Cross-Sectional Study

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Extensive study on the associations of 12 composite inflammatory indices with colorectal cancer risk and mortality: a cross-sectional analysis of NHANES 2001–2020

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Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide, with inflammation emerging as a critical factor in its development. We conducted the most comprehensive analysis to date of various inflammatory indices, investigating the associations between these indices and both the risk and mortality of CRC, utilizing nationwide data from the National Health and Nutrition Examination Survey (NHANES).

Methods: Data were sourced from NHANES cycles spanning 2001 to 2020. After applying strict inclusion and exclusion criteria, 18 470 eligible samples were analyzed. Twelve composite inflammatory indices were calculated based on peripheral blood cell counts. After adjusting for confounders, we employed logistic regression models to investigate the association between inflammatory indices and CRC risk, supplemented by forest plots, generalized additive model (GAM), and receiver operating characteristic (ROC) curves for a comprehensive understanding. To assess the association between these indices and CRC mortality, we utilized Cox proportional hazards regression analysis, augmented by restricted cubic splines for flexibility, survival curves for visual representation, and ROC curves for discriminative ability.

Results: Elevated neutrophil-to-lymphocyte ratio (NLR) and reduced lymphocyte-to-monocyte ratio (LMR) were significantly associated with increased CRC risk (NLR: Q4 vs. Q1: OR = 2.137, 95% CI = 1.212–3.765, *P*-trend = 0.045; LMR: Q4 vs. Q1: OR = 0.503, 95% CI = 0.274–0.923, *P*-trend = 0.027). In terms of mortality risk, low LMR, high neutrophil-to-platelet ratio (NPR), and high systemic immune-inflammation index (SII) showed associations with adverse outcomes. Higher SII (*P* = 0.0459), NPR (*P* = 0.0333) levels trended toward poorer prognosis, while higher LMR levels predicted better prognosis (*P* = 0.0056). The association between these indicators and the risk and prognosis of CRC tends to be more of a nonlinear correlation. In terms of their performance in assessing the risk and prognosis of CRC, there is no significant difference between single indicators and combined indicators.

Conclusions: Elevated NLR and reduced LMR may serve as non-invasive biomarkers for early detection and risk stratification of CRC. Low LMR, high NPR, and high SII are linked to adverse mortality outcomes. Dynamic monitoring based on these indices has the potential to offer new insights and directions for the diagnosis and treatment of CRC.

Keywords: colorectal cancer, inflammation, inflammatory indices, mortality, risk

Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, posing a significant health burden despite advancements in early detection, treatment, and prevention strategies[1]. The intricate interplay between genetic, environmental, and inflammatory factors in the development and progression of CRC has garnered substantial research interest, with inflammation emerging as a critical component in this multifactorial disease process[2]. Recent studies have underscored the potential role of various inflammatory indices in predicting cancer risk and outcomes, shedding new light on the underlying biology of CRC carcinogenesis[3-5].

Inflammation is inherently a natural immune response. Under normal circumstances, it is beneficial and serves as the body's automatic defense mechanism. However, when inflammation persists or fails to be effectively controlled, it can gradually progress to chronic inflammation. Long-term chronic inflammation may lead to tissue damage and gene mutations, thereby

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increasing the risk of diseases, including cancer, cardiovascular diseases, fibrosis, and cognitive impairments[6,7]. Inflammation indicators can be categorized into two categories: single indicators and composite indices, which are inflammatory indices calculated based on multiple single indicators. There are numerous related inflammatory indices, among which the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-platelet ratio (NPR), systemic immune-inflammation response index (SIRI), platelet-to-albumin ratio (PAR), C-reactive protein-to-albumin ratio (CAR), C-reactive protein to lymphocyte ratio (CLR), C-reactive protein-albumin-lymphocyte index (CALLY), pan-immune-inflammation value (PIV), and hemoglobin, albumin, lymphocyte, and platelet score (HALP) have a certain evidence-based foundation for predicting systemic inflammation. Derived from routine blood tests, these indices offer a non-invasive and cost-effective approach to assessing systemic inflammation and immune status, which may serve as surrogate markers for cancer risk and prognosis[8-10]. In the surgical context, these inflammatory indices may also guide perioperative decision-making. For instance, elevated NLR is associated with poor prognosis and an increased risk of postoperative complications including intra-abdominal infection after radical resection of CRC[11,12]. LMR, as a potential prognostic factor, may aid in risk stratification before elective colorectal surgery, informing closer follow-up or adjuvant therapy decisions[13-15].

The National Health and Nutrition Examination Survey (NHANES), a population-based study conducted by the Centers for Disease Control and Prevention (CDC), provides an invaluable resource for investigating the associations between inflammatory indices and CRC outcomes. NHANES collects comprehensive data on demographic characteristics, lifestyle factors, health conditions, and biochemical measurements, including complete blood counts and inflammatory markers, from a representative sample of the U.S. population. By leveraging the power of NHANES data, researchers can conduct comprehensive analyses to elucidate the complex association between inflammatory indices and CRC risk and mortality.

Despite the growing body of evidence supporting the role of inflammatory indices in cancer, studies specifically examining their associations with CRC using NHANES data are scarce. Moreover, most existing studies have focused on individual indices in isolation, neglecting the potential synergistic effects of multiple indices. Therefore, the primary objective of this study is to investigate the associations between a wide range of inflammatory indices (SII, PLR, LMR, NPR, SIRI, PAR, CAR, CLR, CALLY, PIV, HALP) and both CRC risk and mortality using NHANES data. By employing robust statistical methods and accounting for potential confounding factors, we aim to provide comprehensive insights into the predictive value of these indices for CRC risk and outcomes. Ultimately, this study seeks to contribute to the expanding knowledge base on the role of inflammation in CRC and to inform clinical practice and public health policies aimed at reducing the burden of this disease.

HIGHLIGHTS

- Comprehensive analysis of 12 inflammatory indices and their associations with CRC risk and mortality using NHANES data (2001–2020).
- Elevated neutrophil-to-lymphocyte ratio (NLR) and reduced lymphocyte-to-monocyte ratio (LMR) associated with increased CRC risk.
- Low LMR, high neutrophil-to-platelet ratio (NPR), and high systemic immune-inflammation index (SII) linked to mortality risk.
- Non-linear relationships between inflammatory indices and CRC outcomes elucidated using restricted cubic splines and generalized additive model.
- Potential of NLR, LMR, SII, and NPR as non-invasive biomarkers for early detection and prognostic assessment in CRC.

Methods

Study design and population

This cross-sectional study adheres to the updated STROCSS 2025 guideline[16]. The data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States. We integrated nine cycles of NHANES from 2001 to 2020 (pre-pandemic). After integrating data from various cycles based on the required experimental indicators, a total of 97 657 individuals were eligible during this timeframe. We applied strict inclusion and exclusion criteria, participants were excluded if they were under 20 years old, lacked complete blood test indicators, lacked information on cancer diagnosis, were suffering from tumors other than CRC, lacked information on survival outcomes, or were pregnant. And ultimately, we obtained 18 470 statistically viable samples.

The definition and calculation of inflammatory indices

The inflammatory indices analyzed in this study are based on calculations of corresponding indicators in peripheral blood. The indicators involved encompass neutrophil count ($\times 10^9$/L), lymphocyte count ($\times 10^9$/L), monocyte count ($\times 10^9$/L), platelet count ($\times 10^9$/L), hemoglobin level (g/L), albumin level (g/L), and C-reactive protein level (mg/L), all of which are derived from the laboratory data section of the database. These markers were calculated using the following formulas:

SII = platelet count × neutrophil count/lymphocyte count

NLR = neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

LMR = lymphocyte count/monocyte count

NPR = neutrophil count/platelet count

SIRI = neutrophil count × monocyte count/lymphocyte count

PAR = platelet count/albumin level

CAR = C-reactive protein level/albumin level

CLR = C-reactive protein level/lymphocyte count

CALLY = albumin level × lymphocyte count/(C-reactive protein level × 10)

PIV = neutrophil count × monocyte count × platelet count/lymphocyte count

HALP = hemoglobin level × albumin level × lymphocyte count/platelet count.

Determination of CRC

The cancer history information was collected through questionnaire data related to medical conditions. Participants were queried, "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" If they responded affirmatively, a follow-up question was posed to ascertain the precise diagnosis: "What kind was it?"

Ascertainment of mortality

The prognostic information of the participants was sourced from the NCHS database and was integrated and annotated with reference to the "Sample R program" The follow-up period for prognosis ended on 31 December 2019. The data used for analysis included survival status and the number of survival months since the start of follow-up.

Assessment of covariates

This study considered a range of covariates encompassing basic demographic characteristics and health-related information. Demographic data encompassed age, gender (male or female), race (Mexican American, non-Hispanic white, non-Hispanic black, or other), and education level (less than high school, high school or equivalent, or some college or higher). Health-related variables took into account body mass index (BMI), categorized as normal/underweight (<25), overweight (25–30), or obese (>30); smoking status, classified as smoking every day, some days, or not at all; alcohol consumption status, further subdivided into any alcohol consumption and heavy alcohol consumption based on daily intake (≥5 drinks daily are considered as heavy alcohol consumption); chronic underlying conditions, including hypertension and diabetes.

Statistical analyses

The baseline characteristics of both the case group and the control group are described using percentages for categorical variables or mean ± SEM (standard error of the mean) for continuous variables. For categorical variables, we use the chi-square test to compare differences between the two groups. For continuous variables, we first conduct a normality test on the data. For data that do not conform to a normal distribution, we performed the Mann–Whitney U test.

The levels of serum inflammation indices were divided into quartiles (quartile 1, 25th percentile; quartile 2, 25th to 50th percentile; quartile 3, 50th to 75th percentile; quartile 4, >75th percentile). Univariate logistic regression analysis was conducted to evaluate the crude association between serum inflammation indices and CRC. Subsequently, three different confounding factor-adjusted models were established, using multivariable logistic regression methods to analyze the association between these inflammatory indicators and CRC risk. Model 1 was adjusted for age; Model 2 was adjusted for age, gender, race, and education level; and Model 3 was further adjusted for age, gender, race, education level, BMI, smoking status, alcohol consumption, diabetes, and hypertension. The results are presented in terms of odds ratios (ORs) and 95% confidence intervals (95% CIs). The generalized estimating equation (GEE) model with cluster-robust standard errors was implemented to confirm the associations between inflammation indices and CRC risk while adjusting for intra-cluster correlations inherent in the complex sampling design. A post-hoc power analysis was employed to evaluate the reliability of the conclusions under the sample conditions of this study. We employed the Generalized Additive Model (GAM) to flexibly model potential nonlinear associations between inflammatory indices and CRC risk, which cannot be adequately captured by conventional logistic regression.

The association between inflammation indices and all-cause mortality was quantified using Cox proportional hazards regression analysis and presented as hazard ratios (HRs) with 95% CIs before and after adjusting for confounding factors. All Cox models were assessed for proportional hazards assumption using Schoenfeld residuals to ensure that the variables meet the assumptions. First, only age was adjusted. Second, age, gender, race and education level were adjusted. Third, age, gender, race, education level, BMI, smoking status, alcohol consumption, diabetes, and hypertension were adjusted. The multivariable-adjusted restricted cubic splines (RCS) with four knots at the 5th, 35th, 65th, and 95th centiles were utilized to evaluate the non-linear correlation between inflammation indices and all-cause mortality. Kaplan–Meier (K-M) survival curves are used to assess the association between high or low levels of indicators and the prognosis of CRC patients. The receiver operating characteristic (ROC) curve, followed by Delong test, is used to compare the discriminatory power differences between single inflammatory markers and combined inflammatory markers in predicting CRC risk and prognosis.

All analyses were conducted using R (http://www.R-project.org, version 4.3.3) and SPSS software (version 26, IBM, USA). Results associated with a P value <0.05 were regarded as statistically significant.

Results

Baseline characteristics of study participants

After excluding individuals who did not meet the inclusion criteria, a total of 18 470 individuals were included in our survey. The characteristics of these participants are shown in Table 1. In both CRC and non-CRC (control) populations, there were no differences in gender, education level, BMI, and alcohol consumption. However, differences were observed between the two groups in terms of age, race, smoking intensity, daily alcohol intake, and the incidence of diabetes and hypertension. The CRC population comprised more elderly individuals ($P < 0.001$), and most of them had hypertension ($P < 0.001$) and diabetes ($P < 0.001$). We further employed multivariable regression analysis to investigate the differences among these variables between CRC and non-CRC populations, and the results showed that the risk of CRC increased significantly with elderly age (P-trend < 0.001). In terms of race, Mexican Americans appeared to be a group with a lower risk of CRC (P-trend = 0.001). The association between diabetes and CRC risk was no longer statistically significant, while hypertension remained associated with CRC risk (P-trend = 0.007) (Table 1).

Regarding the serological indicators investigated in this study, the CRC population had higher lymphocyte counts ($P < 0.001$), platelet counts ($P < 0.001$), and albumin levels ($P < 0.001$) compared to the normal population, while hemoglobin levels were lower in the CRC group ($P = 0.011$). After calculating and combining these indicators into inflammatory indices, all except

Table 1

Baseline characteristics and multivariable analysis of participants with and without CRC in NHANES 2001–2020

Variable n (%)	Cases (unweighted n = 126; weighted n = 681 641)	Controls (unweighted n = 18 344; weighted n = 148 858 095)	Test of significance (χ2 value)	*P*[a]	Multivariable regression OR (95% CI)	*P*-trend[b]
Gender			0.375	0.540		0.963
Male	65 (45.9%)	8961(49.2%)			1	
Female	61(54.1%)	9383(50.8%)			0.991 (0.675–1.455)	
Age			275.293	<0.001		<0.001
<40	5 (7.82%)	10 149 (62.2%)			1	
40-65	22 (18.83%)	4548 (25.1%)			7.422 (2.763–19.942)	
>65	99 (73.34%)	3647 (12.7%)			39.164(15.461–99.207)	
Race			40.924	<0.001		0.001
Mexican American	6(1.4%)	3711(8.7%)			1	
Other Hispanic	4(2.3%)	1399(4.5%)			1.813 (0.507–6.484)	
Non-Hispanic White	93(86.1%)	8704(69.4%)			4.942 (2.107–11.594)	
Non-Hispanic Black	22(9.2%)	3661(11.2%)			3.289 (1.310–8.255)	
Other Race	1(0.9%)	869(6.1%)			0.750 (0.089–6.321)	
Education			7.420	0.284		0.989
<high school	45(25.7%)	5354(18.7%)			1	
≥high school	81(74.3%)	12 966(81.2%)			1.030 (0.695–1.526)	
BMI						
Normal	32 (30.6%)	5350 (32%)	1.351	0.509	1	
Overweight	48 (37.0%)	6244 (33.4%)			1.078 (0.682–1.704)	
Obese	42 (30.2%)	6497 (33.5%)			0.927 (0.573–1.498)	
Smoking status			26.851	<0.001		0.763
Never	54(42.0%)	4418(23.4%)			1	
Some days	1(0.3%)	727(3.7%)			0.447 (0.061–3.286)	
Every day	14(10.3%)	3458(19.9%)			0.820 (0.437–1.539)	
Any alcohol use			5.961	0.114		0.227
No	15(11.7%)	2344(10.32%)			1	
Yes	27(23.7%)	2553(12.55%)			1.707 (0.874–3.332)	
Heavy alcohol use			6.393	0.011		0.788
No	56(47.1%)	9178(56.1%)			1	
Yes	3(2%)	1969(10.7%)			0.6777 (0.206–2.218)	
Diabetes			29.668	<0.001		0.609
No	93(77.0%)	16 116(91.1%)			1	
Borderline	1(0.5%)	288(1.4%)			0.330 (0.046–2.400)	
Yes	32(22.7%)	1924(7.4%)			1.176 (0.758–1.825)	
Hypertension			92.755	<0.001		0.007
No	35(31.5%)	12 425(71.67%)			1	
Yes	90(68.3%)	5848(27.98%)			1.908 (1.253–2.905)	

[a]Chi-square tests.
[b]Logistic regression analysis.
BMI, body mass index; CRC, colorectal cancer; CI, confidence interval; OR, odds ratio.

for CAR exhibited statistically significant differences between the CRC and control groups (all $P < 0.05$) (Table 2).

NLR and MLR are associated with CRC risk

We grouped the participants based on quartiles of their inflammatory markers (Q1: 0–25%; Q2: 25–50%; Q3: 50–75%; Q4: 75–100%), with the lowest quartile (Q1) serving as the reference group. We employed three progressively adjusted models. Prior to any adjustment, multiple inflammatory markers were associated with CRC risk, with the risk increasing as the levels of NLR ($P < 0.001$), PLR ($P = 0.031$), NPR ($P = 0.035$), SIRI ($P = 0.002$), and PIV ($P = 0.011$) rose, whereas increased levels of LMR ($P < 0.001$), CALLY ($P = 0.035$), and HALP ($P = 0.012$) were associated with a decreased CRC risk. However, after adjusting for age in Model 1, statistical differences were only observable for LMR ($P = 0.017$) and PIV ($P = 0.037$). With further adjustments in Model 3, only changes in NLR and LMR levels were associated with CRC risk, where an elevated NLR level was related to an increased CRC risk [Q2 (vs. Q1) OR = 1.358, 95% CI = 0.720–2.562; Q3 (vs. Q1) OR = 1.776, 95% CI = 0.979–3.222; Q4 (vs. Q1) OR = 2.137, 95% CI = 1.212–3.765 (P-trend = 0.045)], while the opposite was true for LMR[Q2 (vs. Q1) OR = 0.541, 95% CI = 0.338–0.865; Q3 (vs. Q1) OR = 0.696, 95% CI = 0.420–1.156; Q4 (vs. Q1) OR = 0.503, 95% CI = 0.274–0.923 (P-trend = 0.027)] (Table 3). The GEE cluster-adjusted model further confirms the association between inflammatory indices and CRC risk despite being influenced by the clustering effects in the sampling process (Supplementary Digital Content, Table 1, available at: http://links.lww.com/JS9/E643). Post-hoc power analysis indicates that the tumor sample size in this study was relatively small. Further in-depth validation of our conclusions requires

Table 2

Baseline differences in single inflammatory indicators and composite inflammatory indices between the CRC and the control group

Variable (Mean ± SEM)	Cases (unweighted n = 126; weighted n = 681 641)	Controls (unweighted n = 18 344; weighted n = 148 858 095)	Test of significance (Z-value)	P [a]
Single inflammatory indicators				
Neutrophil (×10^9/L)	4.319 ± 0.002	4.343 ± 0.000	−0.615	0.539
Lymphocyte (×10^9/L)	1.930 ± 0.002	2.145 ± 0.000	5.685	<0.001
Platelet (×10^9/L)	239.67 ± 0.087	264.530 ± 0.006	3.786	<0.001
Monocyte (×10^9/L)	0.576 ± 0.000	0.550 ± 0.000	−1.884	0.060
Albumin (g/L)	41.11 ± 0.004	42.63 ± 0.000	4.223	<0.001
CRP (mg/L)	4.559 ± 0.007	4.019 ± 0.001	−1.633	0.103
Hb (g/L)	139.66 ± 0.014	144.25 ± 0.001	2.542	0.011
Composite inflammatory indices				
SII	639.150 ± 0.501	584.294 ± 0.030	−2.126	0.033
NLR	2.596 ± 0.002	2.199 ± 0.000	−4.742	<0.001
PLR	148.177 ± 0.089	134.650 ± 0.004	−2.505	0.012
LMR	3.580 ± 0.002	4.177 ± 0.000	5.680	<0.001
NPR	0.019 ± 0.000	0.172 ± 0.000	−3.102	0.002
SIRI	1.489 ± 0.001	1.123 ± 0.000	−4.194	<0.001
PAR	5.871 ± 0.002	6.266 ± 0.000	2.478	0.013
CAR	0.115 ± 0.000	0.100 ± 0.000	−1.834	0.067
CLR	2.658 ± 0.004	2.070 ± 0.000	−3.035	0.002
CALLY	6.771 ± 0.011	11.351 ± 0.002	3.190	0.001
PIV	370.249 ± 0.352	329.292 ± 0.022	−2.377	0.017
HALP	49.899 ± 0.045	52.970 ± 0.003	3.262	0.001

[a]Mann–Whitney U test.

CALLY, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-to-albumin ratio; CLR, C-reactive protein to lymphocyte ratio; CRC, colorectal cancer; CRP, C-reactive protein; HALP, hemoglobin, albumin, lymphocyte, and platelet score; Hb, hemoglobin; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; PAR, platelet-to-albumin ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; SEM, standard error of the mean; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index.

larger and more balanced sample studies (Supplementary Digital Content, Table 2, available at: http://links.lww.com/JS9/E643). The stratified analysis of various inflammatory indicators and CRC risk has also been more intuitively presented in the form of a forest plot (Fig. 1).

We next utilized GAM combined with smooth curve fitting to further demonstrate the association between levels of inflammatory indicators and CRC risk. This approach allowed us to flexibly capture potential nonlinear associations in the data and more intuitively observe how CRC risk fluctuates as the levels of inflammatory indicators change. It can be observed that these inflammatory indicators tend to have a nonlinear association with CRC risk (Fig. 2).

To explore the diagnostic value of NLR and LMR in CRC risk, we adopted the ROC curve based on the CRC risk probability. The ROC curve revealed that the AUC value (NLR, AUC = 0.622; LMR, AUC = 0.647; NLR + LMR, AUC = 0.644) did not show significant difference either in the single indicator or combination group, which indicated that all of them had certain and similar diagnostic value in CRC (Supplementary Digital Content, Figure S1, available at: http://links.lww.com/JS9/E643).

Associations of inflammation indices with CRC mortality

In the follow-up data of 126 CRC patients, as of December 2019, 71 patients had deceased. We designed three adjusted Cox regression models and Schoenfeld Residuals test to explore the association between inflammatory indicators and patient mortality. All 12 inflammatory indices showed no evidence of violating the proportional hazards assumption (P >0.05 for Schoenfeld residual tests) (Supplementary Digital Content, Table 3, available at: http://links.lww.com/JS9/E643). Across different models, NLR and LMR, which were previously associated with CRC risk, did not achieve statistically significant results in predicting mortality risk (Table 4). However, it is not difficult to observe that as NLR levels increase, the survival probability increases [Q2 (vs. Q1) HR = 1.134, 95% CI = 0.442–2.914; Q3 (vs. Q1) HR = 1.064, 95% CI = 0.451–2.513; Q4 (vs. Q1) HR = 1.403, 95% CI = 0.631–3.122 (P-trend = 0.786)], whereas higher MLR levels indicate a lower survival rate [Q2 (vs. Q1) HR = 0.795, 95% CI = 0.406–1.556; Q3 (vs. Q1) HR = 0.838, 95% CI = 0.412–1.706; Q4 (vs. Q1) HR = 0.538, 95% CI = 0.189–1.531 (P-trend = 0.642)] (Table 4 and Fig. 3). This aligns with the trend of their correlation with CRC risk. We similarly conducted analogous analyses on the association of other inflammatory indicators with mortality risk, but none of the results yielded statistically significant differences (Supplementary Digital Content, Table 4, available at: http://links.lww.com/JS9/E643).

For adjusted model 3, we used RCS curves to demonstrate the associations between inflammation indices and the risk of all-cause mortality. The results indicate that these inflammatory indicators tend to exhibit a nonlinear association with the risk of CRC mortality (Fig. 4).

We further conducted survival analysis on these inflammatory indices with regard to the prognosis of CRC patients. We observed that the survival curves of multiple indices showed relatively significant differences. However, despite the lack of significant differences in the Cox hazard analysis model, the SII

Table 3

Odds ratios (95% confidence intervals) of CRC across quartiles of inflammatory indices level

	Quintiles				
Item	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
SII					
Range	<357	357–501.158	507.158–706	≥706	
Cases/Controls	27/4599	22/4587	37/4581	40/4577	
Crude OR	1	0.817	1.376	1.489	0.084
(95%CI)		(0.465–1.437)	(0.836–2.263)	(0.912–2.430)	
Model 1	1	0.838	1.421	1.441	0.111
OR (95%CI)		(0.475–1.478)	(0.861–2.347)	(0.879–2.361)	
Model 2	1	0.855	1.485	1.491	0.084
OR (95%CI)		(0.484–1.509)	(0.897–2.456)	(0.908–2.448)	
Model 3	1	0.855	1.359	1.481	0.140
OR (95%CI)		(0.484–1.510)	(0.813–2.273)	(0.898–2.441)	
NLR					
Range	<1.48	1.48–1.967	1.967–2.647	≥2.647	
Cases/Controls	17/4619	24/4576	35/4570	50/4579	
Crude OR	1	1.425	2.081	2.967	<0.001
(95%CI)		(0.765–2.656)	(1.164–3.720)	(1.709–5.152)	
Model 1	1	1.356	1.783	2.025	0.063
OR (95%CI)		(0.725–2.536)	(0.993–3.199)	(1.160–3.535)	
Model 2	1	1.435	1.911	2.150	0.042
OR (95%CI)		(0.765–2.690)	(1.060–3.445)	(1.223–3.779)	
Model 3	1	1.358	1.776	2.137	0.045
OR (95%CI)		(0.720–2.562)	(0.979–3.222)	(1.212–3.765)	
PLR					
Range	<98.235	98.235–124.286	124.286–157.143	≥157.143	
Cases/Controls	28/4590	25/4590	27/4588	46/4576	
Crude OR	1	0.893	0.965	1.648	0.031
(95%CI)		(0.520–1.533)	(0.568–1.639)	(1.028–2.641)	
Model 1	1	0.927	1.040	1.409	0.293
OR (95%CI)		(0.538–1.597)	(0.610–1.774)	(0.876–2.267)	
Model 2	1	0.929	1.043	1.403	0.310
OR (95%CI)		(0.539–1.601)	(0.611–1.780)	(0.870–2.263)	
Model 3	1	0.953	1.167	1.594	0.138
OR (95%CI)		(0.540–1.681)	(0.675–2.017)	(0.973–2.610)	
LMR					
Range	<3	3–4	4–5	≥5	
Cases/Controls	62/4485	26/5316	24/4197	14/4346	
Crude OR	1	0.354	0.414	0.233	<0.001
(95%CI)		(0.223–0.560)	(0.258–0.664)	(0.130–0.417)	
Model 1	1	0.524	0.740	0.503	0.017
OR (95%CI)		(0.330–0.834)	(0.457–1.197)	(0.278–0.908)	
Model 2	1	0.528	0.740	0.490	0.019
OR (95%CI)		(0.331–0.843)	(0.454–1.207)	(0.268–0.896)	
Model 3	1	0.541	0.696	0.503	0.027
OR (95%CI)		(0.338–0.865)	(0.420–1.156)	(0.274–0.923)	
NPR					
Range	<0.012	0.012–0.016	0.016–0.021	≥0.021	
Cases/Controls	20/4597	29/4589	34/4584	43/4574	
Crude OR	1	1.453	1.705	2.161	0.035
(95%CI)		(0.820–2.571)	(0.980–2.966)	(1.269–3.679)	
Model 1	1	1,262	1.382	1.628	0.339
OR (95%CI)		(0.710–2.243)	(0.791–2.416)	(0.951–2.785)	
Model 2	1	1.341	1.505	1.774	0.227
OR (95%CI)		(0.752–2.389)	(0.855–2.649)	(1.021–3.081)	
Model 3	1	1.341	1.423	1.617	0.418
OR (95%CI)		(0.752–2.391)	(0.804–2.519)	(0.920–2.841)	
SIRI					
Range	<0.7	0.7–1.024	1.024–1.491	≥1.491	
Cases/Controls	19/4618	27/4570	31/4587	49/4569	
Crude OR	1	1.436	1.643	2.607	0.002

(*Continues*)

Table 3

(Continued).

Item	Quintiles				*P* for trend
	Q1	Q2	Q3	Q4	
(95%CI)		(0.797–2.586)	(0.927–2.912)	(1.532–4.434)	
Model 1	1	1.249	1.276	1.641	0.296
OR (95%CI)		(0.691–2.259)	(0.716–2.272)	(0.958–2.810)	
Model 2	1	1.347	1.397	1.757	0.233
OR (95%CI)		(0.741–2.446)	(0.778–2.511)	(1.014–3.045)	
Model 3	1	1.327	1.301	0.666	0.323
OR (95%CI)		(0.730–2.413)	(0.718–2.356)	(0.957–2.902)	
PAR					
Range	<5.023	5.023–6.024	6.024–7.239	≥7.239	
Cases/Controls	37/4589	38/4589	28/4575	23/4591	
Crude OR	1	1.027	0.759	0.621	0.182
(95%CI)		(0.652–1.618)	(0.464–1.242)	(0.369–1.047)	
Model 1	1	1.261	1.009	0.957	0.674
OR (95%CI)		(0.797–1.994)	(0.614–1.659)	(0.565–1.621)	
Model 2	1	1.265	1.022	0.972	0.690
OR (95%CI)		(0.798–2.008)	(0.617–1.694)	(0.563–1.678)	
Model 3	1	1.168	1.014	0.943	0.865
OR (95%CI)		(0.729–1.873)	(0.611–1.682)	(0.540–1.648)	
CAR					
Range	<0.019	0.019–0.049	0.049–0.118	≥0.118	
Cases/Controls	26/4655	29/4522	32/4584	39/4583	
Crude OR	1	1.148	1.250	1.524	0.390
(95%CI)		(0.675–1.953)	(0.744–2.100)	(0.926–2.507)	
Model 1	1	0.838	0.867	1.150	0.547
OR (95%CI)		(0.490–1.431)	(0.514–1.469)	(0.696–1.901)	
Model 2	1	0.863	0.905	1.188	0.563
OR (95%CI)		(0.505–1.477)	(0.535–1.531)	(0.717–1.971)	
Model 3	1	0.854	0.837	1.134	0.580
OR (95%CI)		(0.496–1.469)	(0.482–1.451)	(0.663–1.940)	
CLR					
Range	<0.4	0.4–1	1–2.357	≥2.357	
Cases/Controls	25/4616	26/4640	31/4517	44/4571	
Crude OR	1	1.035	1.267	1.777	0.062
(95%CI)		(0.597–1.794)	(0.747–2.150)	(1.086–2.909)	
Model 1	1	0.756	0.845	1.159	0.320
OR (95%CI)		(0.434–1.318)	(0.496–1.440)	(0.705–1.980)	
Model 2	1	0.778	0.880	1.190	0.344
OR (95%CI)		(0.446–1.357)	(0.515–1.503)	(0.722–1.962)	
Model 3	1	0.768	0.821	1.149	0.352
OR (95%CI)		(0.439–1.345)	(0.471–1.429)	(0.682–1.935)	
CALLY					
Range	<1.727	1.727–4.209	4.209–10.75	≥10.75	
Cases/Controls	44/4574	34/4582	24/4610	24/4578	
Crude OR	1	0.771	0.541	0.545	0.035
(95%CI)		(0.492–1.209)	(0.329–0.891)	(0.331–0.898)	
Model 1	1	0.764	0.604	0.846	0.252
OR (95%CI)		(0.486–1.202)	(0.365–0.998)	(0.511–1.402)	
Model 2	1	0.773	0.605	0.826	0.265
OR (95%CI)		(0.491–1.217)	(0.366–1.001)	(0.498–1.371)	
Model 3	1	0.755	0.615	0.855	0.290
OR (95%CI)		(0.473–1.205)	(0.368–1.028)	(0.503–1.452)	
PIV					
Range	<169	169–258.202	258.202–397.367	≥397.367	
Cases/Controls	31/4586	18/4600	32/4586	45/4572	
Crude OR	1	0.579	1.032	1.456	0.011
(95%CI)		(0.323–1.036)	(0.629–1.694)	(0.920–2.305)	
Model 1	1	0.532	0.916	1.198	0.037
OR (95%CI)		(0.296–0.955)	(0.556–1.511)	(0.753–1.907)	
Model 2	1	0.558	0.972	1.253	0.041

(*Continues*)

Table 3
(Continued).

Item	Quintiles				*P* for trend
	Q1	Q2	Q3	Q4	
OR (95%CI)		(0.310–1.004)	(0.587–1.608)	(0.783–2.004)	
Model 3	1	0.552	0.912	1.196	0.057
OR (95%CI)		(0.307–0.994)	(0.546–1.523)	(0.743–1.927)	
HALP					
Range	<36.328	36.328–48.551	48.551–63.152	≥63.152	
Cases/Controls	47/4570	30/4588	27/4590	22/4596	
Crude OR	1	0.636	0.572	0.465	0.012
(95%CI)		(0.401–1.007)	(0.356–0.920)	(0.280–0.774)	
Model 1	1	0.724	0.716	0.628	0.248
OR (95%CI)		(0.456–1.152)	(0.443–1.157)	(0.376–1.049)	
Model 2	1	0.724	0.721	0.628	0.265
OR (95%CI)		(0.455–1.153)	(0.445–1.168)	(0.372–1.058)	
Model 3	1	0.718	0.627	0.581	0.134
OR (95%CI)		(0.451–1.145)	(0.379–1.037)	(0.341–0.991)	

Model 1 adjusted for age.
Model 2 adjusted for age, gender, race, education.
Model 3 adjusted for age, gender, race, education, body mass index (BMI), smoking status, heavy alcohol use, diabetes, hypertension.
BMI, body mass index; CALLY, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; CLR, C-reactive protein to lymphocyte ratio; CRC, colorectal cancer; HALP, hemoglobin, albumin, lymphocyte, and platelet score; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; OR, odds ratio; PAR, platelet-to-albumin ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index.

(P = 0.0459) and NPR (P = 0.0333) showed significant prognostic value in CRC. The elevated expression levels of both indicators are associated with adverse prognosis (Fig. 5).

Due to the reduction in the sample size of CRC patients during data integration, which was done to include as many blood test indicators as possible, and considering the statistically significant predictive value of NLR and LMR for CRC risk, we focused on the hematological indicators involved in these two ratios (neutrophil count, lymphocyte count, monocyte count). After re-screening the data, we ultimately obtained 239 CRC samples with complete information. Cox proportional hazards regression analysis was performed on these samples, yet again, no statistically significant differences were found (Supplementary Digital Content, Table 5, available at: http://links.lww.com/JS9/E643). However, when we divide the indicators into high and low expression groups based on the median for survival analysis, the results indicated a trend of poorer prognosis associated with higher NLR values, albeit without statistical significance (P = 0.0816), while higher LMR values predicted a better prognosis (P = 0.0056) (Fig. 6). This suggests that LMR is not only an indicator negatively correlated with CRC risk but also serves as a predictor of poor prognosis.

Given the potential of SII, NLR, LMR, and NPR in predicting CRC risk and prognosis, we further plotted ROC curves and Delong test to investigate whether combining these four indicators would provide better predictive performance for mortality risk compared to using a single indicator. The results showed that combining the four indicators yielded slightly higher AUC values (mean ΔAUC = 0.027) compared to using a single indicator, but the intergroup differences were not statistically significant (Fig. 7). We further conducted an exploratory and comprehensive comparison of the predictive power of these 12 indices for CRC prognosis. The results demonstrated that, in addition to the established markers (such as NLR and LMR), SII, SIRI, and PIV exhibited superior predictive efficacy. This suggests that these indicators will play an important predictive role in tumor prognosis assessment and are worthy of further investigation with an expanded sample size (Fig. 8).

Discussion

This study aims to comprehensively investigate the associations between a range of inflammatory indices and the risk and mortality of CRC using data from NHANES. Our findings indicate that an elevated NLR and a reduced LMR are associated with increased CRC risk. In terms of prognostic prediction, patients with low LMR, high NPR, and high SII levels are associated with adverse outcomes. These results highlight the potential role of systemic inflammation-related indices, based on peripheral blood tests, in CRC development and provide important insights into the predictive value of inflammatory indices in CRC prognosis.

Previous studies have demonstrated that various inflammatory indices, based on peripheral blood tests, are closely related to cancer development. Among them, NLR has been extensively studied and is associated with adverse prognosis, lymph node metastasis, and distant metastasis risk in CRC[17-19]. Additionally, NLR has the potential to serve as a predictive marker for the efficacy of chemotherapy and immunotherapy[19-21]. Despite the extensive research on NLR in CRC, our study, using NHANES data for the first time, complements previous findings by providing a more robust theoretical basis for NLR as a predictive indicator of CRC risk. LMR, another inflammatory index, has gradually gained attention and been explored in CRC. Lower LMR levels are often associated with poorer prognosis and increased risks of tumor recurrence[14,22,23]. Our study, based on NHANES data, similarly revealed the predictive value of LMR for CRC progression, including predicting CRC prognosis and susceptibility.

Although the study identifies NLR and LMR as CRC risk markers, the immunological interplay between these ratios

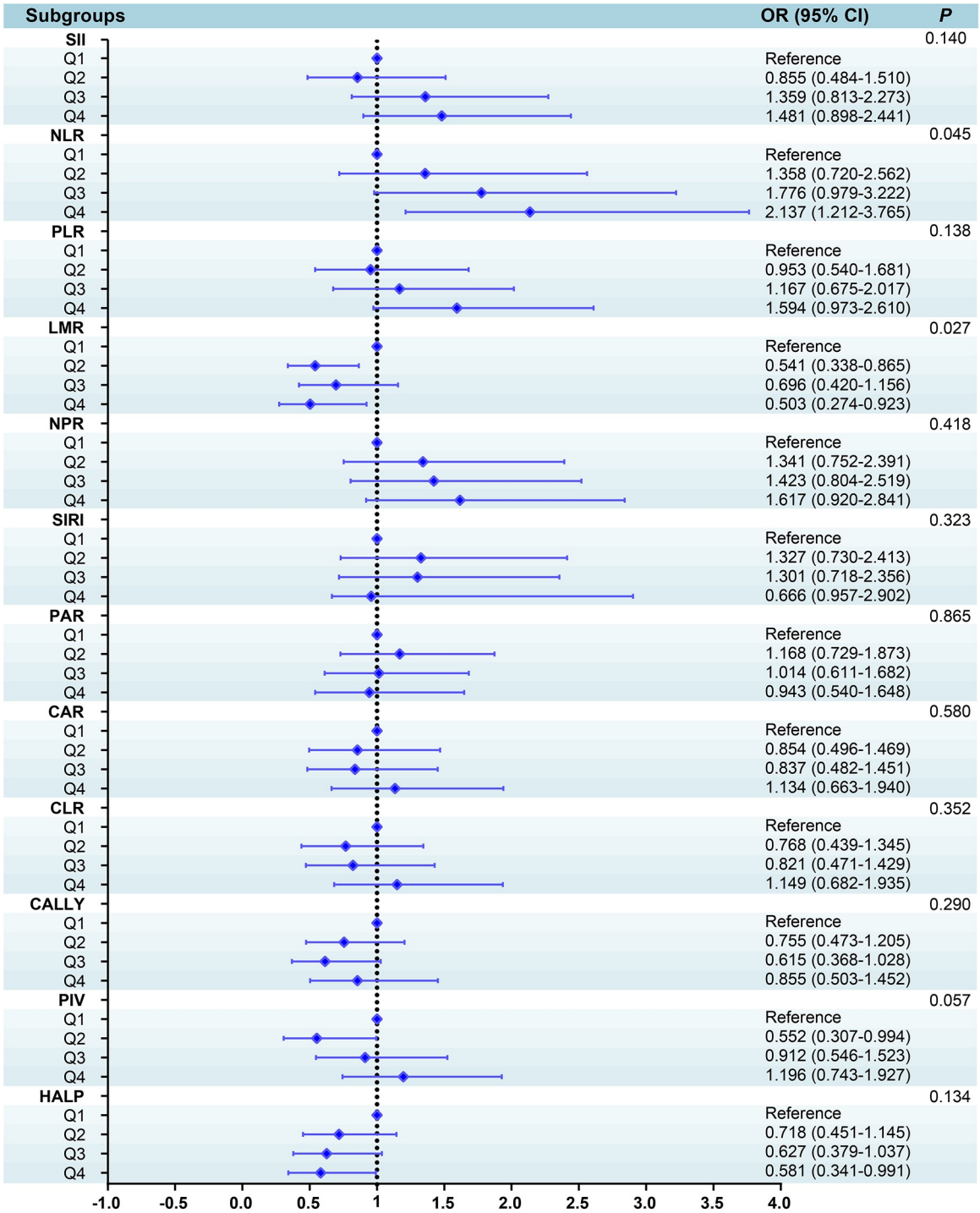

Figure 1. Forest plots display the risk association between inflammatory indices and CRC. The levels of inflammatory indices were divided into quartiles. The ORs and 95% confidence intervals for different subgroups are listed, with the lowest level group as a reference. Vertical dashed line indicates the null reference value of "1".

warrants deeper scrutiny. Lymphocytes, as the common denominator in both ratios, may not merely passively reflect inflammation but actively modulate tumor immunosurveillance. Elevated lymphocyte levels could signify enhanced antitumor immunity through cytotoxic T-cell and NK-cell activity[24]. Lymphocytes also modulate tumor cells and macrophages through cytokine secretion (e.g., interferon), induce overexpression of antigen presentation in adjacent macrophages and tumor cells, including the overexpression of MHC class II invariant chain CD74, thereby reversing the immunosuppressive tumor microenvironment[25]. Furthermore, the prognostic evaluation consistency between peripheral blood lymphocytes and tumor-infiltrating lymphocytes (TILs) suggesting

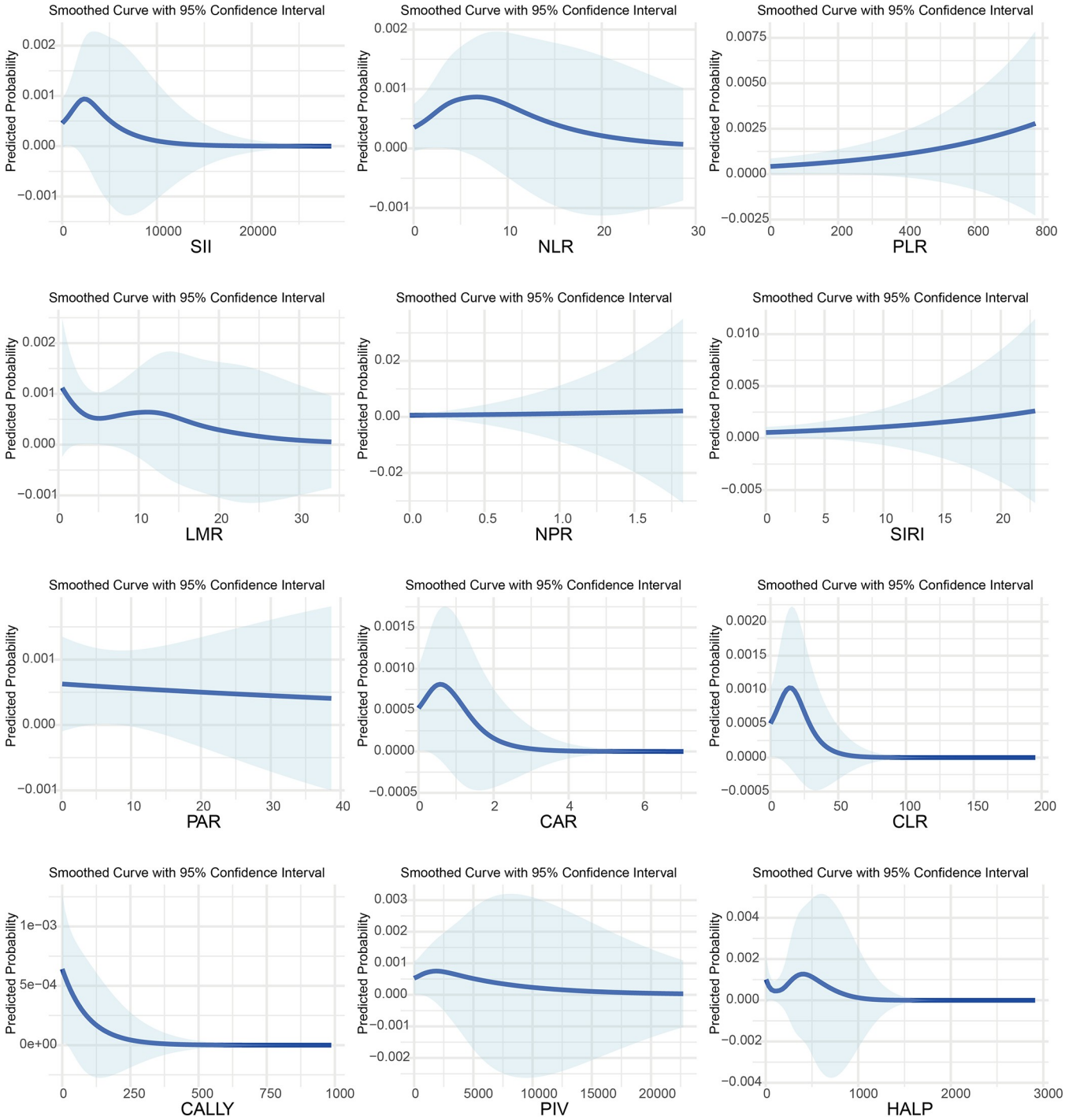

Figure 2. Generalized additive models depict the nonlinear association between inflammatory indices and CRC risk. The Y-axis represents the predicted CRC risk values from the GAM model, and the X-axis represents the level of inflammatory indicators. The blue lines with the shaded areas embody the estimated ORs of CRC risk with 95% CIs.

a potential correlation between the quantity and subtypes of lymphocytes in peripheral blood and those within the tumor microenvironment, which underscores the necessity for in-depth investigation into peripheral blood lymphocytes[26]. Future studies will focus on utilizing flow cytometry to perform detailed subtyping of peripheral blood lymphocytes, clarifying the proportions of CD4+/CD8+/Treg/B/NK cells, and assessing lymphocyte activation (e.g., CD69, CD25), exhaustion (e.g., PD-1, CTLA-4, TIM-3), or cytokine secretion (e.g., IFN-γ, IL-2, TNF-α) to further explore the underlying mechanisms by which lymphocytes play

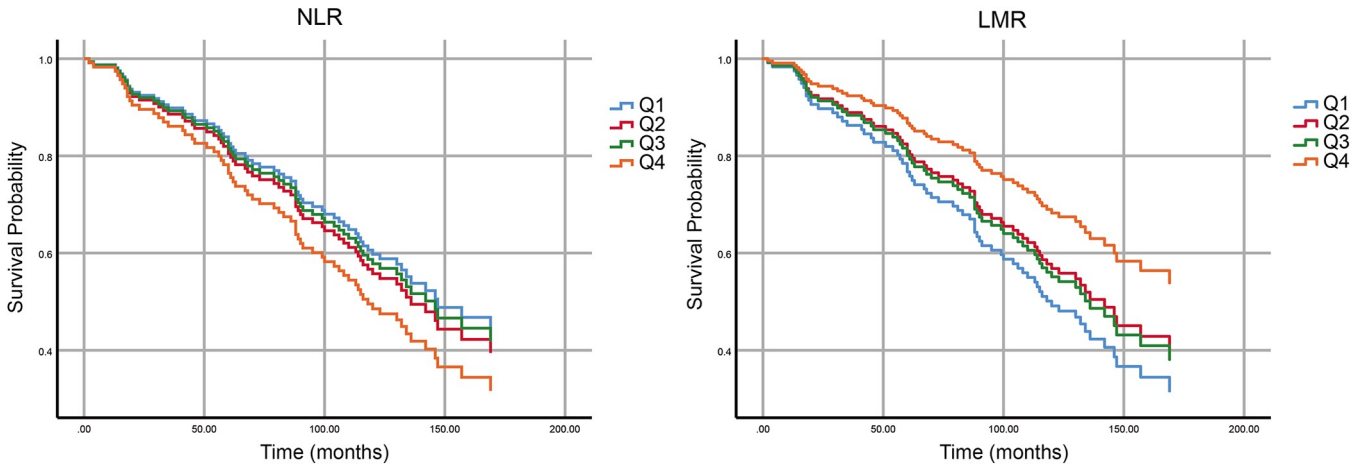

Figure 3. Survival probability curves of NLR and LMR based on four quartiles. The Y-axis shows the survival probability estimated by Cox regression analysis. X-axis shows the follow-up period (months).

a crucial role in CRC risk and prognosis. These investigations will be supplemented by more direct functional assays (e.g., ELISpot, intracellular staining) for accurate evaluation. Furthermore, dynamic perioperative monitoring of NLR and LMR is warranted.

As for SII, it has also been shown to be associated with an increased risk of CRC development and poor prognosis[27,28]. Our study pioneers the analysis of the clinical predictive value of SII in CRC using NHANES data, further confirming the universal predictive significance of SII. Research on NPR in tumors, including CRC, is limited[29]. Our study, based on a large-scale, randomly sampled population, is the first to reveal its indicative role in the prognosis of CRC patients. Furthermore, in our exploration of the association between NPR and CRC risk, we also observed a significant positive correlation, indicating that an increase in NPR levels is associated with an elevated risk of CRC occurrence. However, statistically significant differences were not observed, possibly due to the limited sample size.

In terms of clinical predictive performance, the combined use of the aforementioned CRC risk and prognosis-related indices (NLR, LMR, SII, and NPR) did not demonstrate superior predictive efficacy compared to individual indicators, possibly due to overlapping components in the computational formulas and

Table 4

Multivariable Cox regression models analysis of the relationship between NLR, LMR and CRC mortality

	Quintiles				
Item	**Q1**	**Q2**	**Q3**	**Q4**	***P*-trend**
NLR					
Range	<1.48	1.48–1.967	1.967–2.647	≥2.647	
Number of deaths (%)	9 (7.1%)	12 (9.5%)	17 (13.5%)	33 (26.2%)	
Crude HR	1	1.017	0.917	1.340	0.581
(95% CI)		(0.428–2.414)	(0.409–2.058)	(0.641–2.803)	
Model 1	1	0.934	0.945	1.281	0.673
HR (95% CI)		(0.392–2.228)	(0.421–2.122)	(0.611–2.684)	
Model 2	1	1.021	0.938	1.262	0.762
HR (95% CI)		(0.424–2.462)	(0.415–2.123)	(0.602–2.647)	
Model 3	1	1.134	1.064	1.403	0.786
HR (95% CI)		(0.442–2.914)	(0.451–2.513)	(0.631–3.122)	
LMR					
Range	<3	3–4	4–5	≥5	
Number of deaths (%)	40 (31.7%)	13 (10.3%)	13 (10.3%)	5 (4.0%)	
Crude HR	1	0.696	0.793	0.392	0.206
(95% CI)		(0.371–1.304)	(0.424–1.485)	(0.154–0.997)	
Model 1	1	0.719	0.817	0.495	0.368
HR (95% CI)		(0.383–1.349)	(0.436–1.531)	(0.176–1.194)	
Model 2	1	0.760	0.861	0.580	0.680
HR (95% CI)		(0.395–1.463)	(0.425–1.744)	(0.206–1.631)	
Model 3	1	0.795	0.838	0.538	0.642
HR (95% CI)		(0.406–1.556)	(0.412–1.706)	(0.189–1.531)	

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

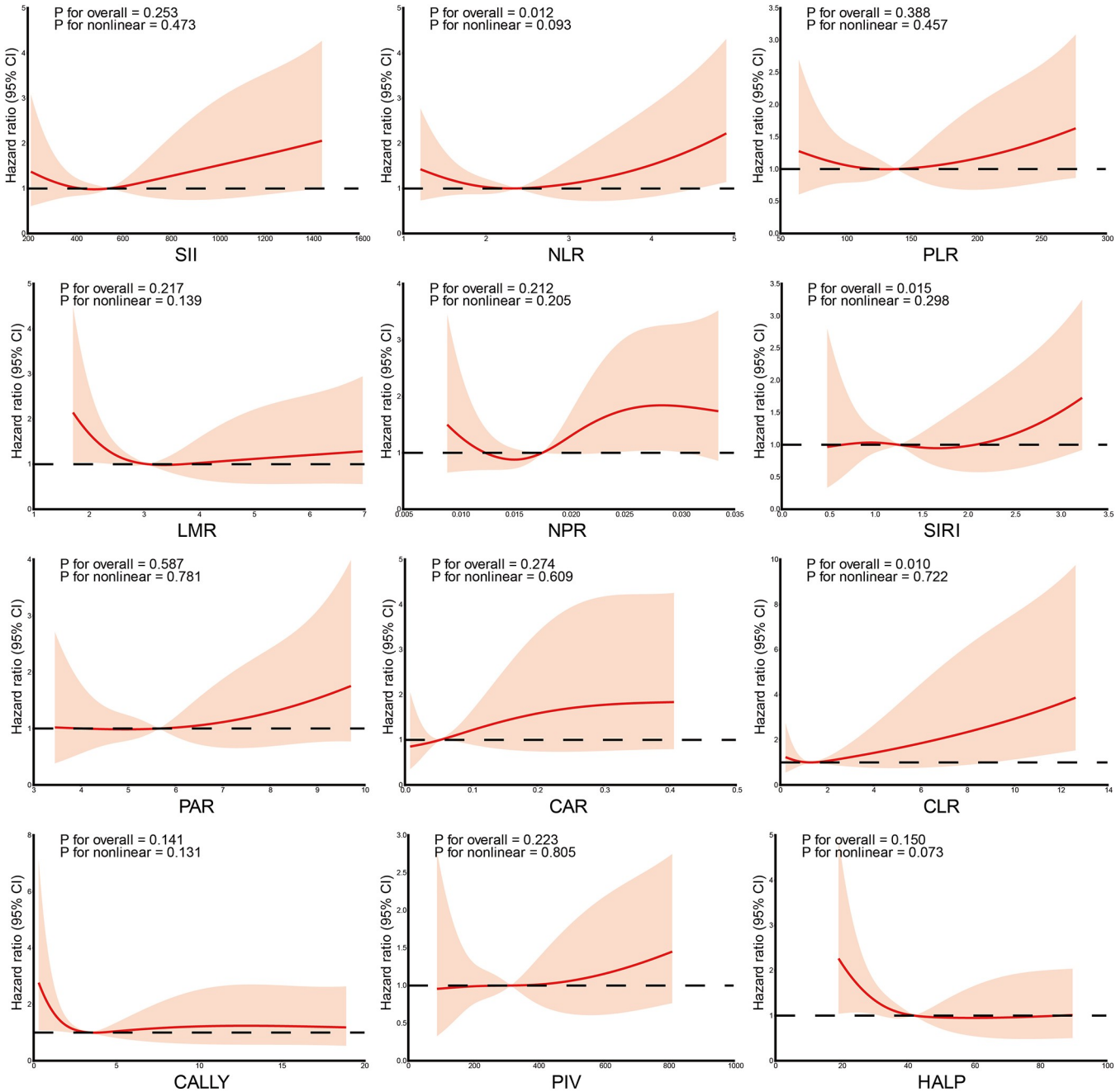

Figure 4. Multivariable-adjusted RCS analyses identified significant linear concentration–response associations between inflammatory indices and the risk of all-cause mortality. The inflammatory indices were modeled using an RCS analysis with four knots located at the 5th, 35th, 65th, and 95th centiles. The Y-axis represents the HRs for the inflammatory indices. The red lines with the shaded areas embody the estimated HRs of all-cause mortality with 95% CIs. The model was adjusted for age, gender, race, education, BMI, smoking status, heavy alcohol use, diabetes, and hypertension.

limited sample size. However, a comprehensive comparison of the individual predictive performance of all 12 indices using ROC curves revealed that the performance of SII, SIRI, and PIV in prognostic prediction was not inferior to that of traditional indicators such as NLR and LMR. Notably, these indicators are derived from calculations combining multiple indicators, indicating that inflammatory indices integrating multiple parameters may indeed possess more significant predictive value compared to simpler two-parameter indicators. Overall, our research incorporates a comprehensive set of inflammatory indices, significantly expands the scope of existing literature, thereby providing a more holistic view of the inflammatory landscape in CRC.

The abnormal changes in these inflammatory indicators may influence the progression and prognosis of colorectal cancer through various mechanisms. Neutrophils exhibit significant heterogeneity and plasticity within the tumor microenvironment[30]. Studies have shown that tumor-associated neutrophils (TANs) can undergo phenotypic switching, transitioning from an anti-

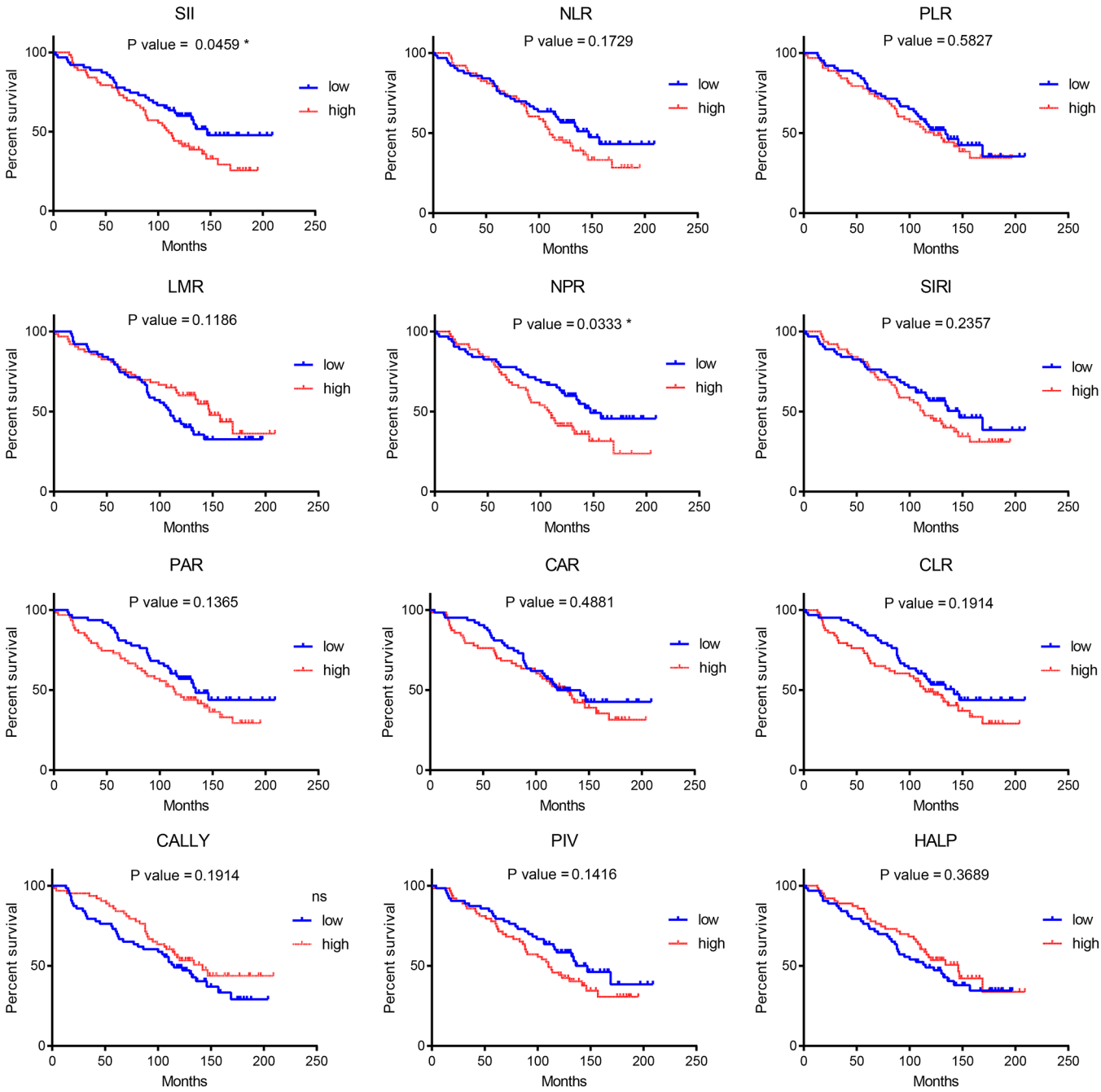

Figure 5. K-M survival curves for high and low expression groups of inflammatory indicators based on their medians among 126 CRC patients. The 126 CRC patients were divided into high and low groups based on the median expression levels of various inflammatory indicators. Survival curves were plotted according to the survival time, and the statistical differences between groups were calculated using the log-rank test method.

tumor phenotype to a pro-tumor phenotype[31]. TANs exhibit enhanced glycolysis and hypoxic signaling, enabling them to secrete angiogenic factors (like Spp1 and Mmp14), thereby promoting tumor angiogenesis and growth[32]. Cytokines secreted by neutrophils can facilitate the formation of premetastatic niche[33]. Meanwhile, AGR2 derived from TANs can promote metastatic ability of CRC cells[34]. Additionally, neutrophils undergo NETosis, producing NETs that are closely related to the survival of circulating tumor cells, distant colonization of tumor cells, chemotherapy resistance and immune evasion[34-36]. Markers related to NETs, such as H3cit, as well as NETs-associated gene sets, are closely associated with poor response to ICI immunotherapy and unfavorable treatment prognosis[37-39]. Monocytes, on the other hand, primarily promote tumor growth and metastasis by differentiating into tumor-associated macrophages (TAMs). Circulating monocytes are the primary source of TAMs in tumor sites. The impact of TAMs on the progression of CRC has received considerable attention and exploration. Upon

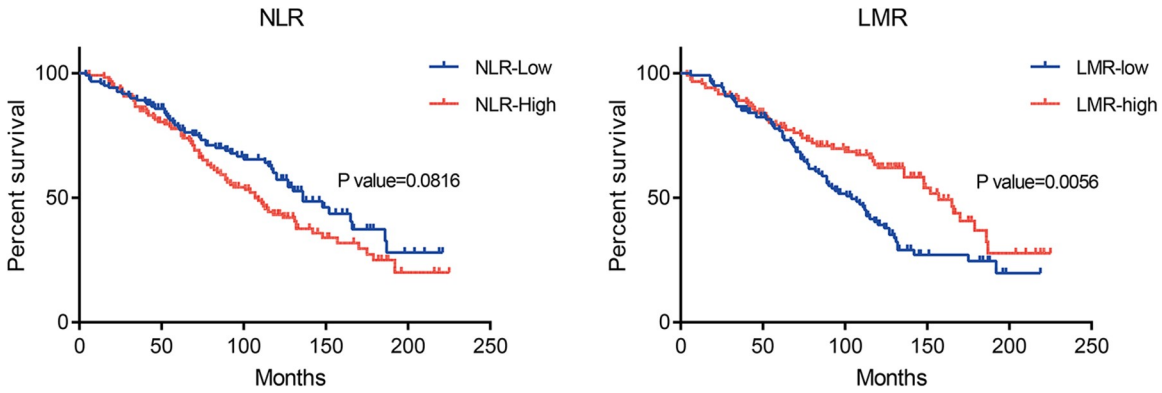

Figure 6. K-M survival curves for high and low expression groups of inflammatory indicators based on their medians among 239 CRC patients. Based on median inflammatory indicator levels, 239 CRC patients were divided into high and low groups. K-M survival curves were plotted, and statistical differences were assessed using the log-rank test.

recruitment by signals from the tumor microenvironment, monocytes infiltrate the tumor tissue and are programmed into a malignant phenotype that promotes tumor proliferation, metastasis, angiogenesis, and immune evasion, thereby playing a crucial role in cancer progression[40-42]. Platelets primarily support tumor progression by protecting circulating tumor cells[43]. Platelets derived chimeric extracellular vesicles can also promote CRC metastasis through EMT and endothelial activation[44]. Meanwhile, by activating the C5a/C5aR1 axis in TAMs, platelets can promote CRC growth and metastasis[45]. PD-L1 positive platelets can even mediate resistance to immune checkpoint inhibitors in patients with CRC[46]. As essential guardians of the body, the reduction in lymphocytes directly weakens the body's anti-tumor immune response, leading to immune evasion by tumor cells[24,26]. The significant roles of the aforementioned components in CRC progression provide an important theoretical foundation for clinical prediction using these indicators. The delicate and subtle balance among them may serve as a crucial switch in controlling the progression of CRC. Through more refined classification of these cells based on technologies such as single-cell sequencing, it may be possible to develop more sensitive and accurate inflammatory indicators.

Our findings have multifaceted clinical applications. First, NLR and LMR can serve as powerful tools for early detection and risk stratification in CRC screening programs. Furthermore, incorporating peripheral blood-based inflammatory indices into survival prediction is more operationally feasible. By integrating these indices (NLR, LMR, SII, NPR) into existing screening protocols, healthcare providers can dynamically and conveniently identify high-risk individuals for CRC and use them as

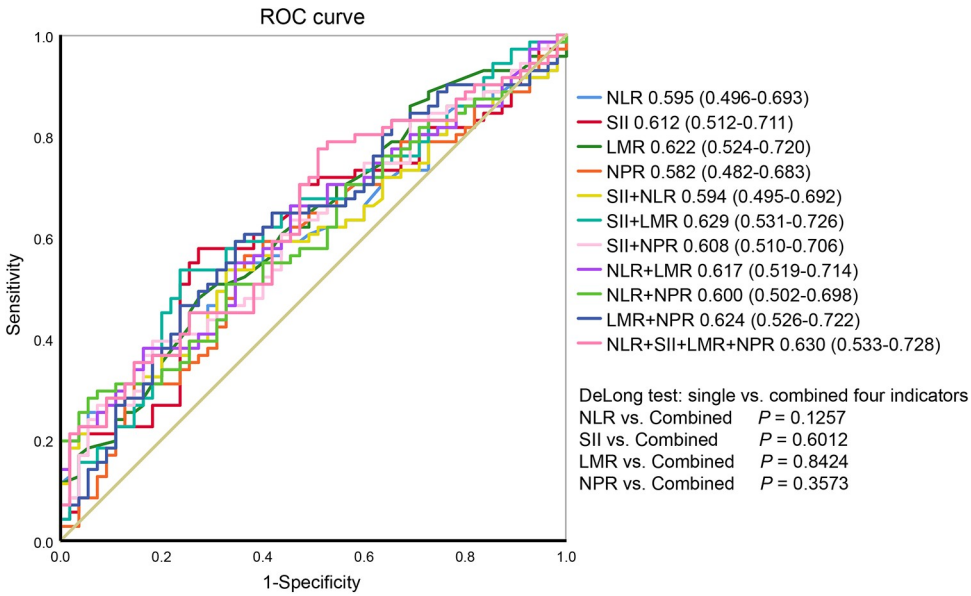

Figure 7. ROC curve evaluates the predictive performance of SII, NLR, LMR, NPR, and their combination for CRC mortality risk. The curve plots sensitivity on the Y-axis and false positive rate on the X-axis. The diagonal line represents the result of random guessing, with an AUC value of 0.5 serving as a reference. The figure is accompanied by the AUC values and confidence intervals for each indicator. All the ROC curves in this analysis lie above the diagonal line. No statistically significant differences were observed between individual indices or their combination (DeLong's test for pairwise comparisons, all $P > 0.05$).

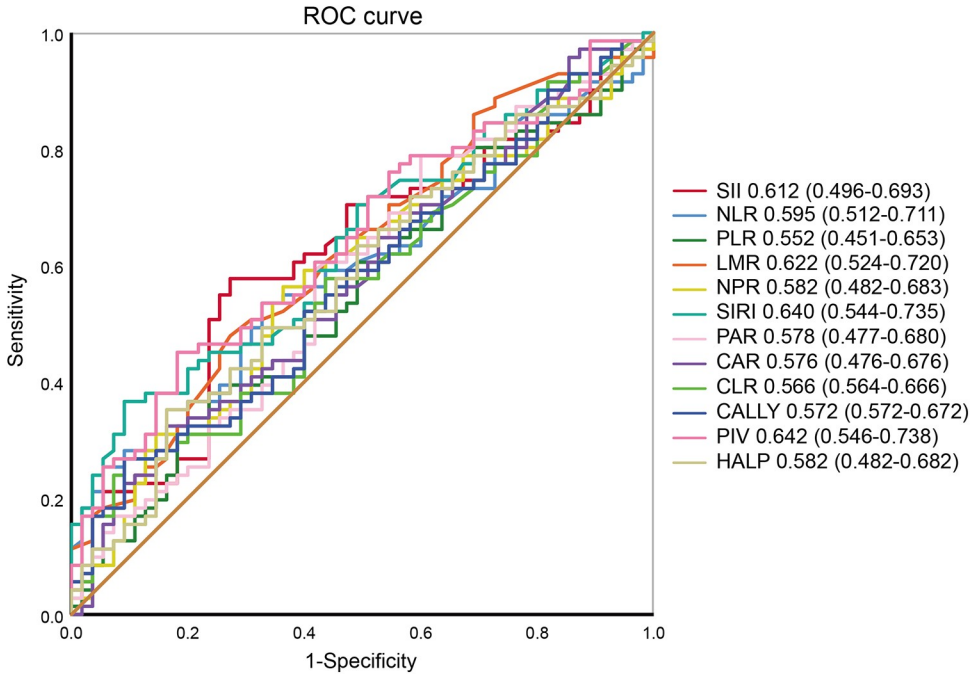

Figure 8. ROC curve evaluates the predictive performance of all 12 inflammation indices for CRC mortality risk. The curve plots sensitivity on the Y-axis and false positive rate on the X-axis. The diagonal line represents the result of random guessing, with an AUC value of 0.5 serving as a reference. The figure is accompanied by the AUC values and confidence intervals for each indicator. All the ROC curves in this analysis lie above the diagonal line.

auxiliary indicators for prognostic assessment in certain quality schemes. Our findings will also offer new insights and directions for related research. It is essential to conduct longitudinal studies to establish the temporal association between inflammatory indicators and CRC progression. Furthermore, further exploration of the biological mechanisms underlying the associations between NLR, LMR, SII, NPR, and CRC risk and prognosis is necessary, which may involve investigating the roles of specific inflammatory pathways or genetic factors that regulate these indicators. Additionally, the clinical utility of NLR and LMR as screening tools should be validated across diverse populations and clinical settings. Lastly, our results also highlight the potential for developing novel therapeutic strategies targeting inflammatory pathways. Modulating systemic inflammation through pharmacological interventions or lifestyle changes may help reduce CRC risk and improve patient outcomes.

This study has several strengths. The use of NHANES data ensures a large, diverse, and representative sample, thereby enhancing the generalizability of our findings. We comprehensively adjusted for potential confounders, including demographic characteristics, lifestyle factors, and comorbidities, which strengthens the robustness of our results. Additionally, we conducted the most comprehensive analysis of multiple reported inflammatory indices and employed robust statistical methods, such as multivariable regression and generalized additive models, to provide a detailed understanding of the association between inflammation and CRC risk.

However, there are also limitations to our study. First, the cross-sectional nature of NHANES data limits our ability to establish causal association between inflammatory indices and CRC risk. Future prospective cohort studies or randomized controlled trials are needed to validate our findings. Second, the relatively small number of CRC cases in our study may have limited the statistical power to detect significant associations for some indices. Third, our analysis relies on self-reported cancer diagnosis data, which may introduce recall bias. The lack of information such as tumor staging and treatment details also limits the accuracy of this study. Lastly, although we adjusted for a wide range of covariates, the potential for unmeasured confounders cannot be entirely ruled out. More refined and large-scale clinical sample studies based on this research are needed to address the aforementioned issues and guide clinical practice.

Conclusions

In conclusion, our study provides new insights into the role of inflammatory indices in CRC risk and highlights the potential clinical application value of NLR, LMR, SII, and NPR as non-invasive biomarkers in CRC. By elucidating the complex associations between inflammatory indices and CRC risk and prognosis, our findings further support the importance of inflammation in cancer development and offer new directions for future research and clinical practice.

Ethical approval

The dataset was obtained from the NHANES database and all data were ethically approved before recording into the database.

Consent

Not applicable.

Sources of funding

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Author contributions

M.Z.: writing – review & editing, writing – original draft, visualization, validation, formal analysis, data curation, conceptualization; Q.G. and M.Z.: writing – review & editing, validation, formal analysis, data curation; S.Y. and Y.L.: writing – review & editing, data curation; B.G., B.X., A.H., and J.X.: writing – review & editing; D.Y.: writing – review & editing, funding acquisition, data curation, conceptualization.

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The authors declare that they have no competing interests.

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The datasets that were obtained in this study can be made available by the corresponding author upon reasonable request.

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No AI was used in the research and manuscript development.

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