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Review Article

Prognostic value of the neutrophil to lymphocyte ratio for cardiovascular diseases: research progress

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Abstract: The neutrophil to lymphocyte ratio (NLR) is a simple, reliable, and easily accessible composite index that has garnered increasing attention in cardiovascular research. NLR is closely associated with the onset, progression, and prognosis of various cardiovascular diseases. This article reviews the etiological and prognostic roles of NLR in cardiovascular conditions such as coronary atherosclerotic heart disease, hypertension, arrhythmia, heart failure, and valvular heart disease. Studies have shown that NLR is involved in the pathophysiologic processes of these diseases and holds significant predictive value for their prognosis. Additionally, compared to other inflammatory markers, NLR offers advantages such as low cost, repeatability, and the ability to be measured at the community-level primary healthcare settings, thus providing new insight for prognostic prediction in conditions like coronary artery disease, arrhythmia, hypertension, heart failure, and valvular heart disease.

Keywords: NLR, cardiovascular diseases, prognosis, forecast, research progress

Introduction

Cardiovascular disease includes disorders of blood vessels or the heart such as coronary heart disease, heart failure, myocardial infarction, and arrhythmia [1]. With improved living standards and an aging population, epidemiological studies have shown rising morbidity and mortality rates associated with cardiovascular diseases, particularly among younger age groups. Cardiovascular diseases have become one of the most significant threats to global health and life expectancy [2, 3]. Despite advances in cardiovascular-related drugs and medical devices, the morbidity and mortality rates in China remain high, with no significant decline, and cardiovascular diseases continue to be the leading cause of death [4, 5]. Accurate risk assessment, risk stratification, and prognosis evaluation, particularly for high-risk cardiovascular patients, are essential for reducing prevalence, improving treatment efficacy, and lowering recurrence and mortality rates. These factors are critical for enhancing prevention and management strategies and are key to individualized diagnosis and treatment [6]. Therefore, identifying convenient and effective predictive indicators for cardiovascular disease prevention and control is of paramount importance. The reports on the prediction of cardiovascular disease prognosis by NLR are presented in **Table 1**, and a structural diagram is shown in **Figure 1**.

Previous studies have highlighted the significant roles of inflammation and oxidative stress in the pathogenesis of cardiovascular diseases, driving interest in inflammatory markers. Inflammatory markers such as C-reactive protein (CRP) [7], interleukin-6 (IL-6) [8], interleukin-8 (IL-8) [9], and tumor necrosis factor (TNF-α) [10] have been closely linked to the development and progression of these diseases. The neutrophil-to-lymphocyte ratio (NLR) is an emerging cardiovascular risk predictor that is easy to obtain, cost-effective, and clinically significant. It plays a crucial role in diagnosing and assessing the prognosis of various cardiovascular conditions, providing early predictive insight for effective disease management and enabling timely treatment [11, 12]. This study synthesizes and analyzes the predictive value of NLR for cardiovascular disease prognosis, offering new directions for its diagnosis and treatment.

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Table 1. Studies reporting NLR's prognostic value in cardiovascular disease

Study type	Classification of disease	Diseases and cases	NLR cutoff value	Prognostic factors	Research conclusion	Reference Number
Single-center retrospective analysis	Coronary heart disease	4110 patients with unstable angina pectoris	2.76	Cardiovascular related deaths	Diabetes, Lymphocytes, NLR, and SYNTAX Score as Predictors of Cardiovascular Death Due to Long-Term Cardiovascular Mortality in Patients With Unstable Angina Pectoris.	[16]
Forward-looking analysis	Coronary heart disease	Total 308 patients with NSTEMI and UAP	3.04	Cardiovascular deaths	NLR is an independent predictor of 3-year cardiovascular mortality in patients with NSTEMI and UAP.	[17]
Retrospective analysis	Coronary heart disease	40 STEMI, 38 NSTEMI, 37 UAP patients	--	Death	Troponin, NLR, and MLR predict death in high-risk ACS patients and are independent risk factors for predicting ACS prognosis.	[18]
Retrospective analysis	Coronary heart disease	Patients with coronary stent implantation	2.73	ISR	Preoperative high NLR is an independent predictor of stent restenosis in patients with stable and unstable angina pectoris.	[21]
Forward-looking analysis	Coronary heart disease	Patients with stable angina pectoris treated by PCI	--	ISR or MACE	NLRΔ is associated with the risk of ISR and MACE in patients.	[22]
Retrospective analysis	Hypertension	13,724 cases of hypertensive patients	2.0	All-cause or cardiovascular deaths	Elevated NLR is associated with increased risk of cardiovascular and all-cause mortality and independently predicts cardiovascular mortality outcomes in hypertensive patients.	[27]
Retrospective analysis	Hypertension	2136 patients with coronary heart disease combined with hypertension	2.65	All-cause and cardiovascular deaths	Elevated NLR is an independent prognostic predictor of all-cause and cardiovascular death in patients with coronary heart disease combined with hypertension.	[28]
Retrospective cohort analysis	Hypertension	883 patients with atrial fibrillation combined with heart failure	--	Recurrent atrial fibrillation after radiofrequency ablation	NLR is an independent predictor of recurrent atrial fibrillation after radiofrequency ablation	[34]
Retrospective single-center study	Heart failure	263 cases of NAVF patients	2.33	Late non-valvular recurrence of atrial fibrillation	Combined use of preoperative NLR, hs-CPR, and LAD predicts late nonvalvular recurrence of atrial fibrillation.	[35]
Retrospective analysis	Heart failure	454 patients with heart failure over 65 years old	--	Major cardiovascular events	The combination of GNRI, NLR and FT3 is effective in predicting major cardiovascular events in elderly patients with heart failure.	[40]
Forward-looking analysis	Heart failure	50 cases of CHF as observation group and 50 cases of non-CHF as control group	--	MACE	The combination of NT-proBNP, NLR effectively predicts the occurrence of MACE in elderly patients with chronic heart failure.	[41]
Retrospective study	Heart valve surgery	227 cases of RMVD	2.56	RMS	NLR assists in predicting the presence of mitral stenosis and its severity in patients with RMVD.	[45]
Retrospective analysis	Heart valve surgery	5075 patients with heart valve surgery	3.5	Heart failure or all-cause death 30d postoperatively	CRP and NLR are effective in predicting the occurrence of heart failure and death 30d postoperatively in patients undergoing heart valve surgery.	[46]

Note: STEMI indicates ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UAP: unstable angina; ACS: acute coronary syndrome; ISR: in-stent restenosis; MACE: major adverse cardiovascular event; NAVF: Non-valvular atrial fibrillation; GNRI: Geriatric nutritional risk index; FT3: Free triiodothyronine; CHF: Chronic heart failure in the elderly; NT-proBNP: N-terminal pro B-type natriuretic peptide; RMVD: Rheumatic valve disease; RMS: Rheumatic mitral stenosis; CRP: C-reactive protein.

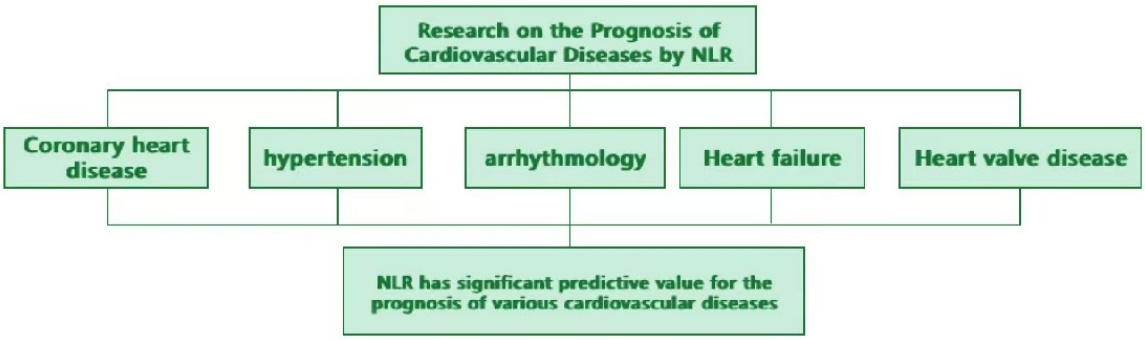

Figure 1. Research component diagram.

NLR for prognosis of coronary heart disease

Coronary heart disease (CHD) is characterized by myocardial ischemia, hypoxia, and necrosis due to coronary atherosclerosis, and includes conditions such as stable or unstable angina pectoris, myocardial infarction, and ischemic cardiomyopathy. CHD remains the most prevalent cardiovascular disease, with high incidence and mortality rates [13]. The pathogenesis of CHD is driven by atherosclerosis, a systemic, lipid-driven immune-inflammatory response [14]. Studies have shown that both the formation and progression of atherosclerotic plaques are closely associated with chronic inflammation [15].

A study by Sunbao et al. [16] analyzed the relationship between NLR and clinical prognosis in patients with unstable angina. This single-center retrospective study included 4,110 patients with unstable angina and followed them for 36 months. A significant positive correlation was found between NLR and the SYNTAX score. Furthermore, diabetes mellitus, lymphocyte count, and NLR were identified as predictors of long-term cardiovascular mortality in these patients. Kaplan-Meier analysis showed a higher incidence of cardiovascular-related deaths if NLR > 2.38. ROC analysis identified an NLR cutoff of 2.76 as predictive of death in patients with unstable angina (sensitivity 69.2%, specificity 64.8%).

Mehmet et al. [17] assessed the prognostic value of NLR in patients with non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). This prospective study included 308 patients, who were followed for up to three years. The patients were grouped based on their NLR values at admission. Kaplan-Meier survival analysis showed that the 3-year mortality rate in the high NLR group was 21.6% compared with 3% in the low NLR group ($P < 0.05$). The optimal NLR cutoff for predicting 3-year cardiovascular mortality in NSTEMI and UAP patients was determined to be 3.4 (ROC area under the curve = 0.86, 95% CI = 0.80-0.92), with a sensitivity of 79% and specificity of 71%. The study concluded that NLR is an independent predictor of 3-year cardiovascular mortality in these patients.

Bryan et al. [18] evaluated the predictive value of troponin, creatine kinase MB (CK-MB), NLR, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), basophil-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio in high-risk acute coronary syndrome (ACS) patients. The study included 40 patients with STEMI, 38 with NSTEMI, and 37 with UAP. The findings indicated that troponin, NLR, and MLR are independent predictors of mortality in high-risk ACS patients and have prognostic value in ACS.

With advances in medical technology, the use of coronary revascularization for treating coronary heart disease has increased. While coronary revascularization can rapidly open infarct-related coronary arteries, alleviate angina symptoms, and improve quality of life, postoperative complications such as in-stent restenosis (ISR), no-reflow, arrhythmias, and contrast-induced nephropathy remain common and significantly affect prognosis. NLR has been shown to predict the occurrence of complications following coronary revascularization [19, 20].

Osman et al. [21] investigated the role of inflammation in ISR and assessed the predictive value of NLR for ISR in patients who underwent coronary stent implantation. In this retrospec-

tive study, 624 patients with coronary stent implantation were classified into three groups based on their preoperative NLR: lowest, intermediate, and highest. The ISR rates were 10.1%, 29.8%, and 51.4%, respectively ($P < 0.05$). Multivariate logistic regression analysis identified smoking, diabetes, stent length, preoperative NLR, and C-reactive protein levels as independent predictors of ISR. ROC curve analysis showed that a preoperative NLR > 2.73 had 80% sensitivity and 75% specificity in predicting ISR.

Li et al. [22] conducted a study involving patients undergoing elective coronary angiography for stable angina pectoris, dividing them into two groups: chronic total occlusion (CTO) (160 cases) and non-CTO (160 cases). NLR values were measured at admission and after percutaneous coronary intervention (PCI), and changes in NLR (NLRΔ ≥ 0.5 or < 0.5) were analyzed. The results showed that white blood cell count, neutrophil count, and NLR were significantly higher in the CTO group compared to the non-CTO group. Multivariate analysis indicated that NLRΔ was associated with the risk of ISR and major adverse cardiovascular events (MACE). Additionally, NLR may serve as a predictor for CTO, and NLRΔ was closely linked to a poor clinical prognosis following PCI.

NLR as a predictor of prognosis in hypertension

Hypertension is a major risk factor for cardiovascular diseases, increasing the likelihood of cardiovascular events, and impairing the structure and function of vital organs [23, 24]. As one of the simplest inflammatory markers, NLR holds predictive value in the onset, progression, and prognosis of hypertension [25, 26].

Shaoqing et al. [27] analyzed data from 13,724 hypertensive patients who participated in the National Health and Nutrition Examination Survey from 2009 to 2018. The National Death Index (NDI) was used to determine the mortality status of participants. Based on the median NLR, participants were categorized into a high NLR group (> 2.0) and a low NLR group (≤ 2.0). With a median follow-up of 64 months, there were 1,619 total deaths, including 522 cardiovascular deaths. The study found that both all-cause mortality (HR: 1.47; 95% CI: 1.22-1.77) and cardiovascular mortality (HR: 2.09; 95% CI: 1.52-2.86) were significantly higher in the high NLR group. These findings demonstrate that elevated NLR is associated with an increased risk of both cardiovascular and all-cause mortality, making it an independent predictor of cardiovascular death in hypertensive patients.

Similarly, Songhong et al. [28] used data from the NDI for a study involving 2,136 participants from 2001 to 2018. During a median follow-up of 76 months, 801 deaths were recorded. The study revealed that, compared to the lower NLR group (NLR < 2.65), the higher NLR group (NLR > 2.65) had a significantly higher risk of cardiovascular death (HR: 1.58; 95% CI: 1.33-1.82) and all-cause death (HR: 1.46; 95% CI: 1.30-1.62) in based on the Cox proportional hazards model. Additionally, the study quantified the predictive performance for cardiovascular mortality using ROC curves, with areas under the curve of 0.67, 0.65, and 0.64 for predicting mortality risk at 3, 5, and 10 years, respectively. The study concluded that an elevated NLR in hypertensive patients with coronary heart disease is an independent predictor of both all-cause and cardiovascular mortality.

NLR as a predictor of prognosis in arrhythmia

Arrhythmia refers to abnormalities in the frequency, rhythm, origin, conduction velocity, or sequence of cardiac impulses. Atrial fibrillation (AF) is one of the most common types of cardiac arrhythmias, significantly increasing the risk of cerebral infarction, which can be life-threatening and can worsen patients' quality of life [29]. Pathologic studies have shown increased inflammatory cell infiltration in the atrial myocardium of patients with AF, suggesting that inflammation plays a role in the pathogenesis of AF [30, 31]. Several studies have indicated that the neutrophil-to-lymphocyte ratio (NLR) has predictive value for the diagnosis, treatment, and prognosis of AF [32, 33].

Duan et al. [34] conducted a retrospective cohort study involving 883 patients with AF complicated by heart failure who underwent radiofrequency ablation from January 2019 to June 2020. Patients were followed up at 3, 6, and 12 months postoperatively and categorized into a recurrence group (246 patients) and a non-recurrence group (637 patients). The study found that NLR was an independent risk factor for AF recurrence after radiofrequency ablation. ROC

curve analysis showed that the area under the curve (AUC) for NLR in predicting AF recurrence was 0.15, with a sensitivity of 55.61% and specificity of 84.54%.

Similarly, Ding et al. [35] conducted a retrospective study involving 263 patients with paroxysmal or persistent advanced nonvalvular atrial fibrillation (NAVF) who received their first radiofrequency ablation treatment between January 2017 and January 2019. Patients were categorized into a recurrence group (n = 70) and a non-recurrence group (n = 193). Multivariate analysis during the 12-month follow-up revealed that elevated NLR, high-sensitivity C-reactive protein (hs-CRP), and left atrial diameter (LAD) were independent predictors of AF recurrence. ROC curve analysis showed that the AUC for NLR and hs-CRP were 0.603 and 0.584, respectively, with cutoff values of 2.33 for NLR and 2.025 ng/L for hs-CRP. The study concluded that the combination of preoperative NLR, hs-CRP, and LAD can effectively predict the recurrence of late-stage non-valvular AF.

NLR as a predictor of prognosis in heart failure

Heart failure represents the terminal stage of various cardiovascular diseases. Literature reports indicate that patients with heart failure have a 4-year mortality rate exceeding 50%, and in severe cases, the 1-year mortality rate can reach 50% [36, 37]. Research on the pathogenesis of heart failure is still ongoing, with recent studies highlighting the critical role of inflammation in its onset and progression. The underlying mechanism involves pro-inflammatory cytokines that lead to left ventricular systolic dysfunction [38, 39].

Liu et al. [40] conducted a retrospective analysis of 454 elderly patients (aged 65 and above) with heart failure. The study followed the patients for 18 months, with MACEs as the endpoint, to analyze the predictive value of the geriatric nutritional risk index (GNRI), NLR, and free triiodothyronine (FT3) for MACEs. The study found that low GNRI, low FT3, and high NLR were associated with increased risk of MACEs. Moreover, the combination of GNRI, NLR, and FT3 improved the accuracy of predicting MACEs in elderly heart failure patients.

Li et al. [41] included 50 elderly patients with chronic heart failure and 50 non-CHF patients as the control group. The results showed that N-terminal precursor B-type natriuretic peptide (NT-proBNP) and NLR were significantly higher in the observation group compared to the control group. In elderly heart failure patients, the AUC for NLR in assessing the occurrence of MACEs was 0.841, with a sensitivity of 76.92% and specificity of 100%. When both NLR and NT-proBNP were used together, the AUC increased to 0.954, with a sensitivity of 92.31% and specificity of 91.89%.

NLR predicts prognosis in heart valve diseases

Heart valve disease is a cardiac condition characterized by the narrowing and/or incomplete closure of heart valves due to various etiologies. Rheumatic fever is a significant cause of valvular heart disease, with valve damage resulting from rheumatic inflammation, known as rheumatic heart disease. Mitral valve involvement is commonly observed in this condition [42]. Recent reports have highlighted the critical role of inflammation in the pathophysiology of rheumatic heart valve disease [43, 44].

Polat et al. [45] conducted a retrospective analysis including 227 patients with rheumatic mitral valve disease. The study found that NLR was significantly higher in patients with severe mitral stenosis (MS) compared to those with mild to moderate MS. When the NLR threshold was set at 2.56, the sensitivity for predicting severe MS was 75%, and the specificity was 74%. The study concluded that NLR may help predict the presence and severity of MS in RMVD patients. Tian et al. [46] screened 5075 patients undergoing heart valve surgery using a medical record system. The study found significant differences in CRP, erythrocyte sedimentation rate, and NLR between patients with and without adverse postoperative outcomes. ROC curve analysis showed that CRP > 5 mg/L was effective in predicting postoperative heart failure, while NLR > 3.5 was effective in predicting all-cause mortality 30 days postoperatively.

Summary and outlook

NLR plays a significant role in the pathologic and physiologic processes of various cardiovascular diseases and holds important prognostic value. Compared to other inflammatory

markers, NLR is cost-effective and reproducible. In community-level primary care, NLR offers substantial advantages and provides new insight for the prognosis of conditions including coronary heart disease, arrhythmia, hypertension, heart failure, and heart valve disease. However, the mechanisms by which NLR influences the prognosis of cardiovascular diseases require further exploration to support early prediction of adverse outcomes. This would be invaluable for timely intervention.

Despite its utility, NLR has certain limitations. As a non-specific marker of inflammation, it can be influenced by various systemic factors, including infections, malignancies, and autoimmune disorders. Moreover, when used alone, its prognostic value is limited. Therefore, clinical practice should integrate NLR with other biomarkers and clinical findings to provide a more comprehensive assessment of patient outcomes.

To enhance the application of NLR in predicting the prognosis of cardiovascular diseases, future clinical work should focus on improving NLR detection, expanding patient sample sizes, and analyzing NLR changes across a wide range of cardiovascular conditions. This will help establish the NLR-based prognosis risk prediction model, offering a solid foundation for guiding clinical decisions.

Disclosure of conflict of interest

None.

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