoms such as shortness of breath, fatigue, chest tightness, chest pain and dark-purple lips, and secondary symptoms such as palpitations, a dark-purple tongue or ecchymosis, and a thready or intermittent pulse, with at least two main symptoms and two secondary symptoms present; (3) age 45–80 years; and (4) informed consent from the patient and family members.

The exclusion criteria were as follows: (1) heart failure with reduced ejection fraction or mildly reduced ejection fraction; (2) acute myocardial infarction, severe arrhythmia such as atrial fibrillation with rapid ventricular response, or congenital heart disease; (3) malignant tumor, hematologic disease or autoimmune disease; (4) severe hepatic or renal dysfunction; and (5) infection or surgery within the previous month.

2.2 Study methods

Patients were grouped according to the occurrence of MACE within 1 year of follow-up. MACE included cardiovascular death, readmission for heart failure and acute myocardial infarction, as defined with reference to contemporary heart failure guidelines [10]. The MACE group included patients who experienced cardiovascular death, heart failure readmission requiring hospitalization because of worsening heart failure symptoms, or acute myocardial infarction. The non-MACE group included patients without these events.

Demographic characteristics, clinical data and laboratory indicators were collected. Laboratory tests included routine blood parameters, including neutrophil count, lymphocyte count and platelet count, as well as biochemical indicators including creatinine, AST, ALT, LDL-C and NT-proBNP. Within 24 h after admission, 4–5 mL of venous blood was collected from each patient. Lymphocyte, platelet and neutrophil counts were measured using a hematology analyzer. NLR was calculated as neutrophil count divided by lymphocyte count, and PLR was calculated as platelet count divided by lymphocyte count.

All patients were followed for 1 year, with follow-up performed once per month. MACE during follow-up, including heart failure-related events, cardiogenic death and severe arrhythmia, was recorded. Patients were classified into the event group or non-event group according to whether MACE occurred during follow-up.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 27.0. Normally distributed continuous variables are expressed as mean +/- standard deviation and were compared using the t-test. Non-normally distributed variables are expressed as median values and were compared using the Wilcoxon rank-sum test. Categorical variables are expressed as n (%) and were compared using the chi-square test. Binary logistic regression was used to analyze prognostic risk factors. The area under the ROC curve (AUC) was calculated to evaluate the predictive performance of each indicator and the combined model for MACE. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1 Follow-up outcomes and baseline comparison

Among the 154 patients, 51 developed MACE during follow-up, yielding an incidence of 33.1%. The remaining 103 patients (66.9%) did not develop MACE. Compared with the non-MACE group, the MACE

group had higher TCM syndrome scores, serum creatinine, NT-proBNP, NLR and PLR. The comparison of baseline clinical data is shown in Table 1.

Table 1
Comparison of clinical characteristics between the MACE and non-MACE groups

Clinical characteristics	MACE group (n = 51)	Non-MACE group (n = 103)	t/chi-square	P value
Sex (male/female)	29/22	56/47		
Age (years)	72.25 +/- 8.22	72.40 +/- 10.04	t = -0.088	0.930
TCM syndrome score (points)	23.47 +/- 4.28	18.62 +/- 3.94	t = 6.735	< 0.001
History of diabetes, n (%)	31 (60.78)	65 (63.11)	chi-square = 0.023	0.880
Systolic blood pressure (mmHg)	131.96 +/- 29.05	132.86 +/- 23.95	t = -0.203	0.840
Diastolic blood pressure (mmHg)	76.96 +/- 14.92	75.52 +/- 16.40	t = 0.530	0.597
LVEF (%)	54.76 +/- 13.29	51.21 +/- 13.53	t = 1.540	0.126
White blood cell count (x10^9/L)	7.46 +/- 2.81	7.21 +/- 2.54	t = 0.552	0.582
Creatinine (umol/L)	102.35 +/- 34.62	87.61 +/- 28.14	t = 2.824	0.005
AST (U/L)	81.21 +/- 403.99	24.27 +/- 28.05	t = 1.005	0.320
ALT (U/L)	53.30 +/- 255.19	17.54 +/- 11.49	t = 1.000	0.322
LDL-C (mmol/L)	1.87 +/- 0.82	1.89 +/- 0.92	t = -0.150	0.881
NT-proBNP (pg/mL)	5246.83 +/- 2135.27	3612.45 +/- 1864.72	t = 4.827	< 0.001
NLR	4.86 +/- 2.13	3.72 +/- 1.85	t = 3.326	0.001
PLR	204.72 +/- 46.38	179.45 +/- 41.26	t = 3.431	0.001

3.2 Multivariable logistic regression analysis

Binary logistic regression was performed using MACE within 1 year as the dependent variable (no = 0, yes = 1). NLR, PLR, serum creatinine and NT-proBNP were entered as continuous independent variables. The results showed that NLR was independently associated with MACE (P < 0.001), whereas PLR, serum creatinine and NT-proBNP were not statistically significant in this model (Table 2).

Table 2
Binary logistic regression analysis for MACE prediction

Variable	Regression coefficient	Standard error	z value	Wald chi-square	P value	OR	95% CI for OR
NLR	0.279	0.075	3.709	13.753	< 0.001	1.322	1.141–1.532
PLR	0.001	0.002	0.235	0.055	0.814	1.001	0.996–1.005
Creatinine	0.001	0.004	0.161	0.026	0.872	1.001	0.992–1.009
NT-proBNP	0.000	0.000	1.795	3.221	0.073	1.000	1.000–1.000
Intercept	-3.461	0.750	-4.612	21.271	< 0.001	0.031	0.007–0.137

A P value < 0.05 was considered statistically significant.

3.3 ROC curve analysis

ROC curve analysis showed that the combined model based on NLR, PLR, serum creatinine and NT-proBNP had the best predictive performance for MACE within 1 year in patients with HFpEF and qi deficiency and blood stasis syndrome. The AUC of the combined model was 0.799 (95% CI, 0.701–0.898; P < 0.001), which was higher than the AUCs of NLR, PLR, serum creatinine and NT-proBNP alone (Table 3).

Table 3
ROC curve analysis of individual indicators and the combined model

Variable	AUC	95% confidence interval	P value	Optimal cut-off	Sensitivity	Specificity	Youden index
Combined model	0.799	0.701–0.898	< 0.001*	0.3089	0.719	0.876	0.595
NLR	0.769	0.665–0.872	< 0.001*	7.6000	0.562	0.897	0.459
PLR	0.610	0.493–0.726	0.064	198.4200	0.594	0.680	0.274
Creatinine	0.585	0.468–0.702	0.154	78.5000	0.875	0.340	0.215
NT-proBNP	0.648	0.533–0.763	0.012*	5180.0000	0.469	0.773	0.242

4. Discussion

This study evaluated the prognostic value of inflammatory, renal and cardiac biomarkers in patients with HFpEF and qi deficiency and blood stasis syndrome. After excluding extreme outliers beyond 3 standard deviations, forward stepwise binary logistic regression and ROC curve analyses were performed. The combined model incorporating NLR, PLR, serum creatinine and NT-proBNP showed good discrimination for MACE, with an AUC of 0.799 and a 95% CI of 0.701–0.898. At the optimal cut-off value of 0.3089, the sensitivity was 0.719, the specificity was 0.876 and the Youden index was 0.595, indicating clinically meaningful predictive performance.

Among the individual indicators, NLR had the strongest predictive performance, with an AUC of 0.769 and an optimal cut-off value of 7.6. NT-proBNP also showed discriminatory ability, with an AUC of 0.648. In contrast, the individual predictive values of PLR and serum creatinine were relatively limited, with AUCs of 0.610 and 0.585, respectively. Overall, the combined model outperformed each single indicator, suggesting that integrated assessment across inflammatory, cardiac and renal dimensions may better capture the pathophysiological heterogeneity of HFpEF.

The NLR level was significantly higher in the MACE group than in the non-MACE group, and elevated NLR was independently associated with MACE. This finding is consistent with previous evidence linking NLR to adverse cardiovascular outcomes [11–13]. NLR reflects the balance between neutrophil-mediated inflammation and lymphocyte-mediated immune regulation [14]. In HFpEF, chronic inflammation may promote myocardial fibrosis and cardiomyocyte apoptosis through pathways such as NF-kappaB activation. Neutrophils may also contribute to extracellular matrix remodeling and microvascular dysfunction by releasing proteases, reactive oxygen species and inflammatory mediators, thereby worsening ventricular diastolic dysfunction.

From a TCM perspective, qi deficiency and blood stasis syndrome can be interpreted as a pathological state in which deficiency of qi is the root and blood stasis is the manifestation. Qi deficiency weakens defense and regulation, which may increase susceptibility to pathogenic excess and inflammatory responses. Blood stasis impairs the circulation of qi and blood; persistent stasis may generate heat and aggravate inflammatory injury. In this context, elevated NLR may represent an objective biological correlate of the pathological chain of qi deficiency, blood stasis and inflammation. The combined model may therefore help connect TCM syndrome differentiation with measurable inflammatory, cardiac and renal biomarkers.

The clinical value of the combined model lies in its ability to identify patients who appear compensated but have a high inflammatory burden or impaired organ function. Such patients may benefit from earlier risk stratification and targeted integrated management. Potential interventions may include closer follow-up, optimization of heart failure therapy, anti-inflammatory or immune-regulatory strategies when clinically appropriate, and TCM-based treatment principles such as tonifying qi and activating blood circulation.

5. Clinical significance and limitations

This prospective observational study found that elevated NLR was significantly associated with the risk of MACE within 1 year in patients with HFpEF and qi deficiency and blood stasis syndrome. By combining NT-proBNP, serum creatinine, NLR and PLR, the model integrates markers of cardiac functional burden, renal function and inflammatory immune balance. This multidimensional approach may support early identification of high-risk patients and provide a basis for individualized integrated Chinese and Western medical intervention.

Several limitations should be acknowledged. First, this was a single-center observational study with a limited sample size, which may introduce selection bias. Second, although PLR differed between groups in univariate comparison, it was not independently associated with MACE in multivariable regression; this finding requires validation in larger multicenter cohorts. Third, dynamic changes in NLR and PLR were not monitored, and their time-dependent prognostic value remains uncertain. Finally, although TCM syndrome diagnosis followed established criteria, some subjectivity is unavoidable; future studies should incorporate more objective quantitative indicators for syndrome assessment.

6. Conclusion

NLR is an independent risk factor for MACE in patients with HFpEF and qi deficiency and blood stasis syndrome. A combined model incorporating NLR, PLR, NT-proBNP and serum creatinine improves the prediction of MACE compared with single indicators and may help clinicians identify high-risk patients early, guide individualized treatment and improve prognosis.

Abbreviations

AUC
Area under the receiver operating characteristic curve
ALT
Alanine transaminase
AST
Aspartate transaminase
CI
Confidence interval
HFpEF
Heart failure with preserved ejection fraction
LDL-C
Low-density lipoprotein cholesterol
LVEF
Left ventricular ejection fraction
MACE
Major adverse cardiovascular events
NLR

neutrophil-to-lymphocyte ratio
NT-proBNP
N-terminal pro-B-type natriuretic peptide
OR
Odds ratio
PLR
Platelet-to-lymphocyte ratio
ROC
Receiver operating characteristic
TCM
Traditional Chinese medicine

Declarations

1.Human Ethics and Consent to Participate declarations : This multicenter clinical research project titled Study on Innovative Pathogenesis and Clinical Syndrome Differentiation Scheme of Coronary Heart Disease Complicated with Heart Failure was reviewed and approved by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (Ethics Review File No. 2023DZMEC-046-02).

2.Consent for Publication: Not Applicable. No identifiable photographs, distinguishable clinical records, personal demographic particulars or other participant-related sensitive content that could undermine participant anonymity are included within this manuscript. Therefore, dedicated written publication consent from study participants is not demanded.

3.Written informed consent was individually acquired from every enrolled participant prior to study enrollment. All participants were fully briefed on the study objectives, experimental workflows, foreseeable risks, potential benefits and unconditional right to withdraw from the research at any stage without penalty, prior to signing the informed consent documents. All consent archives are properly preserved by the research team.

4.All relevant data are contained within the paper and its Supporting Information files.

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Data Availability

All relevant data are contained within the paper and its Supporting Information files.

References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology, developed with the special contribution of the Heart Failure Association of the ESC. Eur J Heart Fail. 2016;18(8):891–975.

2. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6):e137–61.
3. Chinese Association of Chinese Medicine. Expert consensus on diagnosis and treatment of chronic heart failure with traditional Chinese medicine. J Tradit Chin Med. 2014;55(14):1258–60.
4. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005;95(8):948–54.
5. Franchi F, Virdis A, Ghiadoni L, et al. Neutrophil-to-lymphocyte ratio: a marker of immune system dysfunction in hypertension. J Hypertens. 2018;36(8):1607–15.
6. Tanriverdi H, Sezgin A, Cicek M, et al. The relationship between neutrophil-to-lymphocyte ratio and mortality in patients with heart failure. Int J Cardiol. 2013;167(5):2166–71.
7. Abbate A, Biondi-Zoccai GG, Boemi M, et al. Inflammation and heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(15):1845–60.
8. Heart Failure Group of Cardiovascular Disease Branch, Chinese Medical Association; Heart Failure Professional Committee of Chinese Medical Doctor Association. Editorial Committee of Chinese Journal of Cardiovascular Diseases. Chinese Guidelines for Diagnosis and Treatment of Heart Failure 2018. Chin J Cardiovasc Dis. 2018;46(10):760–89.
9. National Administration of Traditional Chinese Medicine. Criteria for Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine. Nanjing: Nanjing University; 1994. pp. 77–8.
10. Colucci WS, Elkayam U, Horton DP, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–1032.
11. Mosca M, Nigro MC, Pagani R, et al. Neutrophil-to-lymphocyte ratio (NLR) in NSCLC, gastrointestinal, and other solid tumors: immunotherapy and beyond. Biomolecules. 2023;13(12):1803.
12. de Jager W, Hillege HL, et al. Inflammation in heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2008;10(10):1008–14.
13. Kado J, Otsuji Y, Yasunaga H, et al. Neutrophil extracellular traps in heart failure: a link between inflammation, cardiac remodeling, and clinical outcome. Circ Res. 2017;120(11):1785–96.
14. Li Feixia T, Gang Y, Ting, et al. Clinical value of serum CA125 and HE4 combined with PLR, NLR and MLR in the diagnosis of epithelial ovarian cancer. Shandong Med. 2020;60(10):70–2.
15. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. Circulation. 2004;109(24):2967–73.
16. Tudurachi BS, Anghel L, Tudurachi A, et al. Assessment of inflammatory hematological ratios (NLR, PLR, MLR, LMR and monocyte/HDL-cholesterol ratio) in acute myocardial infarction and particularities in young patients. Int J Mol Sci. 2023;24(18):14378.

17. Borlaug BA. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment: a concise review. Mayo Clin Proc. 2014;89(12):1658–71.
18. Zhou Zhongying. Internal Medicine of Traditional Chinese Medicine. Beijing: China Press of Traditional Chinese Medicine; 2003. pp. 136–42.
19. Zhang Boli W, Mianhua. Internal Medicine of Traditional Chinese Medicine. Beijing: People's Medical Publishing House; 2012. pp. 158–65.
20. Chen Keji S. Zaixiang. Practical Theory of Blood Stasis Syndrome. Beijing: People's Medical Publishing House; 1999. pp. 213–8.
21. Wei W. Clinical research progress of qi-tonifying and blood-activating methods in the treatment of chronic heart failure. Chin J Integr Traditional Western Med. 2016;36(9):1140–3.
22. Wang Qingren. Medical Forest Correction. Beijing: People's Medical Publishing House; 2005. pp. 32–5.