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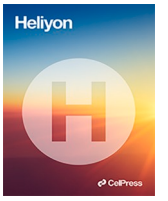

Research article

Association of neutrophil-to-lymphocyte ratio and risk of cardiovascular and all-cause mortality in hypertension patients

Shaoqing Hong [**,1], Hongxia He [1], Peng Fang, Shuai Liu, Changyi Chen [*]

Department of Cardiovascular Medicine, Huangshi Fifth Hospital, No.33 XiaLu Dadao, Xialu District, Huangshi, Hubei, 435005, China

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ABSTRACT

Background and objective: Hypertension affects over a billion people worldwide and is often associated with poor prognoses. The neutrophil-to-lymphocyte ratio (NLR) has become a significant marker, showing a connection to adverse outcomes in cardiovascular diseases (CVDs). The objective of this study is to examine the relationship between the NLR and outcomes in patients with hypertension.

Methods: The study included hypertensive individuals who were surveyed in the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2018. Mortality status was determined using the data from National Death Index (NDI). To investigate the dose-response relationship, restricted cubic spline (RCS) models were used. This study employed adjusted cox proportional hazards regression models to compute hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for all-cause and cardiovascular mortality. The predictive accuracy of the NLR for survival outcomes was assessed utilizing time-dependent receiver operating characteristic (ROC) curve analysis.

Results: A total of 13,724 participants were included in the final analysis, including 7073 males and 6651 females. The cohort was stratified into higher (>2.0) and lower (≤2.0) NLR groups according to the median value. Over a median follow-up of 64 months, there were 1619 all-cause deaths and 522 cardiovascular deaths among participants. The RCS analysis indicated a non-linear relationship between NLR and the risk of mortality. The adjusted model showed that the group with a higher NLR had a significantly higher risk of all-cause (HR 1.47, 95% CI 1.22–1.77) and cardiovascular mortality (HR 2.08, 95% CI 1.52–2.86). ROC analysis showed that the area under the curves (AUCs) of 0.692, 0.662, 0.644, and 0.625 for predicting all-cause mortality, and 0.712, 0.692, 0.687, and 0.660 for cardiovascular mortality at 1, 3, 5, and 10 years.

Conclusion: Elevated NLR is associated with increased risk of cardiovascular and all-cause mortality, and NLR may independently predict outcomes in individuals with hypertension.

* Corresponding author. Department of Cardiovascular Medicine, Huangshi Fifth Hospital, No.98 XiaLu Dadao, Xialu District, Huangshi, Hubei, 435005, China.

** Corresponding author. Department of Cardiovascular Medicine, Huangshi Fifth Hospital, No.98 XiaLu Dadao, Xialu District, Huangshi, Hubei, 435005, China.

E-mail addresses: 13597646662@163.com (S. Hong), 15871171834@163.com (C. Chen).

[1] The two authors contributed equally to share the first authorship.

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1. Introduction

Hypertension is universally acknowledged as a principal risk factor for cardiovascular diseases (CVDs), with over a billion individuals globally affected [1]. Even with advancements in understanding and treatment, it still causes around 8 million deaths each year [2,3]. New findings indicate a possible connection between hypertension and inflammation in the development and complications of atherosclerosis [4,5].

Inflammation represents the body's inherent response to detrimental stimuli, including pathogens, injured cells, or irritants [6]. The process of inflammation plays a crucial role in eliminating harmful factors and repairing tissue damage. However, if inflammation persists, it can potentially lead to the development of various chronic diseases, including hypertension [7]. In studies focused on CVDs, inflammatory markers such as C-reactive protein (CRP), interleukins (ILs), and tumor necrosis factor-alpha (TNF-α) are linked to poor prognosis in people with hypertension by impairing endothelial function and promoting atherosclerosis [8,9]. Yet, the effectiveness of these markers in predicting the outcome of individuals with hypertension is not fully satisfactory.

The neutrophil-to-lymphocyte ratio (NLR), a hematological marker that is simple, cost-effective, and widely accessible, has attracted growing interest in recent years. NLR, composed of neutrophils and lymphocytes, reflects a balance between inflammation and immune responses. Neutrophils are essential in the acute inflammatory response, while lymphocytes are important in regulating immune reactions [10]. NLR is considered a key indicator of whole-body inflammatory status. More and more studies are focusing on the important impact of NLR in individuals with hypertension. Xu JP et al. [11] discovered that a higher NLR is related to an increased risk of hypertension. In Taiwan, a study spanning nine years investigated the link between NLR levels and hypertension development, highlighting that higher NLR quartiles were significantly correlated with an increased risk of hypertension, particularly in older subjects [12]. These studies indicated that NLR may be a better predictive biomarker for hypertension, compared to traditional inflammatory markers, such as systemic inflammatory response syndrome (SIRI) or platelet/lymphocyte ratio (PLR).

Although these studies offer a preliminary understanding of the relationship between NLR and hypertension, research on the connection between NLR and mortality risk in hypertension adult is still limited. Consequently, we endeavor to delve deeper into the pivotal role of NLR in prognosis in hypertensive patients. We also evaluate the potential and effectiveness of NLR as a clinical predictive tool, providing clinicians with a simple yet effective means to enhance health management and prognosis assessment in hypertensive patients.

2. Research design and methods

2.1. Study population

This investigation leverages data obtained from the National Health and Nutrition Examination Survey (NHANES), a project initiated by the National Center for Health Statistics (NCHS). The primary aim of NHANES is to evaluate the health and nutritional status of both adults and children within the United States, utilizing a comprehensive approach that incorporates interviews and physical examinations (*https://wwwn.cdc.gov/nchs/nhanes/Default.aspx*). This study adheres to the ethical standards established by the Institutional Review Board of the NCHS, securing written consent from all participants involved. To ensure the privacy of the participants, all personal information has been de-identified. Moreover, datasets for this analysis, accessible via the official NHANES

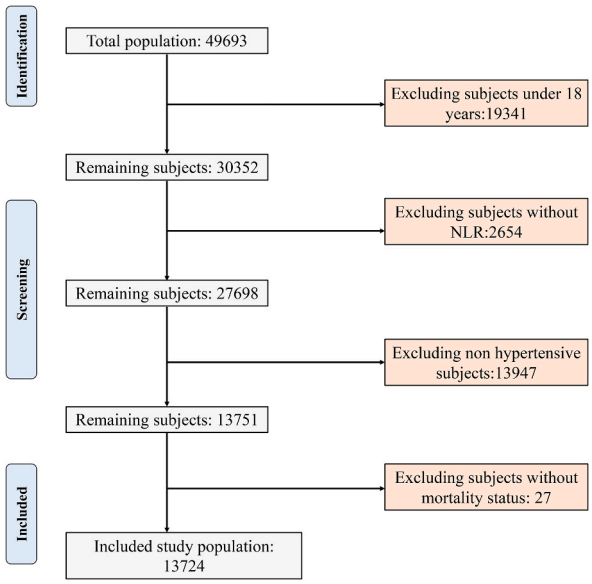

Fig. 1. Diagram illustrating the selection process of the study participants.

website, cover the years 2009–2018 and include linked mortality information from the National Death Index (NDI). Our analysis encompasses subjects who meet specific criteria: adults (18 years or older), a confirmed diagnosis of hypertension, and complete records on NLR, mortality, and other pertinent variables (Fig. 1). In this research, participants were categorized into two separate cohorts based on the median value of NLR: the first group includes those with NLR below or equal to the median, while the second group comprises individuals with NLR above this median value.

2.2. Definition of hypertension

Hypertension was diagnosed either through self-reported use of antihypertensive medication or based on a mean systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg, in accordance with the 2017 American College of Clinical Guidelines [13].

2.3. Exposure measurement

For each participant, a Complete Blood Count (CBC) was conducted twice using the UniCel DxH 800 analyzer and subsequently averaged. This device is a fully automated, quantitative hematology analyzer utilized for in-vitro diagnostics in clinical laboratory settings, especially for large-scale patient screenings. Comprehensive details about the procedures, quality control measures, and handling of data are available on the NHANES website. NLR for each individual was computed by dividing their neutrophil count by their total lymphocyte count.

2.4. Outcome ascertainment

Data on mortality, recorded up to December 31, 2019, were obtained from the CDC's NDI database(*https://www.cdc.gov/nchs/data-linkage/mortality-public.htm*). To classify the causes of death in this research, we used the International Statistical Classification of Diseases, Tenth Revision (ICD-10). Deaths attributed to cardiovascular causes, which include rheumatic heart diseases (codes I00–I09), hypertensive heart and renal disease (code I11), ischemic heart disease (code I13), heart failure(I20–I51) and cerebrovascular diseases (codes I60–I69), were identified according to this classification [14]. The follow time is the number of person-months from NHANES Mobile Examination Center (MEC) examination date. We calculated the duration of each event from the date to their last recorded date of being alive or the last entry in the mortality database.

2.5. Covariates

Potential confounding factors including demographic factors, physical examination data, and comorbidities were considered as covariates. Participants were categorized based on their race/ethnicity as Mexican American or Hispanic, non-Hispanic Black, non-Hispanic White, or other Hispanic ethnicities. Economic status was inferred from the ratio of family income to the poverty threshold, divided into three levels: below 1.30, between 1.30 and 3.50, and above 3.50, where a higher ratio suggests more favorable economic circumstances. The research divided the smoking status of the participants into three distinct categories: nonsmoker, former smoker, and current smoker, using self-reported data on lifetime cigarette consumption and current smoking habits. The alcohol consumption was categorized into three groups: non-drinkers, moderate drinkers (defined as consuming up to one drink per day for women and one to two drinks for men), and heavy drinkers (consuming more than two drinks daily for women and three for men). Educational attainment was classified into three levels: below high school education, completion of high school, and higher education (college or above). Body mass index (BMI) is calculated by dividing an individual's weight in kilograms by the square of their height in meters and is then segmented into three classifications: under 25.0, between 25.0 and 30.0, and over 30.0 kg/m^2. Dyslipidemia was determined based on one or more of the following conditions: a diagnosis from a healthcare provider, the current use of medication to lower lipids, or lipid values reaching or exceeding the benchmarks established by the National Cholesterol Education Program Adult Treatment Panel III, which include fasting triglycerides of 150 mg/dL or higher and/or HDL cholesterol levels below 40 mg/dL in males and 50 mg/dL in females. Diabetes status was determined either through a physician's diagnosis or through biochemical parameters, namely an HbA1c value reaching 6.5% or above, or a fasting plasma glucose concentration exceeding 126 mg/dL.

2.6. Statistical analysis

Acknowledging the intricate and layered sampling strategy of NHANES, which includes multiple stages, stratification, and clustering, we applied appropriate sample weights to adjust for selection and non-response biases, so that the results are representative of the US general population. For descriptive statistics, we computed averages and standard error (SE) for continuous variables, as well as weighted ratios for categorical variables, across each defined group. In evaluating the differences in foundational characteristics between the groups, we employed the Student's t-test for continuous variables and the weighted chi-square test for categorical variables. To analyze long-term survival outcomes pertaining to all-cause and cardiovascular mortality, we adopted the Kaplan-Meier method. The significance of observed disparities was determined through log-rank tests. For the estimation of hazard ratios (HRs) concerning all-cause and cardiovascular mortality, weighted cox proportional hazards regression models, incorporating multiple variables, were utilized. These models took into account various potential confounding factors, ensuring a robust adjustment to accurately reflect the relationship between the observed variables and mortality outcomes. The research utilized four distinct models

for modification. The Model 1 served as the base model without any adjustment, while the Model 2 considered age, gender, and ethnicity. Model 3 extended these adjustments to include alcohol consumption, smoking habits, BMI, economic status relative to poverty, and educational attainment, and Model 4 further incorporated adjustments for diabetes and dyslipidemia. To investigate the potential non-linear association between the NLR and mortality risks, we employed restricted cubic spline (RCS) regression models with four knots (25%, 50%, 75%, and 90%). We also conducted stratified analyses based on several variables like age, sex, ethnic or racial background, economic status, smoking and drinking habits, BMI, and education. Furthermore, to assess the stability of the primary findings, sensitivity analyses were carried out by omitting data from patients who passed away within the first two years, thereby ensuring the reliability of the outcomes by accounting for potential early mortality biases. Finally, to assess the effectiveness of the NLR as a predictor of survival outcomes, we employed time-dependent receiver operating characteristic (ROC) curves. These statistical evaluations were performed using R (version 4.3.0) software with packages such as 'survey', 'tidyverse', 'gtsummary', 'flextable', 'ggplot2', 'rms', 'survival', and 'survivalROC' as well as Stata software (version16.0), considering a *P*-value threshold below 0.05 as an indicator of statistical significance.

3. Results

3.1. Patient characteristics

From the total NHANES population of 49,693 participants, 13,724 individuals were ultimately analyzed, consisting of 7073 (51.4%) men and 6651 (48.6%) women, with an average age of 55.74 years. The median of NLR value was 2.0. Consequently, the study population was segregated into two distinct subgroups based on the median NLR value: a subgroup with a higher NLR (>2.0) and another with a lower NLR (≤2.0). Initial characteristic analysis indicated significant differences in age, gender, ethnicity, BMI, education level, alcohol consumption, smoking status, diabetes, and dyslipidemia among individuals with high NLR compared to those with low NLR, which could potentially impact the survival outcome. Nonetheless, the family income ratio remained consistent across both groups. Over a median follow-up period of 64 months, our study recorded 1619 all-cause deaths and 522 cardiovascular deaths

Table 1
Baseline characteristics of participants with hypertension in the NHANES 2009–2018 cohort.

Characteristic	Overall	NLR		*P value*
		≤2.0	>2.0	
Participants, n	13724	7037	6687	
Gender, %				<0.0001
Male	7073 (51.4%)	3359 (48.41%)	3714(54.12%)	
Female	6651 (48.60%)	3678(51.59%)	2973(45.88%)	
Age, years	55.74(0.17)	54.10(0.24)	57.24(0.24)	<0.0001
Race or ethnicity, %				
Non-Hispanic White	5515 (67.45%)	2166 (59.53%)	33493(74.67%)	<0.0001
Non-Hispanic Black	3482 (13.05%)	2329(18.63%)	1152(7.97%)	
Mexican American or Hispanic	3067 (11.74%)	1575(12.57%)	1492(10.98%)	
Other	1660 (7.76%)	967(9.28%)	693(6.39%)	
BMI, kg/m2, %				<0.0001
<25.0	2781 (18.91%)	1399 (18.88%)	294 (18.91%)	
25.0–29.9	4290 (31.28%)	2285(32.90%)	415 (29.80%)	
≥30.0	6445 (48.64%)	3276 (47.35%)	552 (49.82%)	
Education level, %				0.0052
Less than high school	3502 (16.36%)	1799 (16.64%)	1703 (16.10%)	
High school	3263 (24.62%)	1690(24.96%)	1573 (24.31%)	
College or higher	6824 (58.44%)	3461(57.60%)	3363(59.21%)	
Ratio of family income to poverty, %				
≤1.30	4009 (19.71%)	2044 (20.15%)	1965 (19.31%)	0.6401
1.31–3.50	4816 (34.07%)	2431 (33.93%)	2385 (34.21%)	
>3.50	3551 (38.27%)	1846 (38.11%)	1705 (38.42%)	
Alcohol, %				0.0054
None	3328 (19.04%)	1780 (19.54%)	1548 (18.57%)	
Moderate	3791 (31.98%)	1880 (31.0%)	1911 (32.89%)	
Heavy	2238 (29.42%)	1222 (30.49%)	1016 (28.44%)	
Smoke, %				
Nonsmoker	7207 (52.147%)	3931 (54.27%)	3276 (50.20%)	<0.0001
Former smoker	3928 (29.96%)	1807 (28.32%)	2121 (31.47%)	
Current smoker	2528 (17.63%)	1252 (17.0%)	1276 (18.21%)	
Diabetes, %	3593 (21.20%)	1661 (17.80%)	1932 (24.31%)	<0.0001
Dyslipidemia, %	7566 (54.14%)	3751(52.33%)	3815 (55.80%)	0.0002
Neutrophils number (1000 cell/uL)	4.44 (0.02)	3.54 (0.02)	5.27 (0.03)	<0.0001
Lymphocyte number (1000 cells/uL)	2.15 (0.02)	2.51(0.0.3)	1.81(0.01)	<0.0001
NLR	2.32 (0.01)	1.48 (0.01)	3.08 (0.02)	<0.0001

Values are weighted mean (SE) for continuous variables or numbers (weighted %) for categorical variables. BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; NHANES, National Health and Nutritional Examination Survey.

among participants. The patient characteristics are thoroughly detailed in Table 1, which offers a comprehensive overview of the demographic and clinical profiles of the study population.

3.2. Risk for all-cause and cardiovascular mortality

Table 2 displays the unadjusted and multivariable-adjusted HRs along with the 95% CIs. These are derived from considering the baseline NLR both as a continuous and categorical variable. When analyzing NLR as a continuous variable, an increment of one unit in NLR corresponded to an increased HRs of 1.10 (1.07, 1.13) for all-cause mortality and 1.11 (1.06, 1.15) for cardiovascular mortality in the fully adjusted model, respectively. When analyzed as categorical variables and contrasted with the low NLR group (reference), individuals in the high group had a HR of 1.44 (1.18, 1.75) for all-cause mortality and 1.96 (1.40, 2.76) for cardiovascular mortality, respectively. Elevated NLR levels suggest a high likelihood of increased risk for both all-cause and cardiovascular death. Controlling for possible confounding factors slightly weakened the link between initial NLR levels and all-cause and cardiovascular mortality.

3.3. Kaplan-Meier survival curve analysis

The Kaplan-Meier survival curves indicated a notable disparity in the survival probabilities between the high NLR and low NLR patient groups, with the survival probabilities for both all-cause (Fig. 2A) and cardiovascular mortality (Fig. 2B) being lower in the high NLR group compared to low NLR group, with p-values all <0.0001.

3.4. Smoothing curve fitting

A non-linear relationship was observed between NLR and all-cause mortality, with the lowest HR at NLR value of approximately 1.42, beyond which the HR increased significantly, indicating a greater likelihood of all-cause death as NLR increased. This relationship was statistically significant with p-for non-linearity <0.001 (Fig. 3A). A similar non-linear relationship was found for cardiovascular mortality, with the HR for mortality increasing significantly as NLR values rose above approximately 1.25. This association was also statistically significant (p-non-linear <0.001). (Fig. 3B).

3.5. Subgroup analysis

Table 3 displays the correlation between NLR and the likelihood of all-cause and cardiovascular death in stratified subgroups. The outcomes aligned closely with the initial discoveries. In comparison to the group with lower NLR (reference), the risk associated with high NLR varied across subgroups, with generally higher HRs observed in younger age groups, Non-Hispanic Blacks, and those with lower income levels.

3.6. Sensitivity analyses

Exclusion of patients who died within two years, as demonstrated in Table 4, produced similar outcomes for both all-cause and cardiovascular mortality. Using the group with a lower NLR as a reference, a higher NLR indicates an increased risk of mortality.

3.7. Predictive accuracy of NLR

The effectiveness of NLR for mortality prediction was evaluated using ROC curves. The area under the curve (AUC) for all-cause

Table 2
Associations of NLR with all-cause and cardiovascular mortality in patients with hypertension from the NHANES 2009–2018 cohort.

	No. of Events	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
All-cause mortality					
NLR (continuous)	1619	1.18 (1.13, 1.22)	1.11 (1.07, 1.15)	1.10(1.07, 1.14)	1.10(1.07, 1.13)
NLR (categorical)					
NLR_low	543	1.0	1.0	1.0	1.0
NLR_high	1076	2.00(1.76, 2.27)	1.53 (1.34, 1.74)	1.47(1.22, 1.77)	1.44(1.18, 1.75)
CVD mortality					
NLR (continuous)	522	1.19 (1.14, 1.24)	1.11 (1.06, 1.15)	1.11 (1.07, 1.16)	1.11(1.06, 1.15)
NLR (categorical)					
NLR_low	145	1.0	1.0	1.0	1.0
NLR_high	377	2.87(2.33, 3.54)	2.09(1.68, 2.59)	2.08(1.52, 2.86)	1.96(1.40, 2.76)

Values are n or weighted HR (95% CI). Model 1 is unadjusted; Model 2 is adjusted for: age, sex and race; Model 3 is adjusted for: model 2 + alcohol intake, smoking status, BMI, ratio of family income to poverty, education level; Model 4 is adjusted for: model 3 plus diabetes and dyslipidemia; CVD, cardiovascular disease; BMI, body mass index; NHANES, National Health and Nutritional Examination Survey; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

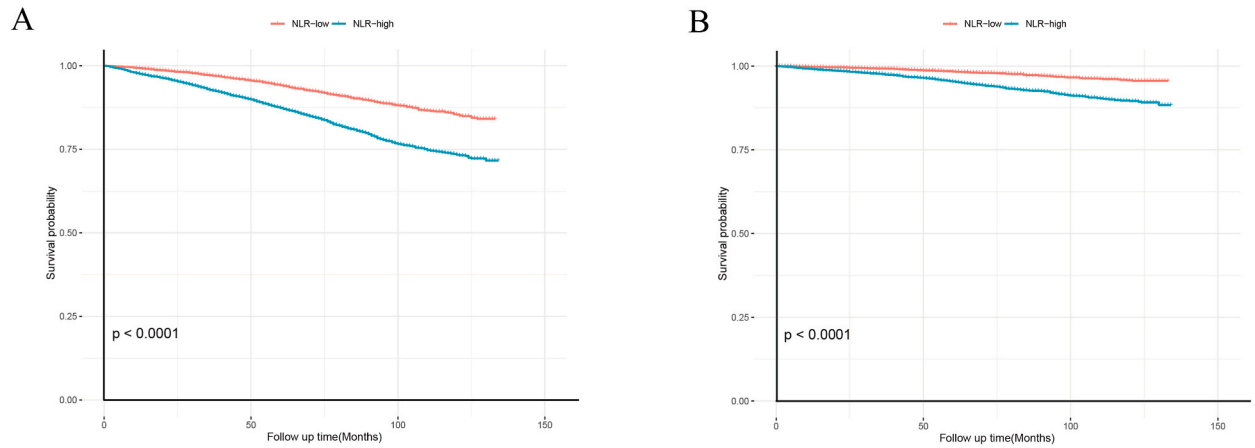

Fig. 2. Kaplan–Meier curves of the survival rate with higher and lower NLR group. A, All-cause mortality; B, cardiovascular mortality. NLR, neutrophil-to-lymphocyte ratio.

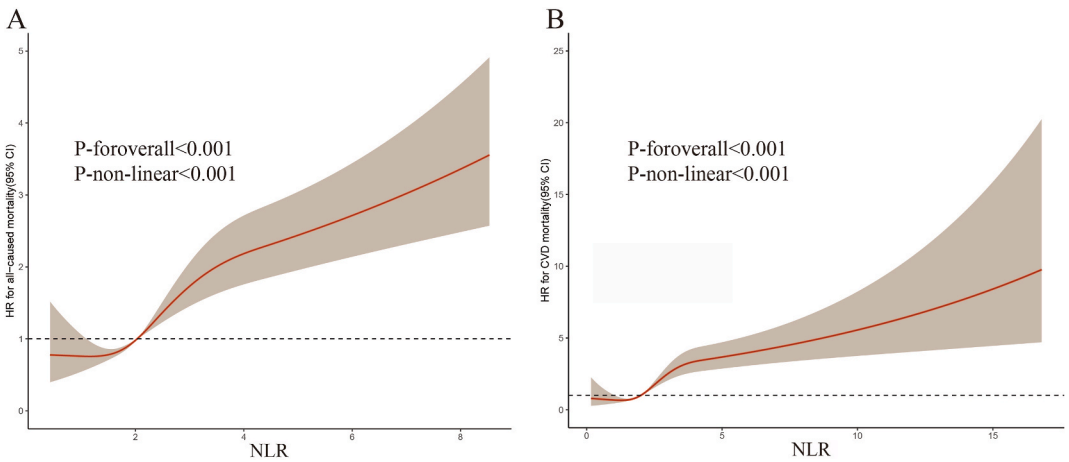

Fig. 3. The adjusted restricted cubic splines depicting the relationships between NLR levels and mortality, based on data from NHANES 2009–2018. A. Association of NLR level with all-cause mortality. P for non-linearity <0.001; P for overall <0.001. The NLR value corresponding to the lowest HR value is 1.25. The NLR value corresponding to the lowest HR value is 1.25. B. Correlation between NLR levels and cardiovascular mortality. P for non-linearity <0.001; P for overall <0.001. The NLR value corresponding to the lowest HR value is 1.42. NLR, neutrophil-to-lymphocyte ratio; NHANES, National Health and Nutritional Examination Survey; CVD, cardiovascular disease, HR, hazard ratio; CI, confidence interval.

mortality was 0.692 at 1 year, 0.662 at 3 years, 0.644 at 5 years, and 0.625 at 10 years (Fig. 4A). For cardiovascular mortality, the AUC was higher as 0.712 at 1 year, 0.692 at 3 years, 0.687 at 5 years, and 0.660 at 10 years (Fig. 4B). The findings suggest that the NLR exhibited moderate predictive power for in both the short- and long-term mortality.

4. Discussion

In our study, we noted a marked increase in the likelihood of both all-cause and cardiovascular deaths in hypertensive individuals with elevated NLR levels. The association remained significant even after adjusting for all potential confounding factors. This finding aligns with prior research, underscoring the importance of monitoring NLR in hypertensive patients and providing a more comprehensive perspective for hypertension management [15,16].

The potential mechanisms linking NLR to mortality in hypertension may involve inflammation and body's immune response, which is closely associated with the progression of target organ damage and arteriosclerosis [10,17]. Neutrophils could intensify endothelial cell damage by releasing inflammatory mediators and oxidative stress agents, leading to further deterioration of vascular function and an increase in blood pressure [18,19]. Lymphocytes are crucial for regulating immune responses and the inflammation process [20]. Thus, an elevated NLR might denote an intensified inflammatory state, aggravating vascular damage and heightening mortality risk.

Subgroup analysis unveiled significant disparities in the correlation between the NLR and mortality risk across diverse populations, emphasizing the importance of personalized medicine in cardiovascular disease management. Compared to the study by Angkananard

Table 3
Variables-stratified, multivariable-adjusted analyses for the associations of NLR with all-cause and cardiovascular mortality in patients with hypertension from NHANES 2009–2018.

Subgroup	NLR			
	All-cause mortality		Cardiovascular mortality	
	NLR_low	NLR_high	NLR_low	NLR_high
Age, years				
≤65	1.0	1.99(1.35, 2.92)	1.0	4.10(1.44, 11.7)
> 65	1.0	1.39(1.14, 1.69)	1.0	1.77(1.25, 2.52)
Sex				
Male	1.0	1.37(1.03, 1.82)	1.0	2.45(1.32, 4.55)
Female	1.0	1.49(1.16, 1.92)	1.0	1.55(0.98, 2.46)
Race				
Non-Hispanic White	1.0	1.31(1.03, 1.68)	1.0	1.65(1.16, 2.36)
Non-Hispanic Black	1.0	1.85(1.44, 2.40)	1.0	3.04(1.90, 4.87)
Mexican American or Hispanic	1.0	1.60(1.34, 2.24)	1.0	1.96(1.04, 3.67)
Other Hispanic	1.0	1.77(0.95, 3.30)	1.0	4.08(1.20, 13.86)
Ratio of family income to poverty				
≤1.3	1.0	1.40(1.01, 1.94)	1.0	1.30(0.70, 2.40)
1.3–3.5	1.0	1.35(0.99, 1.83)	1.0	2.59(170, 3.95)
>3.5	1.0	1.66(1.03, 2.68)	1.0	2.62(1.19, 5.78)
BMI, kg/m2				
≤25	1.0	1.50(1.03, 2.20)	1.0	1.43(0.72, 2.82)
25–30	1.0	1.47(1.09, 1.98)	1.0	1.78(1.02, 3.08)
>30	1.0	1.34(0.94, 1.91)	1.0	2.31(1.23, 4.35)
Education level				
Less than high school	1.0	1.70(1.21, 2.38)	1.0	2.14(1.13, 4.04)
High school	1.0	1.69(1.12, 2.56)	1.0	2.96(1.62, 5.39)
College or higher	1.0	1.20(0.89, 1.62)	1.0	1.39(0.77, 2.52)

Values are weighted HR (95% CI). Model: adjusted for age, sex, race/ethnicity, education level, family income level, smoking status, alcohol intake, dyslipidemia, and diabetes status, with excluding the stratifying factors. BMI, body mass index; NHANES, National Health and Nutritional Examination Survey; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 4
Multivariable-adjusted analyses for the associations of NLR with all-cause and cardiovascular mortality among hypertension from NHANES 2009–2018 after excluding the patients who died within two years.

No. of Events		HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
All-cause mortality					
NLR (continuous)	1227	1.17 (1.12, 1.22)	1.09 (1.05, 1.14)	1.10(1.06, 1.14)	1.09(1.05, 1.13)
NLR (categorical)					
NLR_low	433	1.0	1.0	1.0	1.0
NLR_high	794	1.80(1.58, 2.05)	1.37 (1.20, 1.56)	1.34(1.10, 1.63)	1.31(1.07, 1.61)
Cardiovascular mortality					
NLR (continuous)	397	1.18 (1.13, 1.23)	1.10 (1.05, 1.14)	1.10 (1.06, 1.15)	1.10(1.05, 1.15)
NLR (categorical)					
NLR_low	118	1.0	1.0	1.0	1.0
NLR_high	279	2.54(1.99, 3.24)	184(1.43, 2.36)	1.86(1.29, 2.67)	1.74(1.19, 2.55)

Values are n or weighted HR (95% CI). Model 1 is unadjusted; Model 2 is adjusted for: Age, Sex and Race; Model 3 is adjusted for: model 2 + Alcohol intake, Smoking status, BMI, Ratio of family income to poverty, education level; Model 4 is adjusted for: model 3 plus diabetes and dyslipidemia; NHANES, National Health and Nutritional Examination Survey; NLR, neutrophil-to-lymphocyte ratio; BMI, body mass index; HR, hazard ratio; CI, confidence interval.

T [21], our research provided more detailed subgroup analysis, offering insights into how age, ethnicity, and socioeconomic status influence this relationship. The stability of our sensitivity analysis further corroborates the reliability of our primary findings. Even after excluding patients who died early, the significant association between NLR and mortality risk persisted, highlighting the importance of NLR as an independent predictor.

Our research identified a significant divergence in the HRs for cardiovascular mortality across different age cohorts (≤65 years vs. >65 years). For individuals aged ≤65, the HR associated with a high NLR was 4.10 (95% CI: 1.44–11.7), contrasting with 1.77 (95% CI: 1.25–2.52) in those aged >65. This attenuation might be attributed to age-related physiological and pathological changes that impact cardiovascular health. Furthermore, inflammation might play a more direct and pronounced role in the pathogenesis of cardiovascular conditions among younger individuals, whereas in older populations, the influence of inflammatory markers could be obscured by the cumulative effects of various cardiovascular risk factors.

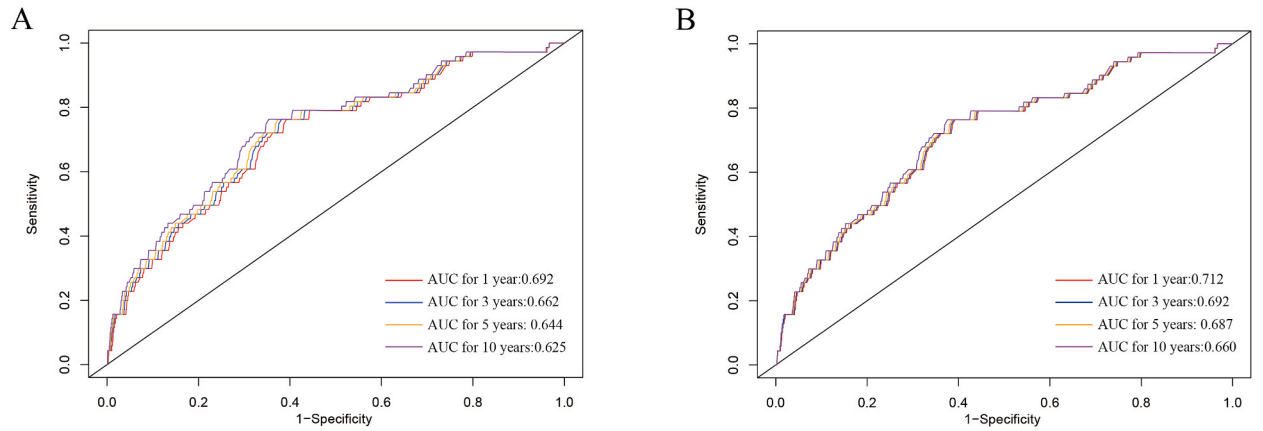

Fig. 4. (A) ROC curves of NLR in predicting 1-,3-, 5-, and 10-year all-cause mortality. (B) ROC curves of NLR in predicting 1-,3-, 5-, and 10-year cardiovascular mortality. NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristics curve; AUC, area under the curve.

Moreover, we observed a nonlinear relationship between NLR and mortality risk in our study, a finding not commonly seen in existing literature. This suggests that the relationship between NLR and cardiovascular risk might vary at different NLR levels, possibly due to the complexity of inflammation and immune responses, offering a new perspective on the role of NLR in cardiovascular diseases. Regular monitoring of NLR may help to reduce mortality. This is based on NLR as an indicator of inflammation and stress state of the body, and its increase is related to many adverse health outcomes. Regular monitoring of NLR helps to identify the changes of inflammatory state at an early stage, allowing timely intervention measures, such as anti-inflammatory treatment, optimizing nutritional intake and improving lifestyle, which may reduce the risk of death related to inflammation.

We further investigated the effectiveness of NLR in predicting cardiovascular and all-cause mortality using time-dependent ROC curves. Compared to traditional biomarkers like CRP and fibrinogen, NLR is more ubiquitous and cost-effective, and provides an index reflecting both inflammation and immune status [22,23]. Studies by García-Escobar A et al. [24] and Kim S et al. [25] have also identified NLR as a reliable marker of inflammation and its prognostic value in various cardiovascular diseases. Our results further confirm that NLR can serve as a candidate predictor for predicting the prognosis of hypertension though the predictive power of NLR is relatively limited. This aligns with the findings of Pourafkari Let al [26] which also highlighted the limitations of NLR as a sole predictor of cardiovascular events. Therefore, it is advisable to combine NLR with other biomarkers in clinical practice to enhance predictive accuracy.

When comparing our study with others, we noted variations in determining the threshold for NLR's correlation with mortality. Azab B et al. [27] discovered that having an NLR greater than 2.4 was linked to a higher likelihood of experiencing cardiovascular events. Similarly, Dong G et al. [28] research indicated a correlation with adverse survival outcomes when NLR >3.48. Unlike these studies, which mainly focused on acute cardiac events, our research specifically targeted the hypertensive population, conducting a more detailed analysis of the specific correlation between NLR and mortality rates in this group.

Our study has its limitations. Being based on observational data, causality cannot be established. Despite adjusting for multiple potential confounders, the influence of other unknown factors on NLR cannot be completely excluded. Finally, our study is based on a specific cohort from the United States, necessitating validation of the results across different global populations. Future research should encompass diverse ethnicities and regions to reinforce the universality of these findings.

5. Conclusion

In conclusion, our research indicates a positive correlation between elevated NLR and an elevated risk of cardiovascular and all-cause mortality in hypertensive individuals. NLR could potentially serve as a valuable prognostic indicator for these patients.

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Data availability statement

The data related to my research is stored in the publicly available repository of the NHANES website (*https://wwwn.cdc.gov/nchs/nhanes/Default.aspx*).

CRediT authorship contribution statement

Shaoqing Hong: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology. **Hongxia He:** Writing – review & editing, Supervision, Software. **Peng Fang:** Validation, Supervision. **Shuai Liu:** Validation, Supervision. **Changyi Chen:** Writing – review & editing, Validation, Supervision, Methodology.

Declaration of competing interest

The authors confirm the absence of any conflicts of interest that need to be disclosed.

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