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Association between the neutrophil-to-lymphocyte ratio and cancer in adults from NHANES 2005–2018: a cross-sectional study

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Inflammation plays a crucial role in cancer development. The neutrophil-to-lymphocyte ratio (NLR), a measure of inflammation, is obtained from a complete blood count. However, little is known about the association between NLR and cancer in the general adult population in the United States. This study aimed to evaluate whether NLR is associated with cancer in American adults. This retrospective cross-sectional study included 28,016 adult participants from the National Health and Nutrition Examination Survey (NHANES) dataset spanning 2005 to 2018. Data on demographics (age, sex, race, marital status, Poverty-Income Ratio, education level), lifestyle factors (smoking, alcohol consumption, body mass index), medical conditions (hypertension, diabetes, cardiovascular disease), and laboratory parameters (hemoglobin, platelet count, alanine aminotransferase, creatinine, albumin, and lactate dehydrogenase), were collected. Logistic regression analysis was used to investigate the research objectives. Of the total 28,016 participants, 2639 had cancer. The mean age was 49.6 ± 17.6 years, and 50% were male. A positive association between NLR and cancer risk was observed after multivariate adjustment (OR = 1.20, 95% confidence interval (CI) = 1.05–1.36, $p = 0.006$). Similar patterns were observed in subgroup analyses (all p-values for interaction > 0.05). A higher NLR was directly correlated with an increased risk of developing cancer in adults.

Keywords Neutrophil, Lymphocyte, Cancer, NHANES, Cross-sectional study

Abbreviations

NLR	Neutrophil-to-lymphocyte ratio
NHANES	National health and nutrition examination survey
OR	Odds ratio
CI	Confidence interval
MEC	Mobile examination center
NCHS	National center for health statistics
CAPI	Computer-assisted personal interviewing
BMI	Body mass index
PIR	Poverty-income ratio
SD	Standard deviation
IQR	Interquartile range
RCS	Restricted cubic splines
TAN	Tumor-associated neutrophil
RCT	Randomized controlled trial
PSCC	Penile squamous cell carcinoma

Cancer is the second leading cause of mortality worldwide[1], accounting for over 8.7 million deaths in 2015[2]. The incidence of cancer is increasing, partly because of increased morbidity from chronic diseases and epidemiological

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transitions in developing countries[3]. As one of the most prevalent chronic diseases, cancer places a significant burden on both patients and the medical system. Early detection of cancer risk provides an opportunity to delay or prevent the onset of the disease. The connection between inflammation and cancer was initially observed by Rudolf Virchow, who detected leukocytes within tumors and hypothesized that inflammation increased cellular proliferation[4]. Since this discovery in the nineteenth century, inflammation has been recognized as one of the six biological processes of tumor development and a hallmark of cancer[5], linked to cancer initiation, progression, and metastasis[6]. The paradoxical role of neutrophils in both preventing and facilitating tumor progression has generated considerable research interest regarding neutrophils in the tumor microenvironment[7].

To predict cancer prognosis and inflammatory conditions, there is a growing interest in simple blood methods such as the neutrophil-to-lymphocyte ratio (NLR). NLR, obtained from complete blood counts, indicates inflammation levels and reflects the balance between the body's inflammatory and immune responses. An imbalance in NLR drives tumor progression and metastasis. The NLR may be a marker of inflammation related to tumor initiation through sustained neutrophil stimulation. Recent studies have indicated that the NLR is not only closely associated with the prognosis of various types of cancer but may also play a role in cancer metastasis and recurrence[8,9]. These findings emphasize the necessity for further research into the role of NLR in the development of cancer. However, little is known about the association between NLR and cancer in the general adult population in the United States. This study aimed to investigate the association between the NLR and cancer risk, with adjustments for several potential confounders.

Methods

Study design

This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention between 2005 and 2018. The NHANES aims to assess the health and nutritional status of non-institutionalized Americans through a comprehensive survey using a stratified multistage probability sampling method[10]. Data collection included demographic information, detailed health assessments, and laboratory tests performed at a mobile examination center (MEC) or through home visits. The study protocols adhered to the Declaration of Helsinki and were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. All adult participants provided written informed consent. Our secondary analysis followed the STROBE guidelines for cross-sectional studies and did not require additional institutional review board approval. The NHANES data used in this study are publicly accessible on its website. The NHANES data are available via the NHANES website (http://www.cdc.gov/nchs/nhanes.htm) (accessed on 1 March 2022).

In this analysis, we initially reviewed data from 93,547 participants collected during the NHANES cycles from 2005 to 2018. We focused on adults aged ≥ 20 years, totaling 39,749 individuals. Participants under 20 were excluded, as only those over 20 participated in the cancer-related surveys in the NHANES database. From this subset, we excluded participants with missing or incomplete data on cancer (30), neutrophil–lymphocyte count (3558), crucial study variables (7434), and 711 pregnant women. After applying these exclusion criteria, the final analytical sample consisted of 28,016 adults, including 2639 individuals with cancer and 25,377 without cancer. The detailed inclusion and exclusion processes are presented in Fig. 1.

Definition of cancer

NHANES includes a section on medical conditions that collects self-reported health information. We identified participants with a history of cancer or malignancy based on their responses to the question, "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" Trained interviewers posed the questions at home using the Computer-Assisted Personal Interviewing (CAPI) system, which was programmed with built-in consistency checks to reduce data entry errors.

Definition of NLR

Neutrophil and lymphocyte counts were obtained from complete blood count analyses of blood samples using a Beckman Coulter automated blood analyzer at a MEC, and the counts were expressed as $\times 10^3$ cells/μL. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Definition of covariates

Various potential covariates were considered in accordance with the existing literature, including age, sex, marital status, race/ethnicity, education level, family income, smoking status, hypertension, diabetes, cardiovascular disease, body mass index (BMI), and laboratory parameters, such as hemoglobin, platelet count, alanine aminotransferase, creatinine, albumin, and lactate dehydrogenase levels. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, or other. Marital status was classified as married, living with a partner, or living alone. Educational attainment was grouped into < 9 years, 9–12 years, and > 12 years of education. Family income was categorized into low (poverty-income ratio, PIR ≤ 1.3), medium (PIR > 1.3 to 3.5), and high (PIR > 3.5) based on a US government report. Smoking status was classified as never smoked (smoked fewer than 100 cigarettes), current smoker, or former smoker (quit smoking after smoking more than 100 cigarettes), following definitions from previous literature. Participants were segmented based on their alcohol consumption patterns, with categories including never drinkers (< 12 drinks in their lifetime), former drinkers (≥ 12 drinks in 1 year but did not drink last year, or did not drink last year but consumed ≥ 12 drinks in their lifetime), current mild alcohol users (≤ 1 drink per day for females, ≤ 2 drinks per day for males), current moderate alcohol users (≥ 2 drinks per day for females, ≥ 3 drinks per day for males, or binge drinking ≥ 2 days per month), and current heavy alcohol users (≥ 3 drinks per day for females, ≥ 4 drinks per day for males, or binge drinking ≥ 4 drinks on the same occasion for females, ≥ 5 drinks on the same occasion for males on 5 or

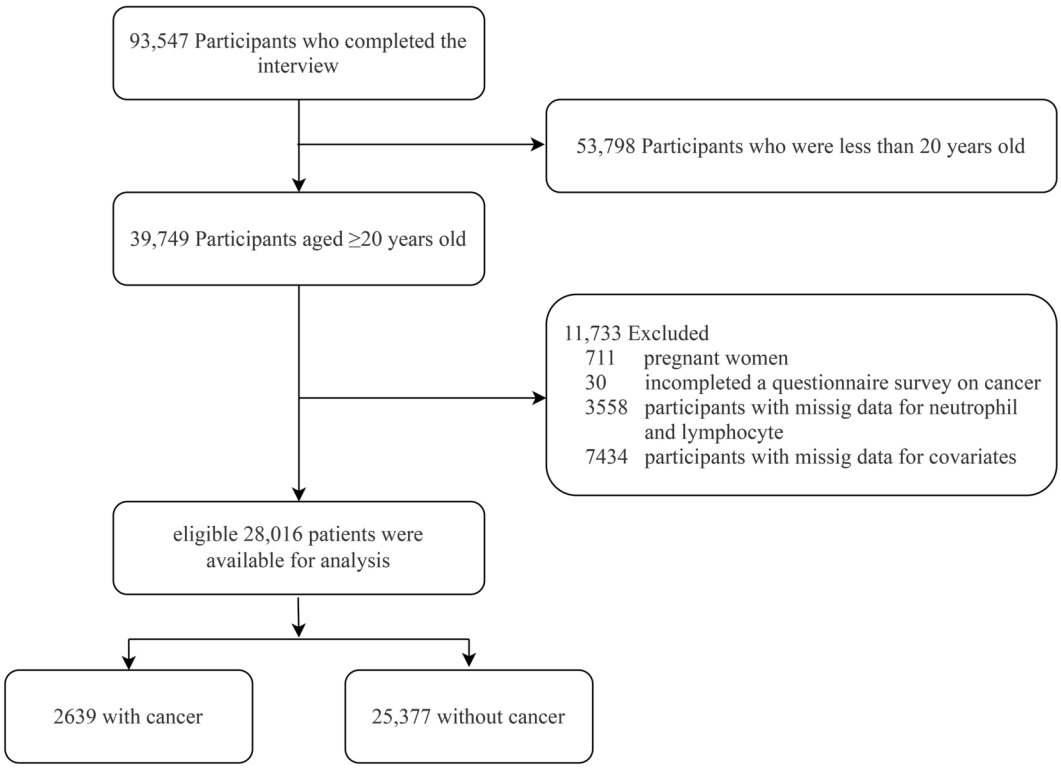

Fig. 1. The flow chart of the study.

more days per month). The presence of previous diseases such as hypertension, diabetes, and cardiovascular disease was determined based on the participants' responses to questions in the questionnaire regarding whether a doctor had diagnosed them with the condition in the past. BMI was calculated using a standardized technique that incorporates weight and height measurements.

Statistical analysis

Histogram distribution, Q-Q plot, and the Kolmogorov–Smirnov test were used to determine whether the variables followed a normal distribution. For normally distributed continuous variables, the mean and standard deviation (SD) were reported, while skewed continuous variables were described using the median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages (%). To compare continuous variables among groups, the independent samples Student's t-test or Mann–Whitney U-test was employed based on the normality of the distribution. Categorical data were compared using the chi-square test or Fisher's exact test, as appropriate.

Logistic regression was used to investigate the association between the NLR and cancer. The NLR was entered as a categorical variable (four quantiles). We selected these confounders based on their judgments. We constructed three models: Model 1 was adjusted for age, sex, race, marital status, PIR, and education. Model 2 was additionally adjusted for Model 1 and smoke, alcohol drinking status, BMI, hypertension, diabetes, and cardiovascular disease, while Model 3 was additionally adjusted for Model 2 and hemoglobin, platelet, alanine aminotransferase, creatinine, albumin, and lactate dehydrogenase levels.

Tests for trends were conducted using multivariate regression models by entering the four quartiles of NLR as a categorical variable. We used a restricted cubic spline model to develop smooth curves and examine the possible non-linear dose–response associations between NLR and cancer. Nonlinearity was assessed using a likelihood ratio test, comparing the model with only a linear term against the model with linear and cubic spline terms. In the case of non-linear correlation, a two-piecewise regression model was applied to determine the threshold effect of the NLR on cancer, and this was illustrated using a smoothing plot. Subgroup analyses were also performed. For the continuous variable, we first converted it to a categorical variable according to four quartiles and then performed an interaction test. Missing data accounted for less than 5% of the dataset and were handled by listwise deletions on an analysis basis. We performed a series of sensitivity analyses to assess the robustness of the study's findings and evaluate how our conclusions might be influenced by employing different association inference models. We report and compare the effect sizes and *p*-values calculated using these models. All analyses were performed using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and Free Statistics Analysis Platform (Version 1.9, Beijing, China, http://www.clinicalscientists.cn/freestatistics)[11]. FreeStatistics is a software package that provides intuitive interfaces for the most common analyses and data visualization. R was used as the underlying statistical engine, and the graphical user interface (GUI) was written

in Python. Most analyses can be performed with only a few clicks. It was designed for reproducible analysis and interactive computing. Statistical significance was defined as a two-sided p-value of < 0.05.

Results

Baseline characteristics

This study included 28,016 participants aged 49.6 ± 17.6 years. The overall cancer prevalence was 9.4%. Table 1 shows the general characteristics of the participants according to the neutrophil–lymphocyte ratio. The four groups differed in age, sex, race, marital status, education, family income, smoking, alcohol consumption,

Characteristic	Neutrophil–lymphocyte ratio					
	Total	Q1 (≤ 1.4)	Q2 (1.4–1.9)	Q3 (1.9–2.6)	Q4 (> 2.6)	*p*-value
No	28,016	6989	6984	7039	7004	
Age (year), mean (SD)	49.6 ± 17.6	47.4 ± 16.9	48.0 ± 17.1	49.1 ± 17.5	53.7 ± 18.3	< 0.001
Sex, n (%)						< 0.001
Male	14,015 (50.0)	3334 (47.7)	3370 (48.3)	3495 (49.7)	3816 (54.5)	
Female	14,001 (50.0)	3655 (52.3)	3614 (51.7)	3544 (50.3)	3188 (45.5)	
Race/ethnicity, n (%)						< 0.001
Non-hispanic white	12,588 (44.9)	2159 (30.9)	3014 (43.2)	3470 (49.3)	3945 (56.3)	
Non-hispanic black	5700 (20.3)	2482 (35.5)	1269 (18.2)	1062 (15.1)	887 (12.7)	
Mexican American	4291 (15.3)	959 (13.7)	1190 (17)	1144 (16.3)	998 (14.2)	
Others	5437 (19.4)	1389 (19.9)	1511 (21.6)	1363 (19.4)	1174 (16.8)	
Marital status, n (%)						< 0.001
Married or living with partners	16,826 (60.1)	4099 (58.6)	4290 (61.4)	4342 (61.7)	4095 (58.5)	
Living alone	11,190 (39.9)	2890 (41.4)	2694 (38.6)	2697 (38.3)	2909 (41.5)	
Education level (year), n (%)						0.026
< 9	6524 (23.3)	1580 (22.6)	1687 (24.2)	1601 (22.7)	1656 (23.6)	
9–12	6429 (22.9)	1583 (22.6)	1561 (22.4)	1604 (22.8)	1681 (24)	
> 12	15,063 (53.8)	3826 (54.7)	3736 (53.5)	3834 (54.5)	3667 (52.4)	
Family income, n (%)						0.008
Low	8612 (30.7)	2202 (31.5)	2088 (29.9)	2128 (30.2)	2194 (31.3)	
Medium	10,599 (37.8)	2624 (37.5)	2623 (37.6)	2634 (37.4)	2718 (38.8)	
High	8805 (31.4)	2163 (30.9)	2273 (32.5)	2277 (32.3)	2092 (29.9)	
Smoking status, n (%)						< 0.001
Never	15,277 (54.5)	4075 (58.3)	4001 (57.3)	3822 (54.3)	3379 (48.2)	
Current	6911 (24.7)	1546 (22.1)	1599 (22.9)	1737 (24.7)	2029 (29)	
Former	5828 (20.8)	1368 (19.6)	1384 (19.8)	1480 (21)	1596 (22.8)	
Alcohol drinking status, n (%)						< 0.001
Never	3848 (13.7)	1056 (15.1)	994 (14.2)	918 (13)	880 (12.6)	
Former	4590 (16.4)	1059 (15.2)	1062 (15.2)	1146 (16.3)	1323 (18.9)	
Mild	9487 (33.9)	2360 (33.8)	2325 (33.3)	2404 (34.2)	2398 (34.2)	
Moderate	4381 (15.6)	1127 (16.1)	1151 (16.5)	1139 (16.2)	964 (13.8)	
Heavy	5710 (20.4)	1387 (19.8)	1452 (20.8)	1432 (20.3)	1439 (20.5)	
Hypertension, n (%)	11,911 (42.5)	2799 (40)	2695 (38.6)	2927 (41.6)	3490 (49.8)	< 0.001
Diabetes, n (%)	5216 (18.6)	1145 (16.4)	1162 (16.6)	1282 (18.2)	1627 (23.2)	< 0.001
Cardiovascular disease, n (%)	3051 (10.9)	563 (8.1)	603 (8.6)	722 (10.3)	1163 (16.6)	< 0.001
Body mass index (kg/m^2), mean (SD)	29.2 ± 7.0	28.8 ± 6.5	29.1 ± 6.6	29.5 ± 7.1	29.6 ± 7.5	< 0.001
Neutrophil (10^9/L), median (IQR)	14.1 ± 1.5	14.0 ± 1.5	14.2 ± 1.5	14.2 ± 1.5	14.2 ± 1.6	< 0.001
Lymphocyte (10^9/L), median (IQR)	4.0 (3.1, 5.1)	2.8 (2.2, 3.5)	3.7 (3.1, 4.5)	4.4 (3.6, 5.2)	5.4 (4.4, 6.6)	< 0.001
Hemoglobin (g/L), mean ± SD	2.1 (1.7, 2.5)	2.5 (2.1, 3.0)	2.2 (1.8, 2.6)	2.0 (1.7, 2.4)	1.6 (1.3, 2.0)	< 0.001
Platelet (10^9/L), mean ± SD	247.9 ± 66.3	244.1 ± 63.4	247.9 ± 63.7	249.8 ± 65.8	249.7 ± 71.7	< 0.001
Alanine transaminase (IU/L), Median (IQR)	21.0 (16.0, 28.0)	21.0 (16.0, 29.0)	21.0 (16.0, 29.0)	21.0 (16.0, 28.0)	20.0 (16.0, 27.0)	< 0.001
Albumin (g/L), mean ± SD	42.4 ± 3.3	42.4 ± 3.3	42.6 ± 3.2	42.5 ± 3.3	42.0 ± 3.5	< 0.001
Creatinine (μ mol/L), median (IQR)	76.0 (63.6, 89.3)	76.0 (63.6, 88.4)	74.3 (62.8, 88.4)	75.1 (63.6, 88.4)	79.6 (65.4, 92.8)	< 0.001
Lactate dehydrogenase (IU/L), Mean ± SD	133.3 ± 32.3	133.2 ± 34.3	132.0 ± 29.5	132.0 ± 29.8	135.8 ± 34.8	< 0.001
Cancer, n (%)	2639 (9.4)	486 (7)	557 (8)	639 (9.1)	957 (13.7)	< 0.001

Table 1. Population characteristics by categories of the neutrophil–lymphocyte ratio.

hypertension, diabetes, cardiovascular disease, BMI, neutrophils, lymphocytes, hemoglobin, platelets, alanine transaminase, albumin, creatinine, and lactate dehydrogenase levels (all p-values < 0.05).

Associations between NLR and cancer

Univariate analysis demonstrated that age, sex, education, race, smoking status, alcohol consumption status, family income, cardiovascular disease, hypertension, diabetes, hemoglobin, platelet count, alanine aminotransferase, creatinine, albumin, and lactate dehydrogenase levels were associated with cancer (Table 2).

Variables	OR (95% CI)	p-value
Age (years)	0.94 (0.93 ~ 0.94)	< 0.001
Gender, n (%)		
Male	1 (reference)	
Female	0.89 (0.82 ~ 0.96)	0.004
Race/ethnicity, n (%)		
Non-hispanic white	1 (reference)	
Non-hispanic black	2.57 (2.29 ~ 2.9)	< 0.001
Mexican American	4.26 (3.62 ~ 5.01)	< 0.001
Others	3.41 (2.98 ~ 3.89)	< 0.001
Education level (year), n (%)		
< 9	1 (reference)	
9–12	0.88 (0.78 ~ 0.99)	0.041
> 12	0.78 (0.71 ~ 0.87)	< 0.001
Family income, n (%)		
Low	1 (reference)	
Medium	0.69 (0.62 ~ 0.77)	< 0.001
High	0.65 (0.58 ~ 0.72)	< 0.001
Smoking status, n (%)		
Never	1 (reference)	
Current	0.47 (0.43 ~ 0.52)	< 0.001
Former	1.08 (0.96 ~ 1.22)	0.179
Body mass index (kg/m^2)	1.00 (1.00 ~ 1.01)	0.504
Marital status, n (%)		
Married or living with partners	1 (reference)	
Living alone	1.03 (0.95 ~ 1.12)	0.476
Alcohol drinking status, n (%)		
Never	1 (reference)	
Former	0.66 (0.57 ~ 0.76)	< 0.001
Mild	0.71 (0.63 ~ 0.81)	< 0.001
Moderate	1.2 (1.02 ~ 1.4)	0.026
Heavy	2.08 (1.75 ~ 2.46)	< 0.001
Cardiovascular disease		
No	1 (reference)	
Yes	0.32 (0.29 ~ 0.36)	< 0.001
Hypertension		
No	1 (reference)	
Yes	0.38 (0.35 ~ 0.41)	< 0.001
Diabetes		
No	1 (reference)	
Yes	0.57 (0.52 ~ 0.63)	< 0.001
Hemoglobin (g/L)	1.12 (1.09 ~ 1.15)	< 0.001
Platelet (10^9/L)	1.00 (0.99 ~ 1.01)	< 0.001
Alanine transaminase (IU/L)	1.01 (1.01 ~ 1.01)	< 0.001
Albumin (g/L)	1.07 (1.05 ~ 1.08)	< 0.001
Creatinine (μ mol/L)	1.00 (0.99 ~ 1.00)	< 0.001
Lactate dehydrogenase (IU/L),	1.00 (0.99 ~ 1.01)	< 0.001

Table 2. Association of covariates and cancer. OR, odds ratio; CI, confidence interval.

Table 3 presents the results of the multivariable logistic regression analysis examining the association between NLR and cancer. A high NLR was associated with an increased prevalence of cancer (OR: 1.06, 95% CI 1.03–1.09, $p < 0.001$), after adjusting for age, sex, marital status, race/ethnicity, educational level, family income, BMI, smoking status, alcohol consumption status, hypertension, diabetes, cardiovascular disease, hemoglobin, platelet, alanine aminotransferase, creatinine, albumin, and lactate dehydrogenase levels. Compared to individuals with lower NLR Q1 (≤ 1.4), the adjusted OR values for NLR and cancer in Q2 (1.4–1.9), Q3 (1.9–2.6), and Q4 (> 2.6) were 1.01 (95% CI 0.88 ~ 1.16, $p = 0.857$), 1.02 (95% CI 0.89–1.17, $p = 0.752$), and 1.20 (95% CI 1.05–1.36, $p = 0.006$), respectively. Analysis using restricted cubic splines (RCS) suggested a linear relationship between NLR and cancer (Fig. 2, p for nonlinearity = 0.261, with the highest and lowest 0.5% trimmed for each NLR measure). The association between NLR and cancer demonstrated an increasing trend as the NLR increased.

Stratified analyses based on additional variables

Stratified analysis was performed across various subgroups to assess potential differences in how NLR relates to cancer. No significant interactions were observed in any subgroup including those stratified by age, marital status, educational level, family income, or BMI (Fig. 3).

Discussion

In this large retrospective cross-sectional study of adults using the NHANES 2005–2018 dataset, NLR was found to be independently associated with a 20% increase in the risk of cancer. Subsequent exploratory subgroup analyses did not reveal any significant interactions. These findings have significant implications for current cancer management strategies, particularly in East Asian countries. This is noteworthy because of the comparatively lower NLR in the general East Asian population compared to that in Caucasians.

Neutrophil and lymphocyte counts, are simple and cost-effective blood tests, providing valuable insights into the systemic inflammatory status and the balance between neutrophils and lymphocytes, which are essential for acquired immunity[12]. The ratio of these counts, known as NLR, is emerging as a more predictive indicator than either parameter alone[13]. Previous studies have documented the prognostic role of neutrophils, particularly the NLR, and their association with poor outcomes across various cancer types[14]. Recent reports have shown that NLR correlates with survival in cancer patients, reflecting the significant role played by inflammatory cells and mediators in the tumor microenvironment and systemic immune status in cancer progression. Moreover, elevated NLR has been linked to increased mortality in patients with chronic lower respiratory diseases, pneumonia, sepsis, and kidney disease[15–18]. These findings suggest that the NLR could serve as a potential prognostic marker for disease progression and mortality risk across various populations.

Our study observed positive linear associations between the NLR and cancer in the adult population from the NHANES 2005–2018. These findings align with results from other observational studies[19–21]. Previous research has explored the relationship between NLR and specific cancers. For example, Hu et al.[20] identified that elevated levels of NLR were independently associated with an increased risk of brain metastases in patients with non-small cell lung cancer (HR = 1.43, 95% CI 1.01–2.03, $P_{trend} = 0.031$). Thomas et al.[19] reported that a higher NLR was significantly linked to an increased risk of hepatocellular carcinoma among patients with nonalcoholic fatty liver disease. Moreover, a recent prospective longitudinal cohort study involving patients with gynecological cancers also demonstrated a significant association between NLR and cancer risk[21], showing that high NLR is associated with adverse overall survival and event-free survival in patients with gynecologic malignancies. Recent meta-analyses have further confirmed this association, demonstrating that the NLR has significant diagnostic and prognostic value in penile squamous cell carcinoma (PSCC)[9]. Elevated NLR is linked to poor outcomes in cancer patients across various diagnoses, stages, and treatments[8,15].

Further investigations are necessary to validate our findings and to delve into the detailed relationships and potential underlying mechanisms. Recent studies have provided additional evidence linking NLR to cancer. For instance, a pooled analysis of prospective cohort studies confirmed a significant association between NLR and cancer incidence[22–30]. Our results not only affirm but also expand upon these earlier findings in the context of

Variable	No	Cancer (%)	Crude model		Model 1		Model 2		Model 3	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
NLR	28,016	9.4	1.22 (1.19 ~ 1.26)	< 0.001	1.07 (1.04 ~ 1.1)	< 0.001	1.06 (1.03 ~ 1.09)	< 0.001	1.06 (1.03 ~ 1.09)	< 0.001
NLR (quartile)										
Q1	6989	7	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Q2	6984	8	1.16 (1.02 ~ 1.32)	0.022	1.02 (0.89 ~ 1.17)	0.789	1.01 (0.88 ~ 1.16)	0.863	1.01 (0.88 ~ 1.16)	0.857
Q3	7039	9.1	1.34 (1.18 ~ 1.51)	< 0.001	1.04 (0.91 ~ 1.19)	0.559	1.02 (0.9 ~ 1.17)	0.725	1.02 (0.89 ~ 1.17)	0.752
Q4	7004	13.7	2.12 (1.89 ~ 2.37)	< 0.001	1.25 (1.1 ~ 1.42)	0.001	1.21 (1.06 ~ 1.37)	0.004	1.20 (1.05 ~ 1.36)	0.006
Trend test				< 0.001		< 0.001		0.002		0.004

Table 3. Association between NLR and cancer in multiple regression model. NLR, neutrophil–lymphocyte ratio; Q, quantiles, Q1 (≤ 1.4), Q2 (1.4–1.9), Q3 (1.9–2.6), Q4 (≥ 2.6); OR, odds ratio; CI, confidence interval; Ref, reference; Model 1: Adjusted for variables (age, sex, race, marry, PIR and education); Model 2: Adjusted for Model 1 and smoke, alcohol drinking status, body mass index (BMI), hypertension, diabetes and cardiovascular disease; Model 3: Adjusted for Model 2 and hemoglobin, platelet, alanine aminotransferase, creatinine, albumin and lactate dehydrogenase levels.

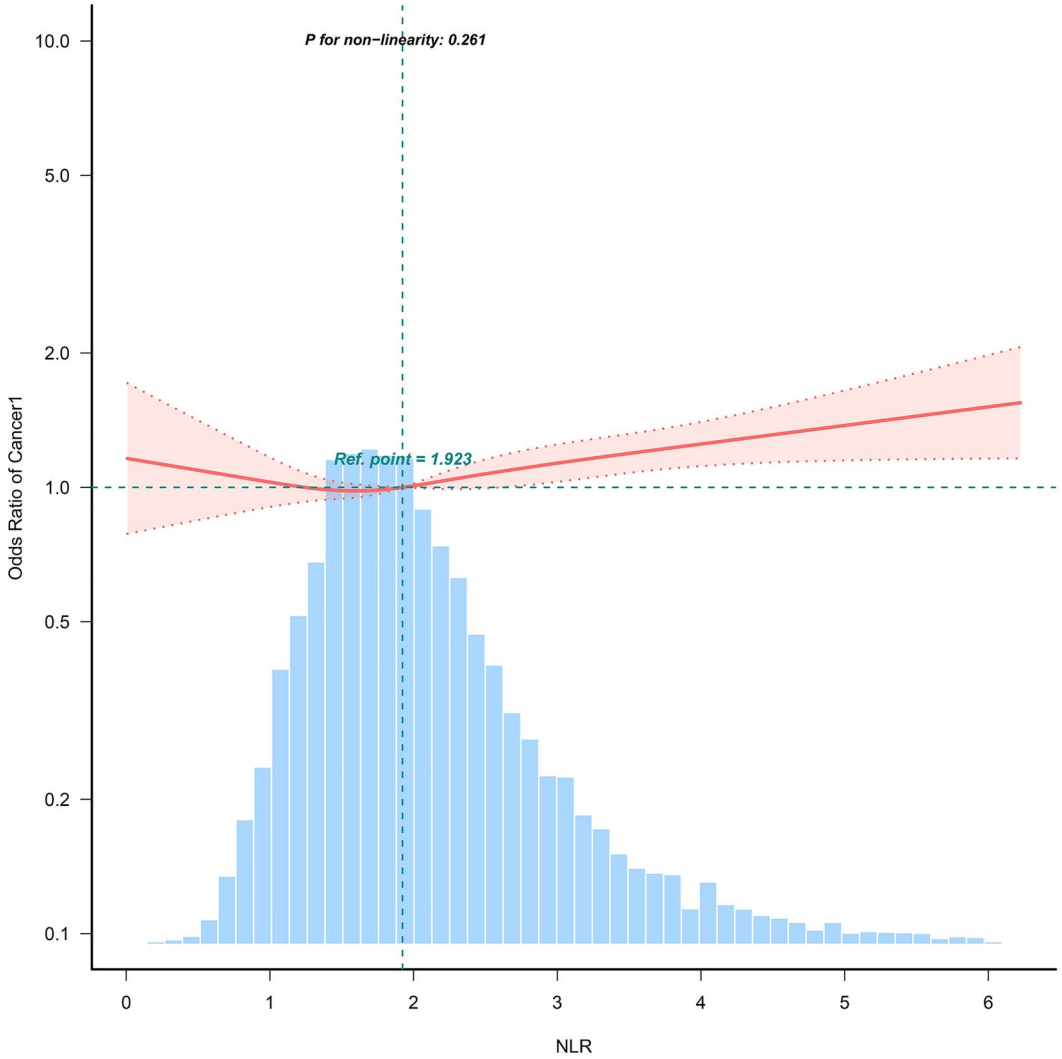

Fig. 2. Adjusted Relationship between NLR and Cancer Odds Ratio. Solid and dashed lines represent the predicted value and 95% confidence intervals. They were adjusted for age, sex, race, marry, PIR, education, smoke, alcohol drinking status, body mass index, hypertension, diabetes, cardiovascular disease, hemoglobin, platelet, alanine aminotransferase, creatinine, albumin and lactate dehydrogenase levels.

the NHANES 2005–2018 adult population. Our study revealed that NLR was independently associated with a 20% increase in the risk of cancer (OR = 1.2, 95% CI 1.05–1.36, P_{trend} = 0.004). Tumor-associated neutrophils (TANs) are a type of immune cell that can be found in and around tumor sites. They have been shown to play a role in promoting tumor growth and progression by creating a pro-tumor environment[31]. TANs have been linked to poor prognosis and survival in various types of cancer, including breast, lung, and colorectal cancer[18,20,32,33]. They can also contribute to treatment resistance and metastasis. Lymphocytes are vital immune cells that play a crucial role in the body's defense against cancer. They are capable of directly engaging in the body's anti-cancer response and can impede the advancement of malignant tumors by promoting anti-tumor immune activity[34]. Conversely, a decrease in lymphocyte count, known as lymphocytopenia, due to cancer treatment has been linked to a poorer prognosis for cancer patients. A reduced lymphocyte count may reflect reduced immune surveillance, which could lead to the escape of malignant cells and tumor growth[35]. Basic studies have demonstrated an association between tumorigenesis and inflammatory processes. When the NLR is elevated, the neutrophil count is relatively increased, the lymphocyte count is relatively decreased, and the equilibrium is disrupted, thus promoting tumor progression.

The study's strengths lie in its large-scale, population-focused approach and its capacity to explore the association between NLR and cancer risk across various subgroups concurrently. Meanwhile, the study leveraged a validated, comprehensive electronic healthcare database, encompassing all diagnoses, hospital stays, and medication records. This has enabled researchers to collect relevant data and minimize common biases present in conventional observational studies, such as selection and recall biases. The research approach adopted in this study is rigorous, novel, and has practical implications for therapy.

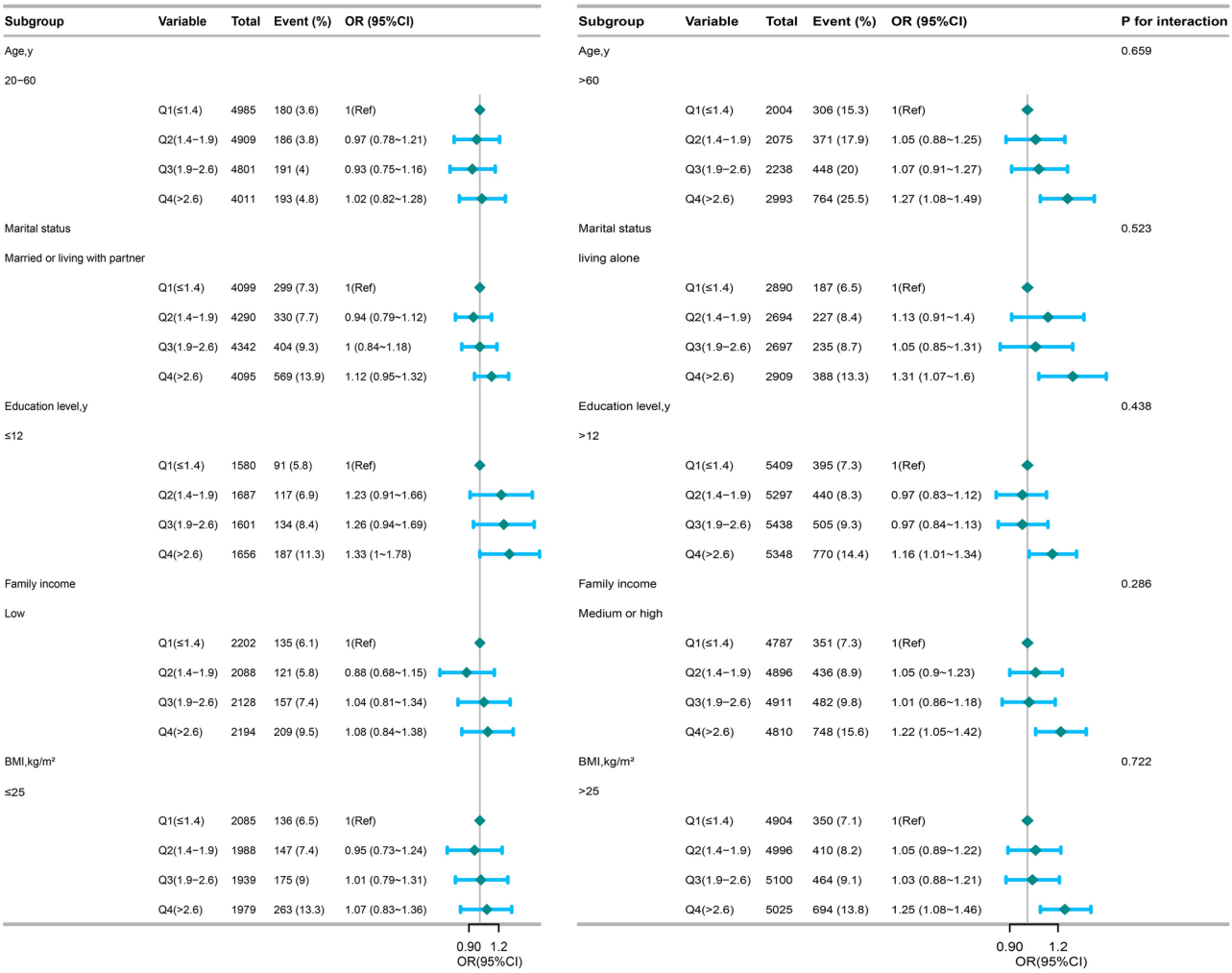

Fig. 3. The relationship between NLR and cancer according to basic features. Except for the stratification component itself, each stratification factor was adjusted for all other variables (age, sex, race, marry, PIR, education, smoke, alcohol drinking status, body mass index, hypertension, diabetes, cardiovascular disease, hemoglobin, platelet, creatinine, alanine aminotransferase, albumin and lactate dehydrogenase levels).

However, it is important to acknowledge the limitations of this study. First, due to the inherent limitations of cross-sectional studies, it is not possible to establish a causal relationship between NLR and cancer. Future longitudinal studies will be needed to confirm any potential link. Second, as an observational study, the results may not directly correspond to those of a randomized controlled trial (RCT), and caution should be exercised when generalizing the findings to real-life scenarios. Third, the information on cancer was obtained from self-reported health data, which may contribute to recall bias. Despite these limitations, this study provides valuable insights into the relationship between NLR and cancer outcomes, contributes additional evidence to the existing literature, and highlights variations across different continents and ethnicities.

Conclusion

In this study, we found that an increase in the NLR is significantly associated with an elevated risk of cancer in adults, which underscores the importance of NLR as a potential biomarker for cancer risk assessment. Clinicians should consider these associations when making treatment decisions for patients with cancer.

Data availability

All the datasets are available on the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

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Author contributions

G.P.L. contributed the central idea, and D.Z., M.H.L., F.F.Y. and X.J.H. analyzed most of the data. G.P.L. wrote the initial draft of the paper, D.J.H., X.D.W. and Y.W.F. guided the theory and design of the research, and revised the article. All authors contributed to refining the ideas, carrying out additional analyses, and finalizing this paper. The author(s) read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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