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ORIGINAL RESEARCH

Association Between Neutrophil-Lymphocyte Ratio and All-Cause Mortality and Cause-Specific Mortality in US Adults, 1999–2014

Yang Chen
Wei Wang
Lizhong Zeng
Ke Mi
Na Li
Jie Shi
Shuanying Yang

Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China

Background: Neutrophil-lymphocyte ratio (NLR) is a novel marker of inflammation. Emerging studies have evaluated the relationship of NLR with cardiovascular diseases and malignant conditions. However, rare studies regarded the association between NLR and long-term health status. This study aimed to evaluate the association of NLR with all-cause mortality and cause-specific mortality among adults in the United States.

Methods: We obtained eight cycles data of National Health and Nutrition Examination Surveys (NHANES) from 1999 to 2014, and enrolled 32328 participants after certain screening. By weighted chi-square test and linear regression analysis, we analyzed the correlation between NLR and baseline characteristics of the participants. Kaplan–Meier curves and Cox regression models were used to assess the survival relevance of NLR. We conducted stratified analysis, interaction analysis, and sensitivity analysis to robustness of our results.

Results: Participants with high NLR levels had a higher risk of death. After adjustment for baseline characteristics, the hazard ratio comparing the higher vs lower NLR levels was 1.43 (95% CI, 1.18–1.73) for all-cause mortality, 1.27 (95% CI, 0.84–1.92) for cancer mortality, and 1.44 (95% CI, 0.96–2.16) for cardiovascular disease mortality. Stratified analysis found that the observed associations between NLR levels and mortality did not differ significantly.

Conclusion: In this nationally representative cohort of US adults, higher NLR was significantly associated with an increased risk of all-cause mortality.

Keywords: inflammation, lymphocyte, neutrophil, mortality

Introduction

Neutrophil-lymphocyte ratio (NLR) is the ratio of neutrophils to lymphocytes in the peripheral blood, which becomes a novel marker of systemic inflammation. NLR reflects the relative balance of myeloid and lymphocyte lineages, and is sensitive to the altered myelopoiesis.[1]

Previous studies have shown that high NLR level associated with unfavorable clinical outcomes in a variety of diseases. Emerging studies indicated that NLR is an effective predictor of prognosis, response to therapy, recurrence in various malignancies.[2–10] Some studies have also shown that NLR associated with prognosis and treatment response in cardiovascular diseases.[11–14] In addition, other researchers have found that NLR levels association with diagnosis and prognosis of infectious diseases such as community-acquired pneumonia,[15] bacteremia, and sepsis.[16–20] Elevated NLR also has been found in patients with chronic diseases

Correspondence: Shuanying Yang
Department of Respiratory Medicine, The Second Affiliated Hospital, Xi'an Jiaotong University School of Medicine in Xi'an, Shaanxi, People's Republic of China
Tel +86-13991392919
Email yangshuanying666@163.com

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including prediabetes and diabetes mellitus,[21,22] autoimmune diseases,[23,24] and metabolic syndrome.[25] These evidence suggest NLR as a risk factor of various diseases, but the insufficient number of participants and the short follow-up period undermine the validity of the results. Only sparse cohort studies examined the association of NLR levels with long-term health outcomes. Moreover, whether NLR is associated with risk of mortality in the general population remains unclear.

Our study aimed to examined the association of NLR levels with long-term all-cause mortality among adults in the US general population, using a large nationally representative data set from the National Health and Nutrition Examination Survey (NHANES). In addition, we evaluated the associations of NLR levels with cancer mortality and cardiovascular diseases mortality.

Methods

Data Source

The NHANES collects health-related data on a nationally representative sample in the US. For each per 2-year cycles of the continuous NHANES, around 5000 participants from 15 counties in the US were selected. Data were obtained by in-home interview, physical examination, and laboratory tests. Our study used the data from the first 8 cycles of continuous NHANES, collected during the period from 1999 to 2014. The protocol of NHANES has been approved by the National Center for Health Statistics (NCHS) Ethics Review Board. Written informed consent was obtained from all participants before participation. And our study was approved by the ethics committee of School of Medicine, Xi'an Jiaotong University. The present analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[26]

Participants

From 1999 to 2014, 82,091 NHANES participants were linked to National Death Index. We included 42,979 participants ≥20-year-old at the baseline survey. We excluded participants who did not have physical examination (n = 2109), who lacked data of baseline blood count (n = 2184), mortality data (n = 48), and study covariates (n = 6310): smoking status (n = 37), alcohol use (n = 2835), education (n = 55), marital status (n = 464), family income-poverty ratio level (n = 2846), body mass index (n = 49), self-reported health status (n = 23). Finally, 32,328 participants were enrolled in our cohort (Figure 1).

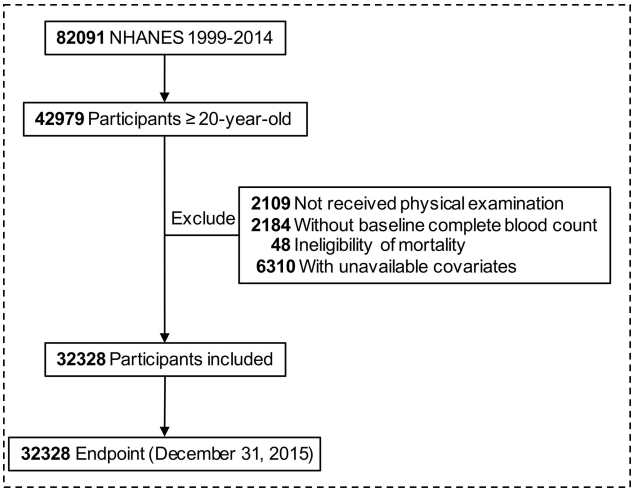

Figure 1 Flow chart of inclusion and exclusion of study participants.

Assessment of NLR Exposure

Neutrophil and lymphocyte counts were obtained from the peripheral whole blood test following established protocol and procedures. Detailed operation process of the test can be found in Laboratory Procedure Manual for NHANES.[27] The test reported neutrophil and lymphocyte counts in 1000 cells/μL. NLR was calculated by dividing the neutrophil count by the lymphocyte count. High NLR was defined as NLR ≥ 3.

Ascertainment of Deaths

Public-Use Linked Mortality Files were provided by the NCHS.[28] We ascertained mortality status by matching the National Death Index (last followed up on 31 December 2015, updated in 2020) by the unique study identifier. Causes of deaths were determined according to the codes of international statistical classification of diseases (tenth revision).[29] In the present study, primary outcome was mortality from all causes, cancers (C00-C97), and cardiovascular diseases (codes I00-I09, I11, I13, I20-I51, and I60-I69). We defined baseline at the time subjects had physical examinations. The person-years was calculated from baseline to death, loss to follow-up or December 31, 2015, whichever occurs first.

Assessment of Covariates

Information on covariates was collected through baseline questionnaires, including age, sex, race/ethnicity, education level, marital status, family income poverty ratio level, drinking and smoking status, body mass index, and self-reported general health. Race/ethnicity was classified into non-Hispanic white, non-Hispanic black, Mexican

American, and others. In accordance with the NCHS classifications,[30,31] the smoking status was divided into 3 categories – never smokers (who had smoked <100 cigarettes in lifetime at the time of survey), current smokers (who smoked >100 cigarettes in lifetime and still smoke), and former smokers (who had smoked >100 cigarettes but stopped smoking). Alcohol drinking was categorized as non-drinker (less than 12 alcohol drinks/lifetime), and drinker (≥12 alcohol drinks/lifetime).[30] A family's income-poverty ratio (PIR) is calculated by dividing family income by a poverty threshold. A higher PIR indicates a higher income. We categorized PIR into three groups (0–1.0, 1.1–2.9, ≥3.0). Body mass index (BMI) was calculated as individual's weight (kg) divided by the square of height (m^2).

Statistical Analysis

Our study followed the analytic guideline by NHANES to account for the complex survey design factors, including sample weights, clustering, and stratification. Data were presented as mean± standard deviation (SD) for continuous variables and as numbers (percentages) for categorical variables. The statistical differences between groups of NLR were tested by weighted chi-square test and linear regression model for categorical variables and continuous variables, respectively. We used Kaplan–Meier analysis and Cox regression models to estimate the hazard ratios and corresponding 95% confidence intervals for associations.

We conducted stratified analyses and interaction analyses by age, gender, race/ethnicity, smoking status, BMI to evaluate whether the associations were different. In addition, we did a series of sensitivity analyses to further test the robustness of the results. Firstly, risk estimates were additionally adjusted by putting baseline history of cancer, diabetes, chronic kidney disease, cardiovascular diseases, hypertension, hyperlipemia, and chronic obstructive pulmonary diseases in the fully adjusted model. Secondly, we excluded participants with the extreme 1% of the NLR ratio to reduce the influence of underlying malignancies or other severe disease states. Thirdly, we removed participants with follow-up time of less than 35 months. Fourthly, we excluded participants with severe illnesses such as diabetes, cardiovascular disease, or cancer in order to minimize potential reverse causation.

All statistical analyses were performed on R software, version 3.6.3 (The R Foundation, Vienna, Austria). A two-sided P value <0.05 was considered statistically significant.

Results

Sample Characteristics

Table 1 shows the baseline characteristics of the participants. Among the 32,328 participants, the weighted mean [SE] age at baseline was 47.4 [16.5] years; 16,484 (51.4%) were women; 16,013 (72.0%) were white. During 254,580 person-years of follow-up (median, 7.5 years; maximum, 16.8 years), 4092 deaths occurred in total, including 884 deaths from cancer and 904 deaths from cardiovascular disease. Compared with the low-NLR group, people with higher NLR were more likely to be older, men, non-Hispanic white, and have lower educational level, lower family income, lower BMI; they more likely to report baseline history of cancer, diabetes, chronic kidney disease, cardiovascular diseases, hypertension, chronic obstructive pulmonary diseases; they less likely to non-smokers, married and to report very good to excellent health status.

Survival Analysis

During 254,580 person-years of follow-up (median, 7.5 years; maximum, 16.8 years), 4092 deaths occurred in total, including 884 deaths from cancer and 904 deaths from cardiovascular disease. Kaplan–Meier curves revealed that all-cause mortality was significantly elevated among high-NLR group versus low-NLR group (Log rank test $P < 0.001$) (Figure 2). In unadjusted Cox proportional hazards regression models, the hazard ratio (HR) of high-NLR group reached 2.20 (Non-adjusted model in Table 2). After adjustment for age and gender, high-NLR group still had higher risk of all-cause mortality (HR 1.53, Model 1 in Table 2). In the fully adjusted model including demographic characteristics, socioeconomic status, lifestyle factors, BMI, and health status, hazards of all-cause death remained elevated in high-NLR group (Model 3 in Table 2). We observed similar results for mortality from cancer (HR, 1.27 [95% CI, 0.84–1.92]) and cardiovascular disease (HR, 1.44 [95% CI, 0.96–2.16]), although those associations were not statistically significant (Table 2).

Subgroup and Sensitivity Analyses

In the stratified analysis, the observed associations between NLR levels and mortality were not significantly different in age, gender, race/ethnicity, or BMI (Table 3;

Table 1 Baseline Characteristics of Study Participants According to NLR Levels [a]

Characteristics	Total	Low-NLR	High-NLR	P value [b]
No. of participants	32,328	26,320	6008	
Age, years	47.4 ± 16.5	46.6 ± 16.1	51.0 ± 18.1	<0.001
Gender				
Male	15,844 (48.6)	12,804 (48.3)	3040 (50.2)	<0.01
Female	16,484 (51.4)	13,516 (51.7)	2968 (49.8)	
Ethnicity				
Non-Hispanic white	16,013 (72)	12,316 (70.5)	3697 (79)	<0.001
Non-Hispanic black	6282 (10.1)	5582 (11.0)	700 (5.8)	
Mexican American	5671 (7.5)	4749 (7.8)	922 (6.1)	
Others	4362 (10.4)	3673 (10.7)	689 (9.1)	
Smoking status				
Never smoker	16,965 (52.3)	14,078 (53.4)	2887 (47.0)	<0.001
Former smoker	8427 (25.5)	6566 (24.6)	1861 (29.6)	
Current smoker	6936 (22.3)	5676 (22.0)	1260 (23.4)	
Alcohol drinking				
Non-drinker or low drinker	9394 (24.4)	7647 (24.4)	1747 (24.3)	0.93
Heavy drinker	22,934 (75.6)	18,673 (75.6)	4261 (75.7)	
Education				
Less than high school	8733 (17.5)	7167 (17.5)	1566 (17.3)	0.003
High school or equivalent	7459 (23.8)	6000 (23.4)	1459 (25.5)	
College or above	16,136 (58.7)	13,153 (59.0)	2983 (57.1)	
Marital status				
Married	19,993 (65.4)	16,380 (66.2)	3613 (61.6)	<0.001
Separated	7313 (19.0)	5767 (18.1)	1546 (23.4)	
Never married	5022 (15.6)	4173 (15.7)	849 (15.0)	
Family income-poverty ratio level				
0–1.0	6835 (14.3)	5623 (14.4)	1212 (13.9)	<0.001
1.1–2.9	13,192 (35.6)	10,611 (35.1)	2581 (38.3)	
≥3.0	12,301 (50.1)	10,086 (50.5)	2215 (47.8)	
BMI				
<18.5	480 (1.5)	357 (1.4)	123 (1.9)	<0.001
18.5–24.9	9964 (32.3)	7911 (31.9)	2053 (34.4)	
25–29.9	11,397 (34.9)	9364 (35.3)	2033 (32.9)	
≥30	10,487 (31.3)	8688 (31.4)	1799 (30.8)	
Self-reported health				
Very good to excellent	13,673 (50.0)	11,272 (51.0)	2401 (45.3)	<0.001
Good	11,170 (33.0)	9144 (32.9)	2026 (33.7)	
Poor to fair	7485 (17.0)	5904 (16.1)	1581 (21.0)	
Self-reported chronic diseases				
Cancer	3015 (9.3)	2194 (8.5)	821 (13.2)	<0.001
Diabetes	5434 (12.6)	4313 (11.9)	1121 (15.6)	<0.001
Chronic kidney disease	4452 (10.5)	3273 (9.3)	1179 (16.2)	<0.001
Cardiovascular diseases	3636 (8.8)	2608 (7.7)	1028 (13.8)	<0.001
Hypertension	13,777 (37.6)	10,936 (36.2)	2841 (44.0)	<0.001
Hyperlipemia	19,904 (60.9)	16,152 (60.9)	3752 (60.9)	0.92
COPD	1403 (4.2)	1012 (3.7)	391 (6.2)	<0.001

Notes: [a]All estimates accounted for complex survey designs. Values are numbers (percentages) unless stated otherwise. [b] For categorical variables, P value was calculated by weighted chi-square test. For continuous variables, P value was calculated by weighted linear regression model.

Abbreviations: NLR, neutrophil-lymphocyte ratio; COPD, chronic obstructive pulmonary diseases; BMI, body mass index.

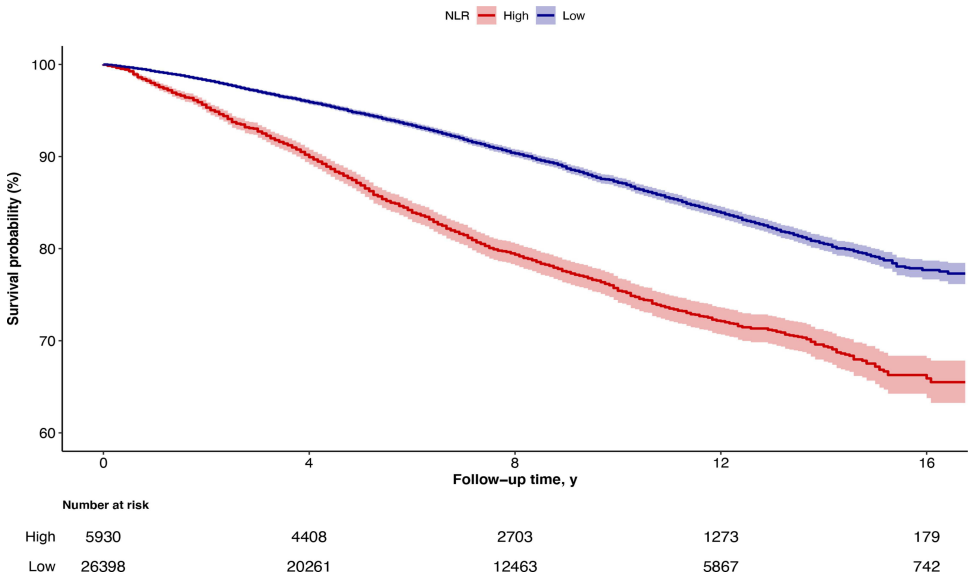

Figure 2 Kaplan-Meier Curves for Survival Probability, with Follow-up in Years. Survival according to NLR levels was determined using Kaplan Meier curves. Participants with higher NLR levels (NLR ≥3, red line) had unfavorable prognosis compared with those with lower (NLR < 3, blue line).

eTables 1 and 2 in the Supplement). In the sensitivity analyses, further adjusting for baseline comorbidities, the significant associations of NLR levels with all-cause mortality remained. The results were still unchanged when we excluded participants with the extreme 1% of the NLR ratio, excluded those with follow-up time less than 35 months, and excluded those with prevalent cancer, diabetes, and cardiovascular disease in baseline (eTable 3 in the Supplement). Similar sensitivity analysis results were observed for cancer mortality and cardiovascular disease mortality (eTables 4 and 5 in the Supplement).

Discussion

This study determined the association of NLR levels with all-cause and cause-specific mortality in US adults. In a cohort of US nationally representative sample, we found a robust association between all-cause mortality and NLR levels in adults. High-NLR group had a high risk of all-cause mortality. The association remained significant after taking account of demographic characteristics, lifestyle factors, socioeconomic status, and BMI. Overall, this study demonstrates that a high NLR is associated with high risk of all-cause mortality in the US general population.

Mounting evidence suggests that NLR had relation with unfavorable clinical outcomes in patients with cardiovascular diseases, malignancies, and other chronic inflammatory diseases.[4,5,11,12,23] In the general population, our results show that elevated NLR is associated with high risk of all-cause mortality. The association remains after excluding participants with cancer, diabetes or cardiovascular diseases at baseline in the sensitivity analyses (eTable 3). However, note that a higher NLR is statistically nonsignificant associated with mortality of specific causes including cardiovascular disease and cancer in our study. The reason may be that we did not have data on incident cancer, incident cardiovascular event, or site-specific cancer mortality. And we just evaluated the NLR levels with long-term outcomes in patients with cancer or cardiovascular disease. Herein, more studies are still needed to examine the associations between NLR levels and risk of cardiovascular disease and cancer.

In the presence of systemic inflammation, molecules or cellular components in the peripheral blood alter accordingly. Indicators for assessing the systemic inflammation have received increased attention and are valuable for predicting clinical outcomes in practice.[32–34] The previous studies reported that C-reactive protein may be a death prognosis factor in general people[35] and in patients with cardiovascular disease,[35,36] lung cancer,[37] or colorectal cancer.[38] Erythrocyte sedimentation rate is also a potential marker for mortality in general people[39] and in patients with nontuberculous mycobacterial pulmonary disease.[40] Other researchers reported that complete blood cell count range and albumin levels were associated with outcomes.[41] Compared with the above indicators, NLR is inexpensive,

Table 2 Association of NLR Levels with All-Cause Mortality and Cause-Specific Mortality [a]

Variable	NLR Level, Hazard Ratio (95% CI)		
	Continuous NLR	**Low-NLR**	**High-NLR**
Median NLR level	2	1.81	3.7
All-cause mortality			
Deaths per person-years	4092 per 254,580	2581 per 209,036	1241 per 45,544
Non-adjusted model	1.22 (1.18, 1.26)	1 [Reference]	2.20 (1.83, 2.64)
Model 1	1.12 (1.08, 1.16)	1 [Reference]	1.53 (1.27, 1.85)
Model 2	1.12 (1.08, 1.17)	1 [Reference]	1.52 (1.26, 1.83)
Model 3	1.11 (1.06, 1.16)	1 [Reference]	1.43 (1.18, 1.73)
Cancer mortality			
Deaths per person-years	884 per 254,580	642 per 209,036	242 per 45,544
Non-adjusted model	1.17 (1.06, 1.29)	1 [Reference]	1.79 (1.20, 2.67)
Model 1	1.06 (0.95, 1.19)	1 [Reference]	1.30 (0.86, 1.95)
Model 2	1.07 (0.96, 1.20)	1 [Reference]	1.31 (0.87, 1.97)
Model 3	1.05 (0.93, 1.19)	1 [Reference]	1.27 (0.84, 1.92)
CVD mortality			
Deaths per person-years	904 per 254,580	622 per 209,036	282 per 45,544
Non-adjusted model	1.24 (1.16, 1.32)	1 [Reference]	2.49 (1.68, 3.70)
Model 1	1.11 (1.02, 1.21)	1 [Reference]	1.55 (1.04, 2.32)
Model 2	1.12 (1.03, 1.22)	1 [Reference]	1.56 (1.04, 2.33)
Model 3	1.09 (0.99, 1.19)	1 [Reference]	1.44 (0.96, 2.16)

Notes: [a]All estimates accounted for complex survey designs. Model 1 was adjusted for baseline age, sex. Model 2 was additionally adjusted for race/ethnicity, education level, marital status, family income poverty ratio level, drinking status, and smoking status. Model 3 was further adjusted for body mass index, and self-reported general health.
Abbreviations: NLR, neutrophil-lymphocyte ratio; CVD, cardiovascular disease.

Table 3 Stratified Analyses for the Association of NLR Levels with All-Cause Mortality [a]

Variable	NLR Level, Hazard Ratio (95% CI)		P value for Interaction
	Low-NLR	**High-NLR**	
Age			
<60	1 [Reference]	1.40 (0.94, 2.08)	0.42
≥60	1 [Reference]	1.63 (1.31, 2.02)	
Gender			
Male	1 [Reference]	1.33 (1.03, 1.72)	0.42
Female	1 [Reference]	1.58 (1.20, 2.09)	
Ethnicity			
Non-Hispanic white	1 [Reference]	1.39 (1.13, 1.71)	0.91
Non-Hispanic black	1 [Reference]	1.74 (0.85, 3.55)	
Mexican American	1 [Reference]	1.51 (0.61, 3.75)	
Others	1 [Reference]	1.24 (0.55, 2.83)	
Smoking status			
Never smoker	1 [Reference]	1.34 (0.99, 1.84)	0.8
Former smoker	1 [Reference]	1.55 (1.15, 2.08)	
Current smoker	1 [Reference]	1.36 (0.90, 2.06)	
BMI			
<18.5	1 [Reference]	1.25 (0.37, 4.25)	0.99
18.5–24.9	1 [Reference]	1.39 (1.00, 1.92)	
25–29.9	1 [Reference]	1.48 (1.07, 2.04)	
>30	1 [Reference]	1.48 (1.03, 2.11)	

Notes: [a]All estimates accounted for complex survey designs. Risk estimates were adjusted for baseline age, sex, race/ethnicity, education level, marital status, family income poverty ratio level, drinking and smoking status, body mass index, and self-reported general health. And group variables were not adjusted for in that subgroup analysis.
Abbreviations: NLR, neutrophil-lymphocyte ratio; BMI, body mass index.

easily available, and potentially modifiable. So NLR may be an attractive marker for systemic inflammation status in medical screening setting.

Our study has some strengths. We used the generalizability of NHANES data that contained a nationally representative sample, which enables us to generalize our findings to a broader population. Another strength of this research is that we adjusted for a variety of potential confounders, including demographic status, lifestyle factors, socioeconomic status, and BMI. Finally, our research spans a longer follow-up period (median, 7.5 years).

Our study also has limitations. Firstly, this study is limited by its observational design. Although we adjusted for many potential confounders and the cohort represents a large sample, residual confounding, especially by unmeasured variables, cannot be excluded. Secondly, we obtained the death data by acquiring the National Death Index. Due to the incomplete linkage some biases could be introduced.[42,43] Thirdly, whether these associations remained for hospitalized patients also warrants additional investigation. Fourthly, because this study only examined baseline NLR, and did not investigate patterns of change in NLR nor its impact on mortality, the results may have been biased in interpretation. Longitudinal studies can be further implemented to make up this limitation.

This study only analyzed the baseline NLR, and did not investigate the change pattern of NLR nor its influence in mortality, which may lead to a potential bias in the interpretation of the present results.

Conclusions

Our findings suggested that elevated NLR significantly associated with an increased risk of long-term all-cause mortality among US general adults. The NLR defined herein emerge from routine complete blood count testing, ensuring that it can be easily applied in clinical practice. The statistically nonsignificant associations of NLR levels with cause-specific mortality desires further investigation.

Abbreviations

NLR, neutrophil-lymphocyte ratio; NHANES, National Health and Nutrition Examination Surveys; NCHS, National Center for Health Statistics; STROBE, strengthening the reporting of observational studies in epidemiology; PIR, income-poverty ratio; BMI, body mass index.

Data Sharing Statement

No additional data are available. NHANES and the NDI linkage data are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm and https://www.cdc.gov/nchs/data-linkage/mortality-public.htm. We intend to provide relevant code on written reasonable request.

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Disclosure

All authors declare no conflicts of interest in this work.

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