Am J Cancer Res 2026;16(5):1907-1921
www.ajcr.us /ISSN:2156-6976/ajcr0169707

Original Article

A novel integrated inflammation response score (IIRS) for predicting all-cause and cardiovascular mortality among cancer survivors

Zhao Liu[1,2], Xiaojie Li[2], Zhaoxing Li[2]

[1]*Medical Faculty Heidelberg, University of Heidelberg, Im Neuenheimer Feld 129, 69120 Heidelberg, Germany;* [2]*Department of General Surgery, The Fourth Affiliated Hospital of Hebei Medical University, Shijiazhuang 050017, Hebei, China*

Received October 31, 2025; Accepted May 6, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: Systemic inflammation represents a crucial pathophysiological link between cancer, cardiovascular disease, and mortality, yet the predictive value of individual inflammatory indices is still unclear. The cohort study of 1,752 cancer survivors developed new Integrated Inflammation Response Scores (IIRS) using principal component analysis. The IIRS-1 predicted all-cause mortality with a C-index of 0.721 over a median follow-up of 113 months with 761 deaths (169 cardiovascular deaths), whereas the parsimonious IIRS-2 (combining neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios) demonstrated exceptional performance for cardiovascular mortality (C-index: 0.771, 10-year AUC: 0.811), greatly outperforming most single indices. An independent external validation cohort of 923 cancer survivors confirmed the discriminatory performance of IIRS-1 (C-index: 0.653) and IIRS-2 (C-index: 0.736). The clinical utility was validated by nomograms and decision curve analysis, and the monocyte-to-lymphocyte ratio demonstrated a nonlinear correlation with the risk of cardiovascular mortality (threshold: 0.3). The IIRS offers a robust, clinically practical tool for risk assessment and precise intervention in cancer survivorship care.

Keywords: Integrated inflammation response score, cancer survivors, cardiovascular diseases, mortality

Introduction

The increasing population of cancer survivors worldwide poses a significant challenge for long-term health management. These individuals still have a much higher long-term mortality than the general population, despite advancements in cancer treatment [1]. A large number of excess deaths are caused by non-cancer causes, especially cardiovascular disease (CVD) [2, 3]. There is growing evidence that chronic, low-grade systemic inflammation serves as a key mechanistic link between cancer and CVD, even though part of this increased risk can be attributed to treatment-related cardiotoxicity (e.g., anthracyclines, radiation) [4, 5]. This inflammatory situation, which is caused and worsened by cancer and its treatments, can increase cardiovascular incidents and overall mortality. This happens through endothelial dysfunction, oxidative stress, and atherogenesis [4, 6-8].

In this context, identifying high-risk survivors and implementing early intervention are important. Effective biomarkers that can quantify this systemic inflammatory burden offer a promising avenue. Due to the low cost and high accessibility, inflammation indices derived from routine complete blood counts (CBC), such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been widely studied [9, 10]. However, these indices are intrinsically fragmentary. They each only capture a single aspect of the intricate inflammation-immune network, failing to represent its overall activity and complexity. This limits their predictive efficacy and stability across different studies and populations, particularly in distinguishing between all-cause and cause-specific mortality. In theory, a shift from the evaluation of single signals to the characterization of the integrated inflammatory state may offer a more comprehensive understanding of the underlying pathophysiological mechanisms. For

https://doi.org/10.62347/CQAN4296

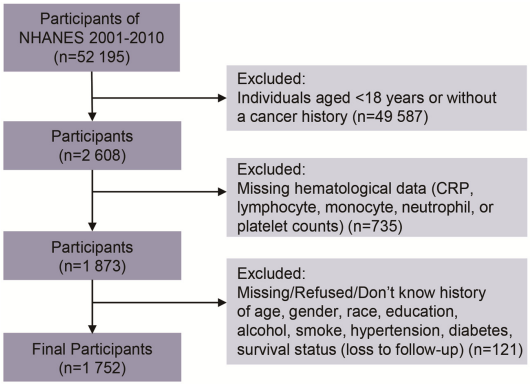


Figure 1. Study participant flow diagram. This flowchart details the selection of the study cohort from the National Health and Nutrition Examination Survey (NHANES, 2001-2010) cycles. The final analytical cohort consisted of 1,752 adult cancer survivors with complete data on inflammation indices, key covariates, and mortality follow-up.

instance, the monocyte-to-lymphocyte ratio (MLR) exemplifies the activation of the monocyte/macrophage axis [11, 12]. It is regarded as a principal factor in the development and instability of atherosclerotic plaque. The neutrophil-to-lymphocyte ratio (NLR) indicates the equilibrium between innate pro-inflammatory (neutrophil) and adaptive immune (lymphocyte) responses [13]. Neutrophils can recruit and activate monocytes, and then the two cell types jointly amplify vascular inflammation and exhibit synergistic effects in atherosclerosis. Thus, integrating indices, such as NLR and MLR, into a single composite score could better capture the synergistic inflammatory pathways that contribute to cardiovascular risk in cancer survivors.

Therefore, we aimed to incorporate multiple complementary inflammatory indices into a comprehensive scoring system. This could provide a more comprehensive and stable quantification of the systemic inflammatory burden in cancer survivors, thereby enabling more precise prediction of the risk of all-cause and cardiovascular mortality [14].

We utilized the large, nationally representative cohort from the National Health and Nutrition Examination Survey (NHANES) to comprehensively assess the associations between various systemic inflammatory indices and mortality outcomes among cancer survivors [4, 9, 15]. In order to better predict all-cause and cardiovascular mortality, we developed and validated new Integrated Inflammation Response Scores, optimized for predicting all-cause and cardiovascular mortality, respectively [15, 16]. Additionally, we conducted a thorough comparison between the predictive performance and clinical net benefit of these new scores and conventional individual indices. Through developing a robust and clinically practical biomarker for long-term risk stratification and precision management in cancer survivors, we offer new insight into the shared inflammatory mechanisms linking cancer and cardiovascular disease.

Methods

Study design and population

Data from successive cycles of the National Health and Nutrition Examination Survey (NHANES, 2001-2010) were used in this retrospective cohort study. All participants provided written informed consent, and the survey protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board.

We included adult participants (age ≥18 years) who self-reported a physician-diagnosed history of cancer. Exclusion criteria were: missing key hematological data (CBC components required for index calculation), missing data on demographics or key clinical characteristics, or missing follow-up survival status information (**Figure 1**). The sample size was determined by data availability; with 761 all-cause deaths and 169 cardiovascular deaths, events per variable exceeded 10, providing adequate statistical power.

An independent validation cohort consisting of adult cancer survivors treated at the Fourth Affiliated Hospital of Hebei Medical University between 2018 and 2021 was used. The same inclusion and exclusion criteria as the NHANES cohort were applied. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2026KT141) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

Follow-up and loss to follow-up

Participants were followed up from the date of the baseline interview until death or December 31, 2019, whichever occurred first. Loss to fol-

low-up was defined as the absence of mortality linkage data or survival status information in the National Death Index (NDI) database. Individuals with missing survival status or follow-up duration were excluded from the analysis. For the external validation cohort, follow-up was conducted through medical record review and telephone interviews, with censoring on the date of last contact or September 30, 2025. Loss to follow-up was defined as inability to ascertain survival status after the last known contact.

Definitions and measurement of variables

Inflammatory indices: Calculated from laboratory measurements of CBC components as follows [9]: NLR: Neutrophil count/Lymphocyte count; PLR: Platelet count/Lymphocyte count; MLR: Monocyte count/Lymphocyte count; SII: (Neutrophil count × Platelet count)/Lymphocyte count; MII-1: NLR × C-reactive protein (CRP); MII-2: PLR × CRP; MII-3: SII × CRP.

Baseline cardiovascular disease (CVD): A history of CVD was defined as self-reported presence of any of the following: congestive heart failure, coronary heart disease, angina/angina pectoris, or heart attack. For the NHANES cohort, this was derived from the questionnaire items MCQ160b-e. The same definition was applied to the external validation cohort using equivalent medical record documentation.

Outcomes: The primary outcomes were all-cause mortality and cardiovascular mortality. Mortality status and cause of death were determined by linkage to the National Death Index (NDI) database through December 31, 2019. Cardiovascular mortality was defined where the underlying cause of death was coded as ICD-10 diseases of the circulatory system.

Covariates: Covariates collected from standardized interviews, questionnaires, and physical examinations included: age, sex, race/ethnicity, education level, smoking, alcohol, and history of hypertension and diabetes.

Statistical analysis

Baseline characteristics: The characteristics of participants were delineated according to their baseline CVD status. Continuous variables are shown as mean (standard deviation), while categorical variables are shown as number (percentage). Student's t-test or Chi-squared test was used to compare groups.

Association analysis: Univariable and multivariable Cox proportional hazards regression models were employed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the correlations between inflammatory indices and all-cause mortality. For cardiovascular mortality, the Fine-Gray subdistribution hazards model was employed, considering non-cardiovascular deaths as competing risks. Multivariable models included age, sex, race/ethnicity, education, smoking, alcohol consumption, hypertension, and diabetes.

Collinearity assessment: The variance inflation factor (VIF) was used to assess multicollinearity among the seven inflammatory indices. A VIF >10 was deemed indicative of significant multicollinearity.

IIRS score construction: Inflammatory indices that showed significant associations with the outcomes in multivariable models were included in a principal component analysis (PCA) to construct the Integrated Inflammation Response Scores (IIRS-1 for all-cause mortality and IIRS-2 for cardiovascular mortality). All indices were standardized using Z-scores before analysis. The IIRS scores were defined as weighted linear combinations of selected indices according to the loadings of the first principal component.

Model performance validation

Discriminatory ability: Harrell's C-index was calculated. Time-dependent ROC curves were plotted, and AUC values at 1, 3, 5, and 10 years were calculated to compare the IIRS scores with individual indices. For each time point, differences in AUC between the IIRS scores and each single index were assessed using DeLong's test for paired AUC comparisons, as implemented in the timeROC package. Clinical cutoffs for IIRS-1 and IIRS-2 were set at their medians.

Clinical utility: Nomograms that included the IIRS scores and key covariates were developed. Decision curve analysis (DCA) was conducted to assess the clinical net benefit. Calibration curves and the Gronnesby-Borgan goodness-

Table 1. Baseline characteristics of cancer survivors by cardiovascular disease (CVD) status

Level	Total	non-CVD	CVD	P
n	1752	1400	352	
Sex (%)				<0.001
Female	925 (52.797)	774 (55.286)	151 (42.898)	
Male	827 (47.203)	626 (44.714)	201 (57.102)	
Age (mean (SD))	66 (15)	64 (15)	72 (10)	<0.001
Race (%)				0.016
Mexican American	106 (6.050)	87 (6.214)	19 (5.398)	
Non-Hispanic Black	208 (11.872)	177 (12.642)	31 (8.807)	
Non-Hispanic White	1344 (76.712)	1053 (75.214)	291 (82.670)	
Other Hispanic	58 (3.311)	54 (3.857)	4 (1.136)	
Other Race	36 (2.055)	29 (2.071)	7 (1.987)	
Education (%)				<0.001
9-11th grade	242 (13.813)	173 (12.357)	69 (19.602)	
College graduate or above	416 (23.744)	358 (25.571)	58 (16.477)	
High school graduate	431 (24.600)	352 (25.143)	79 (22.443)	
Less than 9th grade	200 (11.416)	142 (10.143)	58 (16.477)	
Some college or AA degree	463 (26.427)	375 (26.786)	88 (25.000)	
Alcohol (%)				0.001
No	573 (32.705)	432 (30.857)	141 (40.057)	
Yes	1179 (67.295)	968 (69.143)	211 (59.943)	
Smoke (%)				0.001
No	765 (43.664)	640 (45.714)	125 (35.511)	
Yes	987 (56.336)	760 (54.286)	227 (64.489)	
Hypertension (%)				<0.001
No	780 (44.521)	685 (48.929)	95 (26.989)	
Yes	972 (55.479)	715 (51.071)	257 (73.011)	
Diabetes (%)				<0.001
Borderline	49 (2.797)	32 (2.286)	17 (4.830)	
No	1400 (79.909)	1176 (84.000)	224 (63.636)	
Yes	303 (17.295)	192 (13.714)	111 (31.534)	
NLR (mean (SD))	2.531 (1.362)	2.443 (1.271)	2.892 (1.631)	<0.001
PLR (mean (SD))	144.552 (65.791)	143.933 (64.079)	147.042 (72.238)	0.428
MLR (mean (SD))	0.332 (0.174)	0.321 (0.161)	0.371 (0.170)	<0.001
SII (mean (SD))	628.817 (388.611)	615.826 (376.510)	680.444 (430.145)	0.005
MII-1 (mean (SD))	1.652 (5.170)	1.431 (3.613)	2.551 (8.972)	<0.001
MII-2 (mean (SD))	84.729 (198.553)	77.562 (166.567)	113.223 (291.641)	0.003
MII-3 (mean (SD))	436.800 (1300.832)	387.682 (1024.491)	632.151 (2051.890)	0.002

Data are presented as Mean (Standard Deviation) for normally distributed continuous variables, and Number (Percentage) for categorical variables. *P*-values were derived from Student's t-test, or Chi-squared test, as appropriate. Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; MII, modified inflammation index. CVD was defined as self-report of congestive heart failure, coronary heart disease, angina, or myocardial infarction based on NHANES questionnaire data.

of-fit test were used to evaluate the nomogram.

Subgroup analysis and interaction: Subgroup analyses, based on age, sex, smoking status, alcohol use, hypertension, diabetes, and the type of cancer, were performed. Likelihood ratio tests were used to test for interaction effects.

CVD risk analysis: The relationships between inflammatory indices and prevalent CVD at

Table 2. Univariate Cox regression analysis for associations with all-cause mortality and cardiovascular mortality

Variable	Overall Survival			CVD Survival		
	HR	95% CI	P	HR	95% CI	P
Sex	0.593	0.514-0.685	<0.001	0.563	0.415-0.765	<0.001
Age	4.701	3.888-5.683	<0.001	9.869	5.801-16.792	<0.001
Race	1.227	1.106-1.361	<0.001	1.169	0.939-1.455	0.162
Education	0.840	0.796-0.887	<0.001	0.842	0.752-0.944	<0.001
Alcohol	1.192	1.028-1.382	<0.001	1.325	0.972-1.807	0.075
Smoke	0.763	0.660-0.883	<0.001	0.921	0.680-1.249	0.598
Hypertension	0.565	0.486-0.656	<0.001	0.521	0.377-0.719	<0.001
Diabetes	0.612	0.520-0.719	<0.001	0.495	0.356-0.688	<0.001
NLR	1.282	1.232-1.335	<0.001	1.308	1.205-1.421	<0.001
PLR	1.003	1.002-1.004	<0.001	1.003	1.001-1.005	0.004
MLR	6.951	5.338-9.051	<0.001	9.467	5.947-15.072	<0.001
SII	1.001	1.00-1.001	<0.001	1.001	1.00-1.001	<0.001
MII-1	1.036	1.027-1.045	<0.001	1.036	1.017-1.055	<0.001
MII-2	1.001	1.00-1.001	<0.001	1.001	1.000-1.001	0.012
MII-3	1	1.000-1.000	<0.001	1	1.000-1.000	0.005

Because MLR has a narrow range (0.03-2.25), the HR of 6.951 represents the effect of a one-unit increase.

baseline were evaluated using multivariable logistic regression. Restricted cubic splines (RCS) with 4 knots were used to investigate the nonlinear relationship between MLR and CVD risk.

R software (version 4.2.3) was used for all statistical analyses. Statistical significance was defined as a two-sided *P*-value <0.05.

Results

Study population baseline characteristics

The final analytical cohort comprised 1,752 cancer survivors (**Figure 1**). Among them, 352 (20.1%) had prevalent CVD at baseline. As shown in **Table 1**, compared to survivors without CVD, those with CVD were more likely to be male, older, non-Hispanic White, have lower education levels, be smokers, and have a history of hypertension and diabetes. Regarding inflammatory indices, participants with CVD had significantly higher median levels of NLR, MLR, SII, and all MIIs (all P<0.05), while PLR did not differ significantly between the groups.

Associations of inflammatory indices with mortality risk

Univariable analysis results are presented in **Table 2**. Multivariable Cox regression analysis, after adjusting for covariates, showed that NLR, PLR, MLR, SII, MII-1, MII-2, and MII-3 were all significantly associated with an increased risk of all-cause mortality. In the competing-risk regression model for cardiovascular mortality, NLR, PLR, MLR, SII, and MII-3 exhibited significant independent correlations, while MII-1 and MII-2 did not. Kaplan-Meier survival curves and cumulative incidence function curves visually demonstrated the survival differences when stratified by these indices (**Figure 2**).

Development and performance of the integrated inflammation response scores (IIRS)

Variance inflation factor (VIF) analysis showed no severe multicollinearity among the seven inflammatory indices, with VIF values ranging from 1.98 to 9.65 (NLR: 4.316, PLR: 3.075, SII: 4.200, MLR: 1.978, MII-1: 7.132, MII-2: 5.718, MII-3: 9.646). The correlation matrix was 10.870, which further indicated that collinearity was acceptable. Consequently, all indices were preserved for principal component analysis.

According to the multivariable analysis results, IIRS-1 was constructed using all seven indices to predict all-cause mortality, while IIRS-2 was constructed using NLR and MLR for cardiovascular mortality prediction. The PCA-derived weighting coefficients were as follows:

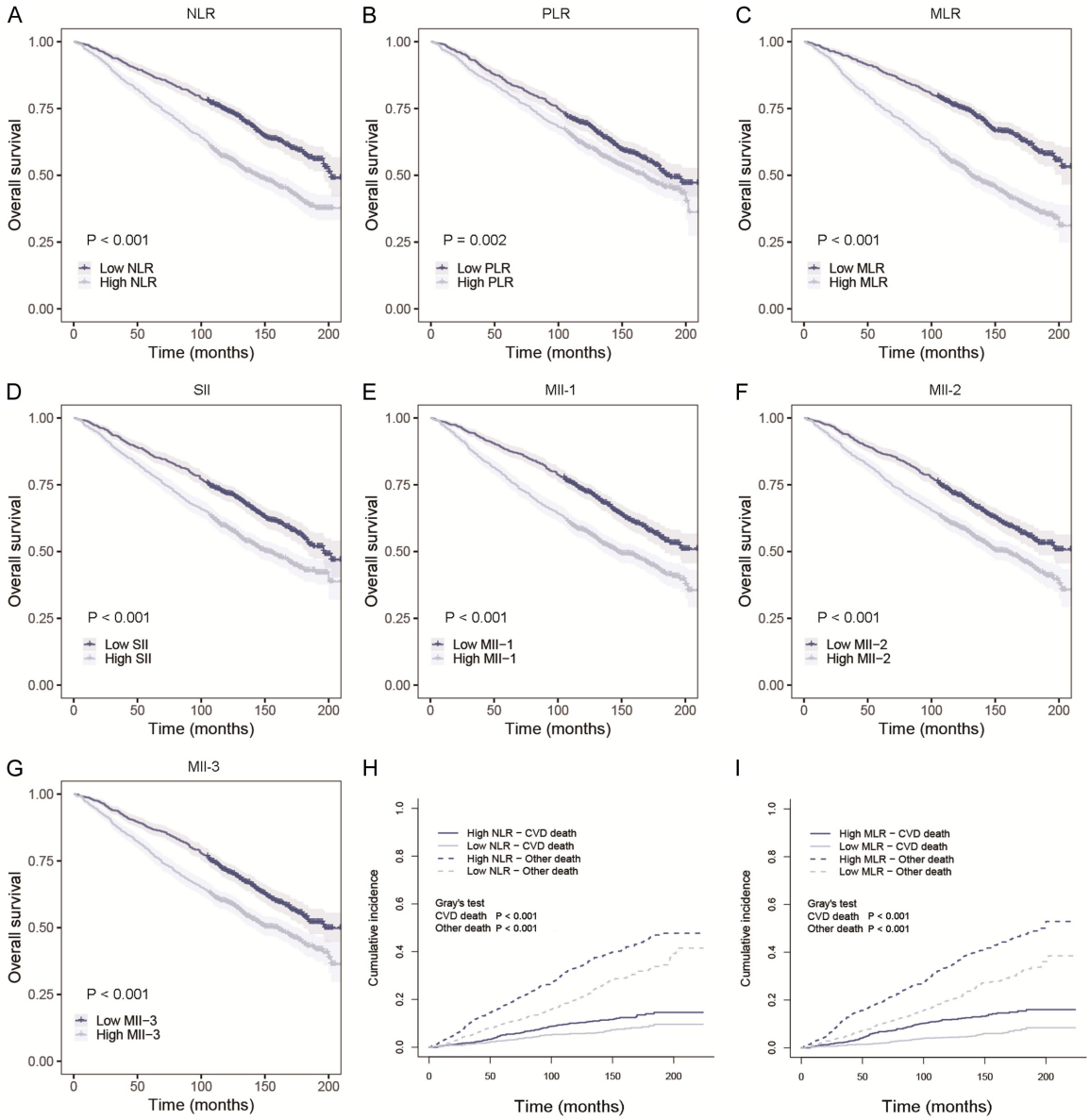


Figure 2. Association of individual inflammation indices with mortality risk. A-G: Kaplan-Meier curves for all-cause mortality, stratified by the median value of each inflammation index. The log-rank test was used for comparisons. H, I: Cumulative incidence function curves for cardiovascular mortality, stratified by the median value of NLR or MLR, with non-cardiovascular deaths treated as competing risks (Gray's test).

IIRS-1 = (0.39 × NLR) + (0.34 × PLR) + (0.41 × SII) + (0.30 × MLR) + (0.38 × MII-1) + (0.40 × MII-2) + (0.41 × MII-3)

IIRS-2 = (0.71 × NLR) + (0.71 × MLR)

Performance validation (**Table 3**) showed that IIRS-1 predicted all-cause mortality with a C-index of 0.721. Its AUC values at 1, 3, 5, and 10 years were 0.703, 0.707, 0.732 and 0.764, respectively, and overall superior to any single index. For cardiovascular mortality, IIRS-2 exhibited superior discrimination (C-index = 0.771) and maintained high long-term predictive accuracy (5-year AUC = 0.803; 10-year AUC = 0.811, **Table 4**). DeLong's test confirmed that the IIRS scores achieved significantly higher AUCs than several individual indices at key time points (**Tables 3**, **4**). Kaplan-Meier and cumulative incidence curves based on the IIRS scores effectively demonstrated their predictive value for risk stratification (**Figure 3A**, **3B**).

Table 3. Predictive performance comparison: IIRS-1 and individual inflammatory indices for all-cause mortality

Variable	C-index	AUC (months)							
		12	P	36	P	60	P	120	P
NLR	0.720	0.678	0.006	0.698	0.020	0.732	0.006	0.766	0.009
PLR	0.710	0.683	0.017	0.687	0.001	0.715	0.001	0.753	0.001
SII	0.715	0.688	0.007	0.692	0.001	0.723	0.001	0.759	0.001
MLR	0.719	0.688	0.054	0.696	0.007	0.733	0.014	0.765	0.032
MII-1	0.709	0.676	0.083	0.688	0.003	0.716	0.053	0.752	0.002
MII-2	0.709	0.678	0.009	0.687	0.004	0.714	0.032	0.752	0.001
MII-3	0.709	0.678	0.008	0.686	0.008	0.715	0.062	0.752	0.012
IIRS1	0.721	0.703	-	0.707	-	0.732	-	0.764	-

P values were calculated using DeLong's test comparing the AUCs of each single index with that of IIRS-1.

Table 4. Predictive performance comparison: IIRS-2 and constituent indices for cardiovascular mortality

Variable	C-index	AUC (months)							
		12	P	36	P	60	P	120	P
NLR	0.763	0.628	0.086	0.717	0.003	0.794	0.008	0.801	0.004
MLR	0.769	0.676	0.006	0.733	0.005	0.796	0.037	0.808	0.002
IIRS2	0.771	0.641	-	0.723	-	0.803	-	0.811	-

P values were calculated using DeLong's test comparing the AUCs of each single index with that of IIRS 2.

To evaluate the generalizability of the IIRS, we validated the scores in an independent cohort of 923 cancer survivors from 2018 to 2021 (**Table 5**). In this external cohort, the discriminative performance of IIRS-1 for all-cause mortality remained robust, with a C-index of 0.653 and 5-year AUC of 0.794. For cardiovascular mortality, IIRS-2 achieved a C-index of 0.736 and a 5-year AUC of 0.863. Both scores categorized patients into high- and low-risk groups for all-cause and cardiovascular mortality, respectively (**Figure 3C**, **3D**). These results support the generalizability and stability of the IIRS across different cohorts.

Nomogram development and clinical utility

To improve clinical utility, nomograms integrating the IIRS with key clinical variables were established (**Figure 4**). The nomogram for predicting 3- and 5-year all-cause mortality had a C-index of 0.714. ROC analysis confirmed the stable and sustained superiority of the IIRS scores during long-term follow-up. DCA indicated that using this nomogram for clinical decision-making provided a net benefit across a wide range of threshold probabilities. The calibration curves at 3 and 5 years demonstrated strong concordance between predicted and observed mortalities. The Gronnesby-Borgan goodness-of-fit test produced non-significant *P*-values (3-year: 0.322; 5-year: 0.261), confirming sufficient calibration. Similarly, the IIRS-2-based nomogram displayed excellent prediction accuracy for cardiovascular mortality (C-index = 0.766).

Subgroup and interaction analysis

Subgroup analysis revealed that IIRS-1 was significantly associated with all-cause mortality risk across all prespecified subgroups, and tests for interaction found no significant heterogeneity (all P for interaction >0.05) (**Figure 5**). IIRS-2 showed similar robustness in predicting the risk of cardiovascular mortality across subgroups.

Association between inflammatory indices and cardiovascular disease risk

According to multivariable logistic regression analysis, only MLR was found to be independently associated with prevalent CVD status at baseline among all inflammatory indices (**Table 6**). RCS analysis (**Figure 6**) showed that MLR

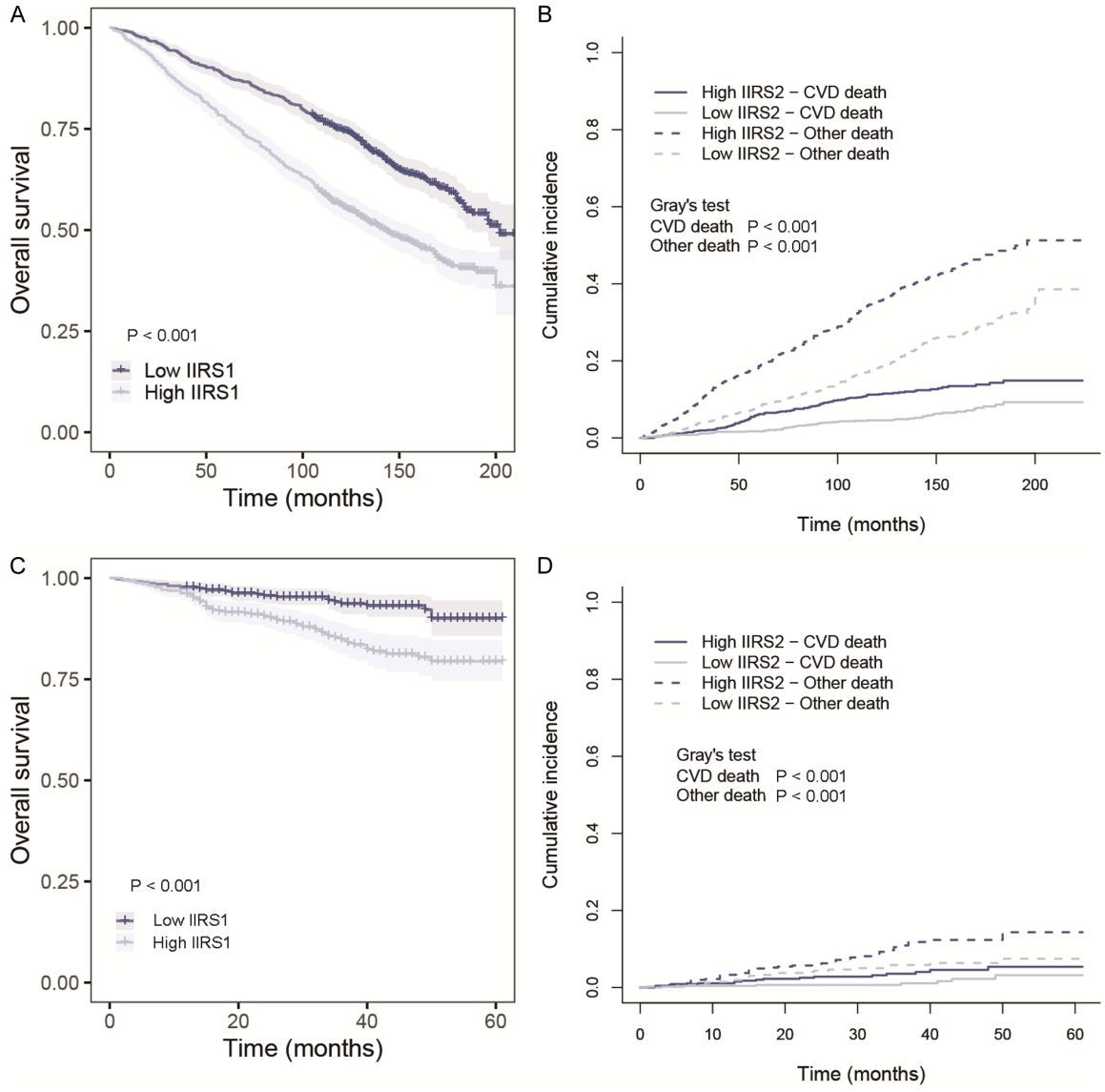


Figure 3. Prognostic performance of the integrated inflammation response scores (IIRS) in the NHANES (A, B) and external validation (C, D) cohorts. (A, C) Kaplan-Meier curves for all-cause mortality stratified by the median IIRS-1 score. (B, D) Cumulative incidence function curves for cardiovascular mortality stratified by the median IIRS-2 score. Both scores demonstrate superior risk stratification compared to individual indices in both cohorts.

and CVD are not linearly related (P for nonlinearity <0.01). A risk threshold was observed at MLR ≈ 0.3, beyond which CVD risk increased dramatically with rising MLR.

Discussion

We developed and validated a novel Integrated Inflammation Response Score (IIRS) and systematically evaluated its predictive value for long-term outcomes in cancer survivors in this nationally representative NHANES-based cohort study. Our results revealed several key findings. First, IIRS-1, which combines seven peripheral blood inflammatory indices, can independently predict all-cause mortality with high accuracy and consistent performance over time. Second, the IIRS-2, comprising NLR and MLR, demonstrated superior performance in predicting cardiovascular mortality, particularly during long-term follow-up. Third, there was a nonlinear link between MLR and baseline CVD risk, with a turning point around 0.3. Finally, both the IIRS-1 and IIRS-2 models dem-

Table 5. Baseline characteristics of the external validation cohort

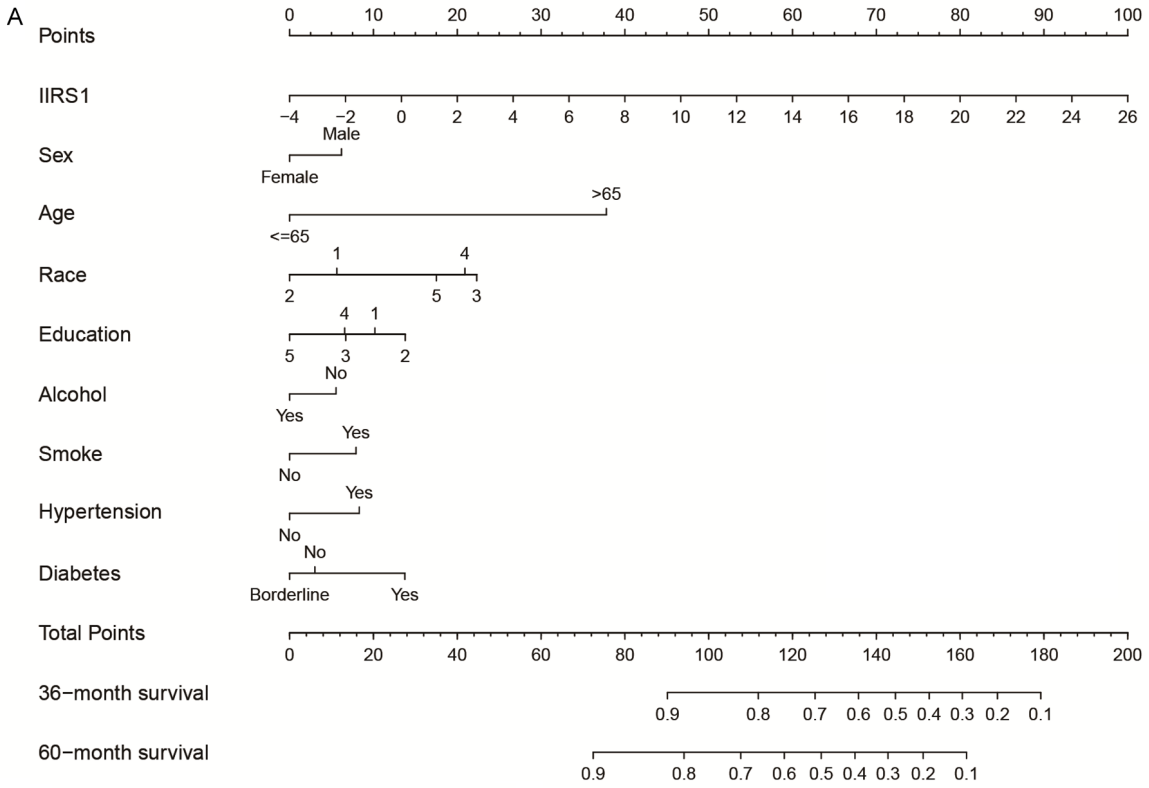
Level	Total	non-CVD	CVD	P
n	923	730	193	
Sex (%)				<0.001
Female	474 (51.354)	403 (55.205)	71 (36.788)	
Male	449 (48.646)	327 (44.795)	122 (63.212)	
Age (mean (SD))	67 (13)	66 (13)	72 (10)	<0.001
Education (%)				0.238
9-11th grade	93 (10.076)	70 (9.682)	23 (11.917)	
College graduate or above	240 (26.002)	202 (27.671)	38 (19.689)	
High school graduate	202 (21.885)	155 (21.233)	47 (24.352)	
Less than 9th grade	61 (6.609)	47 (6.438)	14 (7.254)	
Some college	327 (35.428)	256 (35.068)	71 (36.788)	
Alcohol (%)				1
No	173 (18.743)	137 (18.767)	36 (18.652)	
Yes	750 (81.257)	593 (81.2)	157 (81.347)	
Smoke (%)				<0.001
No	426 (46.154)	365 (50.0)	61 (31.606)	
Yes	497 (53.846)	365 (50.0)	132 (68.394)	
Hypertension (%)				<0.001
No	387 (41.928)	345 (47.260)	42 (21.762)	
Yes	536 (58.072)	385 (52.740)	151 (78.238)	
Diabetes (%)				<0.001
Borderline	41 (4.442)	31 (4.247)	10 (5.181)	
No	669 (72.481)	554 (75.890)	115 (59.585)	
Yes	213 (23.077)	145 (19.863)	68 (35.233)	
NLR (mean (SD))	2.570 (1.841)	2.501 (1.753)	2.844 (2.142)	0.024
PLR (mean (SD))	129.833 (66.262)	130.134 (65.093)	128.673 (70.701)	0.785
MLR (mean (SD))	0.351 (0.192)	0.343 (0.192)	0.391 (0.192)	0.001
SII (mean (SD))	580.771 (479.204)	575.773 (465.801)	599.71 (527.651)	0.537
MII-1 (mean (SD))	1.576 (4.876)	1.399 (4.148)	2.245 (6.948)	0.032
MII-2 (mean (SD))	72.282 (188.332)	68.394 (178.919)	86.987 (220.238)	0.223
MII-3 (mean (SD))	378.848 (125.413)	356.366 (1212.035)	463.886 (1402.139)	0.291

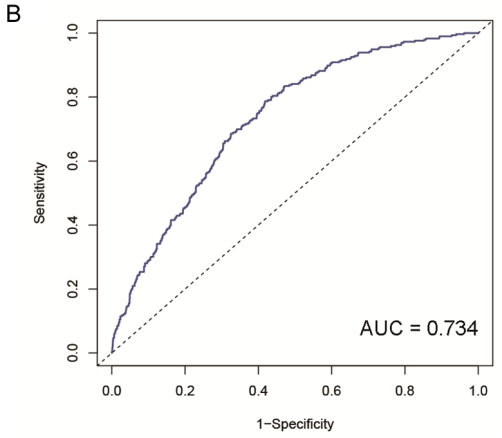
Data are presented as Mean (Standard Deviation) for normally distributed continuous variables, and Number (Percentage) for categorical variables. *P*-values were derived from Student's t-test, or Chi-squared test, as appropriate. Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; MII, modified inflammation index. CVD was defined as self-report of congestive heart failure, coronary heart disease, angina, or myocardial infarction.

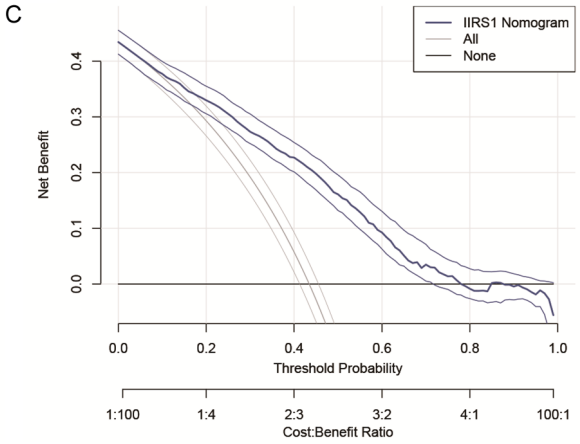
onstrated robust correlations across major demographic and clinical subgroups, validating their generalizability.

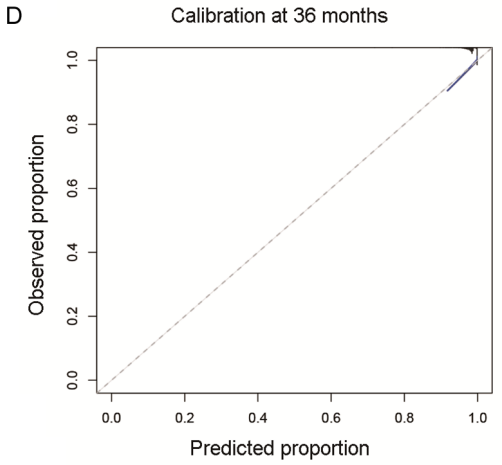
In line with previous studies, our results support the significant link between systemic inflammation and adverse outcomes in cancer survivors. However, a key advancement of this study is the demonstration that the IIRS can surmount the constraints of single indices, marking a paradigm shift from dependence on "single signals" to assessing "network status".

The IIRS's capacity to capture the inflammatory network's activity in multiple dimensions explains its predictive advantage. Different immune and inflammatory pathways are represented by peripheral blood cell indices: NLR represents the innate-adaptive immune balance, neutrophil-driven pro-inflammatory status, and lymphocyte-related immune surveillance capacity [13]; PLR is associated with platelet-involved thrombo-inflammation [10, 17]; MLR represents the monocyte/macrophage axis, which is crucial in the formation, progression, and rupture of atherosclerotic


A
Points
0 10 20 30 40 50 60 70 80 90 100
IIRS1
−4 −2 0 2 4 6 8 10 12 14 16 18 20 22 24 26
Sex
Male
Female
Age
>65
<=65
Race
1 4
2 5 3
Education
4 1
5 3 2
Alcohol
No
Yes
Smoke
Yes
No
Hypertension
Yes
No
Diabetes
No
Borderline Yes
Total Points
0 20 40 60 80 100 120 140 160 180 200
36−month survival
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1
60−month survival
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1


B
Sensitivity
1−Specificity
AUC = 0.734
0.0 0.2 0.4 0.6 0.8 1.0


C
IIRS1 Nomogram
All
None
Net Benefit
Threshold Probability
Cost:Benefit Ratio
1:100 1:4 2:3 3:2 4:1 100:1


D
Calibration at 36 months
Observed proportion
Predicted proportion
0.0 0.2 0.4 0.6 0.8 1.0

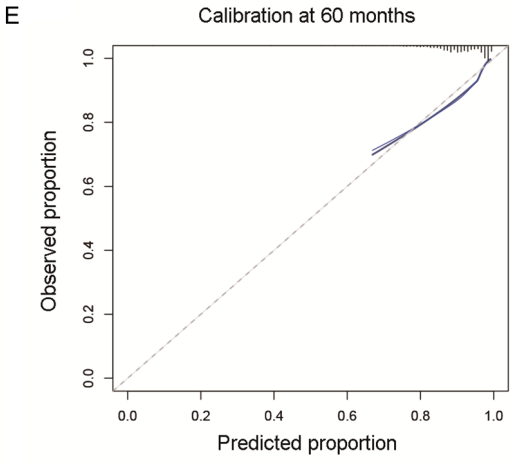

E
Calibration at 60 months
Observed proportion
Predicted proportion
0.0 0.2 0.4 0.6 0.8 1.0

Figure 4. Development and validation of a nomogram for predicting all-cause mortality. A: Nomogram for predicting 3- and 5-year all-cause mortality probability, integrating the IIRS-1 score with key clinical variables. B: Time-dependent receiver operating characteristic (ROC) curves at 5 years. C: Decision curve analysis (DCA) showing the net clinical benefit of the nomogram across a range of threshold probabilities. D: Calibration curve at 3 years. The dashed diagonal line represents perfect calibration; the black line indicates observed mortality probabilities; the blue line represents optimism-corrected estimates derived from 200 bootstrap resamples. E: Calibration curve at 5 years.

A

Variable	Group	HR (95% CI)	P–Value	Interaction P	Forest
Sex	Female	1.550 (1.247–1.928)	<0.001	0.344	
	Male	1.832 (1.503–2.234)	<0.001		
Age	<=65	1.632 (1.153–2.310)	0.006	0.444	
	>65	1.542 (1.312–1.811)	<0.001		
Alcohol	No	1.585 (1.242–2.022)	<0.001	0.773	
	Yes	1.846 (1.539–2.215)	<0.001		
Smoke	Yes	1.939 (1.607–2.339)	<0.001	0.208	
	No	1.512 (1.198–1.907)	0.001		
Hypertension	Yes	1.761 (1.468–2.113)	<0.001	0.610	
	No	1.640 (1.282–2.100)	<0.001		
Diabetes	Yes	1.538 (1.137–2.081)	0.005	0.407	
	No	1.808 (1.526–2.144)	<0.001		
	Borderline	1.104 (0.419–2.910)	0.841		
Cancer Type	Breast Cancer	1.503 (1.309–1.665)	<0.001	0.501	
	Lung Cancer	1.387 (1.201–2.091)	<0.001		
	Colorectal Cancer	1.657 (1.303–1.987)	<0.001		
	Prostate Cancer	1.453 (1.201–1.870)	<0.001		
	Other Solid Tumors	1.386 (1.119–2.065)	0.001		
	Hematologic Tumors	1.701 (1.357–2.209)	0.001		

0.5 2 4
HR (95% CI)

B

Variable	Group	HR (95% CI)	P–Value	Interaction P	Forest
Sex	Female	2.149 (1.345–3.435)	0.001	0.492	
	Male	2.439 (1.524–3.905)	<0.001		
Age	<=65	2.166 (0.779–6.018)	0.138	0.593	
	>65	1.827 (1.298–2.571)	<0.001		
Alcohol	No	1.667 (1.012–2.744)	0.045	0.164	
	Yes	3.274 (2.129–5.034)	<0.001		
Smoke	Yes	2.554 (1.656–3.939)	<0.001	0.910	
	No	2.327 (1.439–3.764)	<0.001		
Hypertension	Yes	2.392 (1.611–3.553)	<0.001	0.980	
	No	2.429 (1.396–4.225)	0.002		
Diabetes	Yes	1.230 (0.685–2.210)	0.488	0.228	
	No	3.487 (2.316–5.250)	<0.001		
	Borderline	0.794 (0.123–5.115)	0.808		
Cancer Type	Breast Cancer	1.623 (1.509–1.955)	<0.001	0.396	
	Lung Cancer	1.687 (1.101–2.891)	0.001		
	Colorectal Cancer	1.907 (1.603–2.268)	<0.001		
	Prostate Cancer	1.559 (1.201–2.167)	<0.001		
	Other Solid Tumors	1.986 (1.219–2.658)	<0.001		
	Hematologic Tumors	2.801 (1.557–3.287)	0.003		

0.5 2 4
HR (95% CI)

Figure 5. Subgroup analysis of the association between IIRS and mortality. Forest plots of hazard ratios for the association between (A) IIRS-1 and all-cause mortality, and (B) IIRS-2 and cardiovascular mortality, across prespecified subgroups. *P*-values for interaction were non-significant in all subgroups, supporting the robustness of the associations. Squares indicate HRs; horizontal bars represent 95% confidence intervals (CIs); the vertical dashed line is the null effect (HR = 1).

plaques [11, 12, 18-20]. Integrating these complementary signals via PCA reduces the noise and instability inherent to single indices, thereby providing a more comprehensive quantification of the long-term, low-grade chronic inflammatory load. The IIRS-2 combines NLR and MLR to capture the synergistic neutrophil-monocyte axis, which is important for atherosclerosis. Neutrophils initiate plaque formation, while monocytes drive plaque progression and rupture; their interaction exacerbates vascular inflammation [17-19]. By integrating both parts of this synergistic process, IIRS-2 better reflects the overall inflammatory burden than either index alone, which explains its superior performance in predicting cardiovascular mortality.

While previous studies have linked individual indices such as NLR, PLR, or SII to the prognosis of cancer or cardiovascular disease, the predictive performance of single indices is limited by short-term fluctuations and population heterogeneity [15, 21]. Our results demonstrate that data-driven composite indices - derived objectively using PCA - can perform better than single indices in terms of discrimination, calibration, and clinical utility. This highlights a shift from assessing isolated inflammatory signals to characterizing the broader immune-inflammatory landscape.

MLR and baseline CVD risk were found to have a nonlinear relationship, with risk increasing significantly beyond MLR ≈ 0.3. This threshold

Table 6. Multivariable logistic regression analysis for the association between inflammatory indices and prevalent cardiovascular disease

	Q1	Q2	Q3	Q4
MLR				
OR	Ref.	1.358	1.918	2.308
95% CI		0.917-2.011	1.295-2.84	1.447-3.681
P-value		0.132	0.002	0.001
NLR				
OR	Ref.	1.018	1.336	1.945
95% CI		0.672-1.54	0.847-2.108	1.297-2.918
P-value		0.935	0.217	0.002
PLR				
OR	Ref.	0.862	0.839	0.875
95% CI		0.605-1.227	0.564-1.248	0.595-1.288
P-value		0.411	0.390	0.501
SII				
OR	Ref.	1.147	1.175	1.494
95% CI		0.766-1.717	0.744-1.858	0.968-2.306
P-value		0.507	0.492	0.075
MII-1				
OR	Ref.	1.312	1.469	2.031
95% CI		0.895-1.924	0.85-2.538	1.312-3.143
P-value		0.169	0.173	0.002
MII-2				
OR	Ref.	0.985	1.228	1.570
95% CI		0.695-1.394	0.775-1.946	1.03-2.392
P-value		0.931	0.385	0.040
MII-3				
OR	Ref.	0.975	1.484	1.522
95% CI		0.689-1.381	0.92-2.395	0.996-2.326
P-value		0.889	0.111	0.057

Abbreviations: OR, Odds Ratio; CI, Confidence Interval. Each inflammatory index was categorized into quartiles (Q1-Q4) based on its distribution in the study population (N = 1,752). The quartile ranges (minimum-maximum) for each index were as follows: NLR: Q1≤1.646, Q2 1.647-2.216, Q3 2.217-3.100, Q4≥3.101; PLR: Q1≤101.487, Q2 101.488-131.726, Q3 131.727-174.245, Q4≥174.246; SII: Q1≤380.152, Q2 380.153-543.708, Q3 543.709-775.689, Q4≥775.690; MLR: Q1≤0.222, Q2 0.223-0.300, Q3 0.301-0.400, Q4≥0.401; MII-1: Q1≤0.200, Q2 0.201-0.507, Q3 0.508-1.331, Q4≥1.332; MII-2: Q1≤12.319, Q2 12.320-29.745, Q3 29.746-77.858, Q4≥77.859; MII-3: Q1≤46.392, Q2 46.393-123.179, Q3 123.180-335.101, Q4≥335.102. Odds ratios for Q2-Q4 are presented relative to Q1 (reference). Quartile cutoffs were derived from the overall sample.

may mark the transition of monocyte-mediated vascular inflammation from a "subclinical" to a "clinically relevant" state. Future studies should investigate whether this threshold can guide risk stratification or early intervention strategies in the care of cancer survivorship.

The IIRS relies only on complete blood count (CBC) parameters, which are routinely measured, reasonably priced and easily accessible [10]. This facilitates the integration of IIRS into routine clinical workflows and screening programs at the population-level. The IIRS may be used for rapid risk screening during follow-up, prioritization for cardiology referral, and risk assessment in settings with limited resources for cancer survivors, a population with an increasing cardiovascular burden [22, 23]. IIRS is well-suited for practical application and potential integration into automated electronic health record systems due to its simplicity.

It is also important to acknowledge the limitations of this study. First, the measurement of

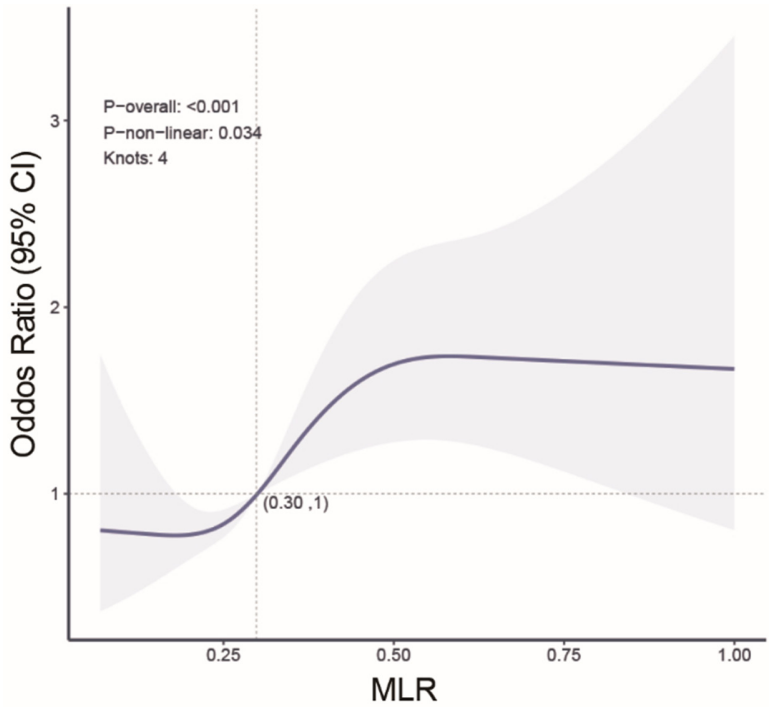


Figure 6. Dose-response relationship between monocyte-to-lymphocyte ratio (MLR) and cardiovascular disease (CVD) risk. Restricted cubic spline plot shows the adjusted odds ratio (solid line) and 95% confidence interval (shaded area) for prevalent CVD across MLR values. A nonlinear association was observed (P for nonlinearity = 0.034), with a threshold effect at MLR ≈ 0.3.

inflammatory indices at a single time point made it hard to assess predictive value of dynamic changes in inflammation. Second, even though the IIRS was robust in our study, external validations across various geographic regions, cancer case mixes, or laboratory platforms are needed.

The following directions should be the focus of future research. First, external validation should be conducted in independent clinical cohorts to verify the discrimination and calibration of IIRS. Second, longitudinal studies ought to be undertaken to investigate whether dynamic fluctuations in IIRS can enhance real-time risk prediction. Third, the IIRS needs to be validated in recent cancer survivor cohorts, especially among those receiving immune checkpoint inhibitors and other novel therapies. These new therapies can significantly alter systemic inflammation [8], and assessing the IIRS in such populations will help recalibrate risk thresholds. Fourth, interventional trials targeting individuals with elevated IIRS are needed to assess whether modifying systemic inflammation levels can reduce cardiovascular events and mortality. Moreover, head-to-head comparisons between the IIRS and established cardiovascular risk scores using NRI and IDI metrics are needed to quantify the incremental predictive value of the IIRS in cardiovascular risk stratification among cancer survivors [24, 25].

Conclusion

In summary, we established the IIRS, a simple yet biologically interpretable tool for assessing the risk of all-cause and cardiovascular mortality in cancer survivors. Particularly, IIRS-2 - a combination of NLR and MLR - demonstrated excellent ability to predict cardiovascular death, highlighting the significance of peripheral immune cell balance in cardiovascular risk among cancer survivors.

Acknowledgements

The authors acknowledge the participants and staff of the National Health and Nutrition Examination Survey (NHANES) for their valuable contributions.

Disclosure of conflict of interest

None.

Address correspondence to: Zhaoxing Li, Department of General Surgery, The Fourth Affiliated Hospital of Hebei Medical University, Jiankang Road 12, Shijiazhuang 050017, Hebei, China. E-mail: lizhaoxing1984@hebmu.edu.cn; Zhao Liu, Medical Faculty Heidelberg, University of Heidelberg, Im Neuenheimer Feld 129, 69120 Heidelberg, Germany. E-mail: zhao.liu@dkfz-heidelberg.de

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 can-

cers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.
[2] Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, Kelly SP and Zaorsky NG. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019; 40: 3889-3897.
[3] Zhang S, Liu L, Shi S, He H, Shen Q, Wang H, Qin S, Chang J and Zhong R. Bidirectional association between cardiovascular disease and lung cancer in a prospective cohort study. J Thorac Oncol 2024; 19: 80-93.
[4] Coussens LM and Werb Z. Inflammation and cancer. Nature 2002; 420: 860-867.
[5] Spray L, Richardson G, Haendeler J, Altschmied J, Rumampouw V, Wallis SB, Georgiopoulos G, White S, Unsworth A, Stellos K, Tual-Chalot S and Spyridopoulos I. Cardiovascular inflammaging: mechanisms, consequences, and therapeutic perspectives. Cell Rep Med 2025; 6: 102264.
[6] Chamorro Á, Dirnagl U, Urra X and Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol 2016; 15: 869-881.
[7] Liu J, Chen K, Tang M, Mu Q, Zhang S, Li J, Liao J, Jiang X and Wang C. Oxidative stress and inflammation mediate the adverse effects of cadmium exposure on all-cause and cause-specific mortality in patients with diabetes and prediabetes. Cardiovasc Diabetol 2025; 24: 145.
[8] Palaskas NL, Ali HJ, Koutroumpakis E, Ganatra S and Deswal A. Cardiovascular toxicity of immune therapies for cancer. BMJ 2024; 385: e075859.
[9] Karabay G, Bayraktar B, Seyhanli Z, Cakir BT, Aktemur G, Sucu ST, Tonyali NV, Bucak M, Ayhan H and Dagdeviren G. Predictive value of inflammatory markers (NLR, PLR, MLR, SII, SIRI, PIV, IG, and MII) for latency period in Preterm premature rupture of membranes (PPROM) pregnancies. BMC Pregnancy Childbirth 2024; 24: 564.
[10] Qin P, Ho FK, Celis-Morales CA and Pell JP. Association between systemic inflammation biomarkers and incident cardiovascular disease in 423,701 individuals: evidence from the UK biobank cohort. Cardiovasc Diabetol 2025; 24: 162.
[11] Orozco SL, Canny SP and Hamerman JA. Signals governing monocyte differentiation during inflammation. Curr Opin Immunol 2021; 73: 16-24.
[12] Wang L, Li X, Liu M, Zhou H and Shao J. Association between monocyte-to-lymphocyte ratio and prostate cancer in the U.S. population: a population-based study. Front Cell Dev Biol 2024; 12: 1372731.
[13] Silvestre-Roig C, Braster Q, Ortega-Gomez A and Soehnlein O. Neutrophils as regulators of cardiovascular inflammation. Nat Rev Cardiol 2020; 17: 327-340.
[14] Xie K, Marathe A, Deng X, Ruiz-Castillo P, Imputiua S, Elobolobo E, Mutepa V, Sale M, Nicolas P, Montana J, Jamisse E, Munguambe H, Materrula F, Casellas A, Rabinovich R, Saute F, Chaccour CJ, Sacoor C and Rist C. Alternative approaches for creating a wealth index: the case of Mozambique. BMJ Glob Health 2023; 8: e012639.
[15] Cao Y, Li P, Zhang Y, Qiu M, Li J, Ma S, Yan Y, Li Y and Han Y. Association of systemic immune inflammatory index with all-cause and cause-specific mortality in hypertensive individuals: results from NHANES. Front Immunol 2023; 14: 1087345.
[16] Zhang Y, Wu Y, Zhang Y, Cao D, He H, Cao X, Wang Y, Jia Z and Jiang J. Dietary inflammatory index, and depression and mortality risk associations in U.S. adults, with a special focus on cancer survivors. Front Nutr 2022; 9: 1034323.
[17] Wang RH, Wen WX, Jiang ZP, Du ZP, Ma ZH, Lu AL, Li HP, Yuan F, Wu SB, Guo JW, Cai YF, Huang Y, Wang LX and Lu HJ. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. Front Immunol 2023; 14: 1115031.
[18] Di D, Zhou H, Cui Z, Zhang J, Liu Q, Yuan T, Zhou T, Luo X, Ling D and Wang Q. Frailty phenotype as mediator between systemic inflammation and osteoporosis and fracture risks: a prospective study. J Cachexia Sarcopenia Muscle 2024; 15: 897-906.
[19] Kadier K, Dilixiati D, Ainiwaer A, Liu X, Lu J, Liu P, Ainiwan M, Yesitayi G, Ma X and Ma Y. Analysis of the relationship between sleep-related disorder and systemic immune-inflammation index in the US population. BMC Psychiatry 2023; 23: 773.
[20] Tort M, Sevil FC, Sevil H and Becit N. Evaluation of systemic immune-inflammation index in acute deep vein thrombosis: a propensity-matched. J Vasc Surg Venous Lymphat Disord 2023; 11: 972-977, e971.
[21] Nøst TH, Alcala K, Urbarova I, Byrne KS, Guida F, Sandanger TM and Johansson M. Systemic inflammation markers and cancer incidence in the UK Biobank. Eur J Epidemiol 2021; 36: 841-848.

[22] Wagle NS, Nogueira L, Devasia TP, Mariotto AB, Yabroff KR, Islami F, Jemal A, Alteri R, Ganz PA and Siegel RL. Cancer treatment and survivorship statistics, 2025. CA Cancer J Clin 2025; 75: 308-340.

[23] Gomes C, Geels J, Debray TPA, Malekzadeh A, Asselbergs FW and Linschoten M. Risk prediction models for cancer therapy related cardiac dysfunction in patients with cancer and cancer survivors: systematic review and meta-analysis. BMJ 2025; 390: e084062.

[24] Hippisley-Cox J, Coupland CAC, Bafadhel M, Russell REK, Sheikh A, Brindle P and Channon KM. Development and validation of a new algorithm for improved cardiovascular risk prediction. Nat Med 2024; 30: 1440-1447.

[25] Marston NA, Pirruccello JP, Melloni GEM, Koyama S, Kamanu FK, Weng LC, Roselli C, Kamatani Y, Komuro I, Aragam KG, Butterworth AS, Ito K, Lubitz SA, Ellinor PT, Sabatine MS and Ruff CT. Predictive utility of a coronary artery disease polygenic risk score in primary prevention. JAMA Cardiol 2023; 8: 130-137.