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Research Article

Physical Activity and Cancer Survival: The Crucial Role of Peripheral Blood Immune/Inflammatory Markers in Reducing Mortality

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A R T I C L E I N F O

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A B S T R A C T

Background: The value of physical activity for prognosis and its underlying mechanisms in cancer survivors remain incompletely understood. This study aimed to investigate the associations between physical activity and all-cause, cancer-specific, and cardiovascular mortality in cancer survivors, and to assess whether these associations are mediated by a panel of peripheral blood immune/inflammatory markers (PBIMs).

Methods: This population-based cohort study included 2,768 adult cancer survivors from ten cycles (1999-2018) of the National Health and Nutrition Examination Survey (NHANES). Physical activity was quantified from questionnaire data and categorized into low and high levels based on established guidelines. Seven PBIMs were calculated from laboratory data. Weighted multivariable Cox proportional hazards models were used to assess the prognostic value of each indicator. Restricted cubic splines were used to characterize nonlinear relationships, with threshold analysis applied where appropriate. Mediation analyses were conducted to estimate the proportion of the physical activity-mortality relationship explained by the PBIMs.

Results: Compared to the low physical activity group, participants with high physical activity demonstrated significantly reduced risks of all-cause mortality (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.59-0.79) and cardiovascular mortality (HR, 0.69; CI, 0.50-0.96). High physical activity was significantly associated with favorable levels of most inflammatory markers, including the C-reactive protein-albumin-lymphocyte (CALLY) index, monocyte-to-lymphocyte ratio (MLR), and neutrophil percentage-to-albumin ratio (NPAR). Notably, the CALLY index and MLR significantly mediated the association between physical activity and all-cause mortality, with mediation proportions of 8.95% and 10.49%, respectively.

Conclusion: Higher physical activity is associated with reduced all-cause mortality in cancer survivors, which partially mediated by improved specific inflammatory biomarkers. These findings confirmed the prognostic value of physical activity and revealed the mediating role of PBIMs in a larger cohort of long-term cancer survivors.

1. Introduction

Cancer is among the world's most prevalent non-communicable diseases and constitutes a leading cause of mortality globally, with approximately 10 million deaths in 2022 (accounting for one in six deaths) and an increasingly heavy burden being imposed upon the world [1]. During the past 20 years, progress in medical technology has led to enhanced treatment methods, which have improved the recovery and survival effects for cancer patients following treatment, therefore we need to pay attention to the question of what lifestyle choices we can adopt to further prolong patients' survival benefits. The prognosis for tumor patients is influenced by multiple factors, including physical activity, diet, obesity, and others [2]. Adequate physical activity was reported to improve the quality of life and prolong overall survival in colon cancer survivors [3]. But its prognostic value has not been confirmed, and the underlying mechanism remains unclear.

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A plethora of studies have demonstrated that physical activity is imperative for the regulation of oxidative stress, the maintenance of immune homeostasis, and the suppression of persistent inflammation [4]. Some studies indicate that extending exercise duration and moderately increasing exercise intensity can enhance lymphocyte anti-tumor activity, reduce immunosuppressive effects and improve the efficacy of anti-tumor treatments, thereby enhancing prognosis [5-10]. Systemic inflammation is commonly assessed using peripheral blood immune/inflammatory markers (PBIMs); there are numerous related inflammatory indices, among which the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil percentage-to-albumin ratio (NPAR), C-reactive protein-albumin-lymphocyte index (CALLY), advanced lung cancer inflammation index (ALI), and prognostic nutritional index (PNI) have a certain evidence-based foundation for predicting systemic inflammation. Obtained from routine blood tests, these indices provide a non-invasive, cost-effective means of evaluating systemic immune and inflammation status, and could act as surrogate markers for cancer risk and prognosis [11-13]. Whether exercise can further improve the prognosis of cancer survivors by modulating immune-inflammatory markers requires further research to confirm.

The National Health and Nutrition Examination Survey (NHANES), a population-based study conducted by the Centers for Disease Control and Prevention (CDC), contains real-world data from long-term follow-ups of cancer survivors, and has collected multi-dimensional data regarding patients' lifestyles, exercise patterns, complete blood counts and inflammatory markers. This provides support for conducting research focused on the long-term survival population of cancer patients. Through harnessing the utility of NHANES data, researchers can perform thorough analyses to clarify the intricate relationship between physical activity, immune/inflammatory indices, and mortality in cancer patients.

While evidence supporting the role of physical activity and inflammatory indices in cancer continues to accumulate, studies based on large samples in cancer survivors remain scarce. Furthermore, most existing studies have focused solely on the role of physical activity or inflammatory indices in isolation, neglecting the potential synergistic effects between them. The primary objective of this study is to, through a large-sample real-world analysis, evaluate whether an active exercise lifestyle can improve the prognosis of cancer survivors, explore the potential role of PBIMs in this process, and provide evidence for improving the long-term survival of cancer patients.

2. Materials and Methods

The National Health and Nutrition Examination Survey (NHANES) is a national, cross-sectional, population-based study that represents the non-institutionalised US civilian population [14]. It has collected data in two-year cycles since 1999. The NHANES study involves in-depth interviews covering demographic characteristics, socioeconomic status, dietary habits and various health aspects. These are complemented by thorough examinations involving medical tests and blood marker evaluations conducted by qualified healthcare professionals. The NHANES research protocol is approved by the NCHS Ethics Review Board, and all participants provide written informed consent. This modeling investigation was exempt from review because it used published deidentified data sets that included no personally identifiable information.

2.1. Study Population

The data for this study were obtained from the NHANES database and spanned 10 cycles from 1999-2018. Cancer diagnosis data were self-reported. Participants were asked, "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind? Participants were defined as cancer survivors if they answered 'yes.' Strict inclusion and exclusion criteria were employed, with participants excluded if they were under 20 years of age, lacked complete blood test indicators, or had no information on cancer diagnosis, physical activity, or survival outcomes. Ultimately, 2,768 statistically viable samples were obtained.

2.2. Assessment of Physical Activity

A physical activity questionnaire was completed by each participant. The questionnaire encompassed inquiries pertaining to all physical activities undertaken within the preceding 30 days. The following data were recorded: activity type, duration, intensity, and number of times performed in the last 30 days. Metabolic equivalent (MET) is defined as the ratio of work metabolic rate to a standard resting metabolic rate (1.0 MET = 4.184 $kJ \cdot kg^{-1} \cdot h^{-1}$, corresponding to quiet sitting), serving to classify the intensity of physical activities and facilitate comparisons across studies, with energy expenditure (e.g., in MET-minutes or kcal) estimated by combining an activity's MET value with its duration and an individual's body weight [15]. MET scores were multiplied by the average duration per session and performance frequency over the past 30 days to derive MET minutes per 30 days (MET min/30d) for each activity. MET min/30d across all activities were summed and subsequently divided by 4.29 to compute total weekly MET minutes. Participants will be divided into a low physical activity group and a high physical activity group in accordance with national physical activity guidelines (low physical activity: $<$ 500 MET/week; high physical activity: $\geq$ 500 MET/week). Approximately 500 MET is equivalent to 3.3 hours of slow walking or 71 minutes of freestyle swimming per week. [16].

2.3. The Definition and Calculation of PBIMs

The inflammatory indices analyzed in this study are calculated based on relevant indicators in peripheral blood. Included among these indicators are total white blood cell count($\times 10^9$/L), neutrophil count ($\times 10^9$/L), lymphocyte count ($\times 10^9$/L), monocyte count ($\times 10^9$/L), platelet count ($\times 10^9$/L), albumin level (g/L), C-reactive protein level (mg/L), lymphocyte percentage, monocyte percentage, and neutrophil percentage—all of which are obtained 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
- MLR = Monocyte count / Lymphocyte count
- NPAR = Neutrophil percentage / Albumin
- ALI = (Lymphocyte percentage × Total white blood cell count) / 100
- CALLY = Albumin level × Lymphocyte count / (C-reactive protein level × 10)
- PNI = 10 × Albumin level + 0.005 × Lymphocyte count

2.4. Sociodemographic Characteristics, Lifestyle Behaviors, and Long-Term Conditions

The self-reported sociodemographic characteristics encompassed the following: sex (male or female); age (<40, 40 to <65, ≥65); race (Mexican American, non-Hispanic Black, other race - including multi-racial/); educational attainment (<high school, high school, > high school); marital status (married, single, never married) and household poverty-to-income ratio (PIR;<1.3, 1.3 to ≤ 3.5, ≥3.5). The lifestyle factors under consideration comprised smoking history (non-smoking, smoking) and alcohol consumption history (non-drinking, drinking). Hypertension was reported by participants for themselves. The diagnosis had been received from a healthcare professional or determined by NHANES-measured blood pressure (≥140 mmHg [systolic] or ≥90 mmHg [diastolic]). A person is diagnosed with hyperlipidemia if they meet any of the following criteria: total cholesterol (TC) ≥ 200 mg/dL; triglycerides (TG) ≥ 150 mg/dL; low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL; high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL for males or ≤ 50 mg/dL for females; additionally, participants who are taking lipid-lowering medications are also considered to have hyperlipidemia. Diabetes mellitus is diagnosed in an individual if they satisfy any one of the subsequent criteria: a documented history of diabetes mellitus, being on insulin therapy, using diabetes medications for blood glucose reduction, a glycated hemoglobin (HbA1c) level of ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL, or 2-hour postprandial blood glucose ≥ 200 mg/dL.

2.5. Assessment of Mortality

The mortality status of NHANES participants was derived from the linked mortality files of the National Death Index. In this study, the primary outcomes of interest included all-cause mortality, cancer mortality, and cardiovascular mortality. Deaths from all causes were defined as all-cause mortality, cardiovascular mortality was defined as deaths from heart disease and cerebrovascular disease, and cancer mortality was defined as ICD-10 codes C00-C97. The follow-up period for the study was from the date of initial diagnosis to the date of death or the conclusion of the study period on 31 December 2019, whichever occurred first.

2.6. Statistical Analysis

In light of the fact that NHANES utilized a complex, multistage probability sampling design for the selection of representative participants, primary sampling units, strata, and sample weights were incorporated into the subsequent data analysis. Weighted analyses were conducted using the 'survey' package in R statistical software to generate nationally representative estimates. This methodological approach ensured the generalizability of findings to the non-institutionalized U.S. population while avoiding the overestimation of statistical significance. In accordance with the NHANES guidelines, the selection of weighting variables was prioritized to reflect small population subgroups, with the application of appropriate weights.

Baseline characteristics of the study participants were summarized according to the two physical activity groups. Given that all continuous variables exhibited skewed distributions, they are presented as medians with interquartile ranges (IQR). Categorical variables are reported as counts and percentages. Differences between groups were assessed using the Mann-Whitney U test for continuous variables and the Rao-Scott chi-square test for categorical variables, accounting for the complex survey design of NHANES. To meet the assumptions of parametric tests in the analysis of the relationship between physical activity and PBIMs, all PBIMs exhibiting a skewed distribution were log10-transformed and analyzed using analysis of covariance (ANCOVA).

We utilized multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of physical activity and peripheral blood inflammatory markers (PBIMs) with all-cause and cause-specific mortality. Three sequential models were fitted: a crude model (Model 1), a model adjusted for demographic factors (Model 2: age, gender, race, education, and poverty-income ratio), and a fully adjusted model (Model 3: Model 2 plus behavioral and clinical covariates, including smoking, alcohol use, hypertension, hyperlipidemia, and diabetes). Given their skewed distributions, all PBIMs were log10-transformed prior to analysis, and HRs for these markers correspond to a one-order-of-magnitude (tenfold) change in their original concentration.

The functional form of the associations between log-transformed PBIMs and mortality was examined using restricted cubic splines (RCS) within the fully adjusted Cox models. The likelihood ratio test was used to assess nonlinearity. For relationships that were significantly nonlinear, we characterized the association by identifying inflection points and performing threshold analysis using piecewise regression. To test the robustness of the primary findings, we conducted sensitivity analyses by excluding mortality events within the first two years of follow-up and performed stratified analyses across subgroups defined by age, gender, race, and comorbidity history.

A mediation analysis was performed to estimate the proportion of the association between physical activity and mortality that was mediated through the PBIMs. Person-time of follow-up was calculated from the baseline survey to the date of death, loss to follow-up, or December 31, 2019, whichever occurred first. All analyses accounted for the complex sampling design of NHANES by incorporating sampling weights. All statistical analyses were performed using R software (version 4.5.2). The "survey" package was employed for all analyses incorporating NHANES sampling weights, and the "mediation" package was used for causal mediation analysis. A two-sided P-value < 0.05 was considered statistically significant.

3. Result

3.1. Population Characteristics

After excluding individuals who did not meet the inclusion criteria, a total of 2768 individuals were included in this study, of whom 56.86% were female. The weighted mean age [SE] of the participants was 61.93 [0.38] years (range: 20-85 years), and the median survival time was 100.00 months (range: 1-249 months). The characteristics of these participants are shown in (Table 1). Among them, there were 1573 individuals with high physical activity, accounting for 56.83%. Participants exhibiting low levels of physical activity were found to be more likely to be older (54.67%), female (61.95%), non-Hispanic White (84.43%), married (62.23%), and more educated (59.37); to have a middle income (41.30%), with all P<0.05. There was no statistically significant difference in smoking history between the two groups (P>0.05).

Table. 1. Baseline characteristics of participants.

Variable, n (%)	Total (n = 2768)	Low physical activity (n=1195)	High physical activity (n=1573)	Test of significance (χ 2 value)	*p*
Sex				χ^2=17.84	<.001
Male	1336 (43.14)	514 (38.05)	822 (46.25)		
Female	1432 (56.86)	681 (61.95)	751 (53.75)		
Age				χ^2=22.87	<.001
<40	292 (13.80)	105 (12.64)	187 (14.51)		
40 to <65	822 (37.31)	327 (32.68)	495 (40.13)		
≥65	1654 (48.89)	763 (54.67)	891 (45.36)		
Race				χ^2=9.85	0.005
Mexican American	196 (2.30)	95 (2.77)	101 (2.00)		
Non-Hispanic White	1981 (86.99)	810 (84.43)	1171 (88.55)		
Non-Hispanic Black	328 (4.64)	160 (5.42)	168 (4.16)		
Other	263 (6.07)	130 (7.37)	133 (5.28)		
PIR				χ^2=87.99	<.001
<1.3	564 (14.28)	299 (18.96)	265 (11.44)		
1.3 to <3.5	1019 (34.17)	474 (41.30)	545 (29.83)		
≥3.5	948 (51.55)	315 (39.75)	633 (58.72)		
Education				χ^2=45.75	<.001
< high school	550 (12.22)	321 (17.35)	229 (9.09)		
high school	652 (22.53)	273 (23.28)	379 (22.07)		
>high school	1564 (65.26)	599 (59.37)	965 (68.84)		
Marital status				χ^2=18.71	0.008
Married	1711 (67.17)	686 (62.23)	1025 (70.18)		
Single	881 (27.19)	429 (31.44)	452 (24.59)		
Never married	166 (5.64)	76 (6.33)	90 (5.23)		
Alcohol use				χ^2=17.89	0.001
No	645 (26.71)	321 (31.79)	324 (23.54)		
Yes	1530 (73.29)	605 (68.21)	925 (76.46)		
Smoking				χ^2=1.97	0.255
No	1235 (46.10)	520 (44.39)	715 (47.14)		
Yes	1531 (53.90)	675 (55.61)	856 (52.86)		
Hypertension				χ^2=35.32	<.001
No	1027 (43.63)	385 (36.44)	642 (48.01)		
Yes	1736 (56.37)	806 (63.56)	930 (51.99)		
Diabetes				χ^2=27.48	<.001
No	2014 (78.92)	798 (73.69)	1216 (82.13)		
Yes	711 (21.08)	379 (26.31)	332 (17.87)		
Hyperlipidemia				χ^2=26.66	<.001
No	522 (18.87)	190 (13.95)	332 (21.87)		
Yes	2246 (81.13)	1005 (86.05)	1241 (78.13)		

χ^2: Chi-square test

PIR: Poverty-Income Ratio.

Among the peripheral blood immune indices detected in this study, high physical activity was correlated with higher levels of PNI (51.50 vs 51.00, high physical activity vs low physical activity, p = 0.046) and CALLY (4.81 vs 3.25, high vs low, p=<.001). However, high physical activity was correlated with lower levels of SII (486.44 vs 541.05, high vs low, p<.001), NPAR (14.04 vs 14.45, high vs low, p<.001), NLR (2.09 vs 2.23, high vs low, p = 0.003) and MLR (0.29 vs 0.31, high vs low, p = 0.002). Detailed results are shown in (Table 2).

Table. 2. Baseline characteristics of peripheral blood immune/inflammatory markers in peripheral blood of participants.

Variable	Total (n = 2768)	Low PA (n=1195)	High PA (n=1573)	Statistic	*p*
SII, M (Q_1, Q_3)	508.26 (357.72, 724.29)	541.05 (379.37, 741.00)	486.44 (347.18, 704.27)	Z=-3.42	<.001
PNI, M (Q_1, Q_3)	51.50 (48.50, 55.00)	51.00 (48.00, 55.00)	51.50 (49.00, 55.00)	Z=-2.00	0.046
NPAR, M (Q_1, Q_3)	14.21 (12.57, 15.90)	14.45 (12.93, 16.20)	14.04 (12.36, 15.63)	Z=-4.21	<.001
ALI, M (Q_1, Q_3)	54.77 (38.97, 77.24)	54.16 (38.58, 74.63)	55.16 (39.28, 77.97)	Z=-1.37	0.170
NLR, M (Q_1, Q_3)	2.13 (1.61, 2.93)	2.23 (1.70, 3.00)	2.09 (1.56, 2.84)	Z=-2.93	0.003
MLR, M (Q_1, Q_3)	0.30 (0.23, 0.38)	0.31 (0.24, 0.40)	0.29 (0.22, 0.38)	Z=-3.11	0.002
CALLY, M (Q_1, Q_3)	4.06 (1.70, 8.84)	3.25 (1.37, 6.75)	4.81 (1.95, 10.02)	Z=-6.11	<.001

M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile,Z: Mann-Whitney test
PA: Physical Activity

3.2. Association between Physical Activity and Mortality

During a mean follow-up of 8.33 years, 831 deaths were recorded, including 255 cancer deaths and 576 non-cancer deaths. We used the low physical activity group as the reference group and employed three progressively adjusted models. Prior to any adjustment, physical activity was associated with all-cause mortality in cancer survivors (p<0.001; HR=0.59; 95% CI: 0.50-0.70), cardiovascular mortality (p=0.005; HR=0.61; 95% CI: 0.43-0.86), and cancer-specific mortality (p=0.037; HR=0.75; 95% CI: 0.57-0.98): higher levels of physical activity were linked to a reduced risk of mortality. Based on the above results, we plotted the KM survival curve for Model 1 (Figure 1). However, after adjusting for age, gender, race, educational level, income, and marital status (Model 2), physical activity was only associated with all-cause mortality (p<0.001; HR=0.63; 95% CI: 0.55-0.73) and cardiovascular mortality (p=0.015; HR=0.66; 95% CI: 0.47-0.92) in cancer survivors. After further adjusting for factors including history of smoking and alcohol consumption, as well as history of hypertension, diabetes, and hyperlipidemia, the above results remained robust (Model 3 & Table 3).

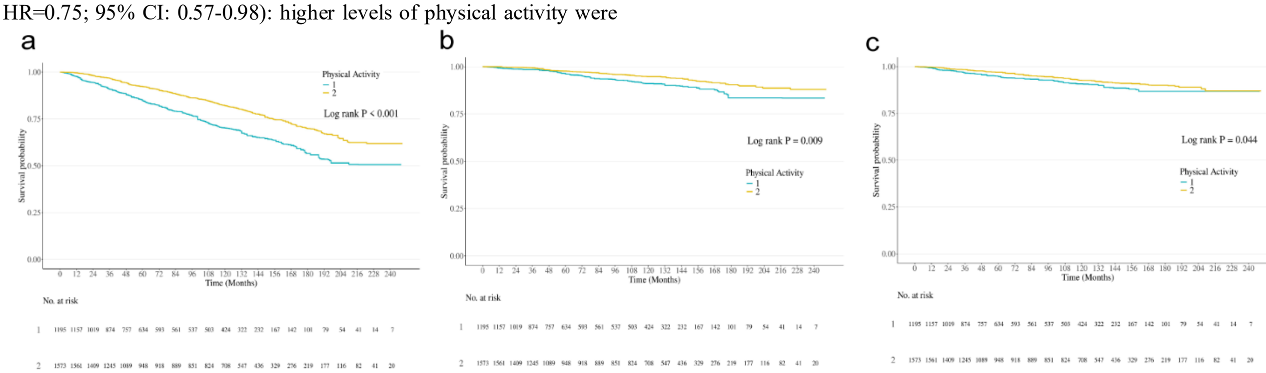

Fig. 1. Kaplan-Meier survival analysis by physical activity level in tumor patients. Kaplan-Meier curves compare survival probabilities between patients with low (Group 1) and high (Group 2) physical activity levels for **a)** all-cause, **b)** cardiovascular, and **c)** cancer-specific mortality. Log-rank P-values indicate statistically significant differences between groups for all endpoints. Numbers at risk at specified time points are shown below each graph.

Table. 3. Association between physical activity and mortality in 3 models.

	All-cause mortality			Cardiovascular mortality			Cancer-specific mortality		
Physical Activity	M1	M2	M3	M1	M2	M3	M1	M2	M3
LowPA (Reference)	1	1	1	1	1	1	1	1	1
High PA (HR, 95% CI)	0.59 (0.50-0.70)0.63	(0.55-0.68 0.73)	(0.59 0.79)	-0.61 0.86)	(0.43-0.66 (0.47 0.92)	0.69 -- 0.96)	(0.50 0.75 0.98)	(0.57-0.78 (0.58 - 1.06)	0.89 (0.64 - 1.23)
p	<.001	<.001	<.001	0.005	0.015	0.028	0.037	0.115	0.481

Model 1 unadjusted.
Model 2 adjusted for age, sex, race, education,poverty-income ratio, marital status.

Model 3 adjusted for age,sex, race, education, poverty-income ratio, marital status, smoking, alcohol use, diabetes, hypertension, and hyperlipidemia.
PA: Physical Activity

3.3. Subgroup Analyses of the Physical Activity-Mortality Association

Based on the established association between physical activity and reduced mortality risk, we further conducted comprehensive subgroup analyses to explore potential effect modifications. Stratified by age, sex, race, smoking status, alcohol consumption, and comorbidities (hypertension, diabetes, hyperlipidemia), these analyses revealed consistent protective effects of higher physical activity levels against all-cause and cardiovascular mortality across all subgroups. Formal tests for interaction yielded no statistically significant results (all P for interaction > 0.05), indicating that the beneficial association of physical activity with survival was homogeneous across these key demographic and clinical characteristics. The results of these subgroup analyses are comprehensively detailed in a forest plot (Figure 2).

Subgroup	n (%)	Low PA	High PA	HR (95%CI)	P	P for interaction
		No. of events/ No. of total				
All patients	2768 (100.00)	419/1195	412/1573	0.68 (0.59 ~ 0.79)	<.001	
Sex						0.373
Male	1336 (48.27)	225/514	283/822	0.76 (0.60 ~ 0.96)	0.022	
Female	1432 (51.73)	194/681	129/751	0.61 (0.46 ~ 0.82)	<.001	
Race						0.070
Mexican American	196 (7.08)	14/95	19/101	2.16 (1.06 ~ 4.36)	0.033	
Non-Hispanic White	1981 (71.57)	323/810	350/1171	0.67 (0.58 ~ 0.79)	<.001	
Non-Hispanic Black	328 (11.85)	58/160	34/168	0.77 (0.46 ~ 1.29)	0.315	
Other	263 (9.50)	24/130	9/133	0.30 (0.10 ~ 0.90)	0.032	
Age						0.738
<40	292 (10.55)	2/105	8/187	1.89 (0.32 ~ 11.14)	0.482	
40 to <65	822 (29.70)	62/327	62/495	0.85 (0.49 ~ 1.48)	0.57	
≥ 65	1654 (59.75)	355/763	342/891	0.61 (0.51 ~ 0.73)	<.001	
Smoking						0.637
No	1235 (44.65)	147/520	152/715	0.64 (0.48 ~ 0.85)	0.002	
Yes	1531 (55.35)	272/675	260/856	0.71 (0.57 ~ 0.87)	<.001	
Alcohol use						0.075
No	645 (29.66)	142/321	103/324	0.55 (0.41 ~ 0.74)	<.001	
Yes	1530 (70.34)	226/605	288/925	0.77 (0.63 ~ 0.93)	0.008	
Hypertension						0.070
No	1027 (37.17)	91/385	121/642	1.01 (0.70 ~ 1.44)	0.977	
Yes	1736 (62.83)	328/806	290/930	0.64 (0.53 ~ 0.76)	<.001	
Diabetes						0.962
No	2014 (73.91)	264/798	297/1216	0.68 (0.57 ~ 0.82)	<.001	
Yes	711 (26.09)	150/379	109/332	0.68 (0.50 ~ 0.92)	0.012	
Hyperlipidemia						0.723
No	522 (18.86)	69/190	82/332	0.75 (0.46 ~ 1.23)	0.258	
Yes	2246 (81.14)	350/1005	330/1241	0.67 (0.57 ~ 0.80)	<.001	

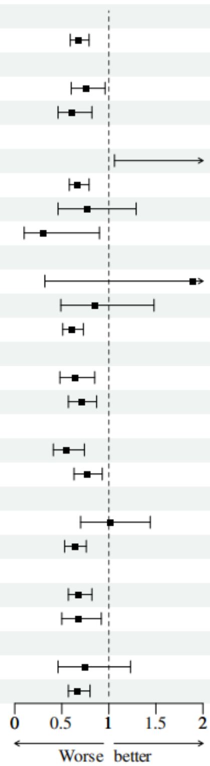

Fig. 2. Forest plot of subgroup analysis for the association between physical activity and all-cause mortality. This forest plot presents the results of a subgroup analysis examining the association between high levels of physical activity (High PA) and risk of all-cause mortality compared to low levels of physical activity (Low PA) among 2,768 cancer patients. P: P-value for the hazard ratio within the specific subgroup. P for interaction: P-value for the interaction test, indicating whether the effect of physical activity differs significantly across the categories of a given subgroup (e.g., Male vs. Female under "Sex").

3.4. Correlation between PA and logPBIMs

Our data confirm that exercise improves the survival of cancer survivors. However, whether exercise can improve patients' immune and inflammatory statuses and thereby affect survival remains unclear. We further explored the role played by common peripheral blood immune indicators in this process. We log-transformed all peripheral blood inflammatory indicators. As shown in (Table 4), with low physical activity as the reference, in the unadjusted model, high physical activity was negatively correlated with the inflammatory indicators logSII (β=-0.10; 95% CI: -0.15 - -0.05; p<0.001), logMLR (β=-0.07; 95% CI: -0.11 - -0.03; p<0.001), logNLR (β=-0.09; 95% CI: -0.14 - -0.04; p=0.001), and logNPAR (β=-0.05; 95% CI: -0.07 - -0.03; p<0.001), and positively correlated with logCALLY (β=0.39; 95% CI: 0.27 - 0.52; p<0.001) and logPNI (β=0.02; 95% CI: 0.01 - 0.03; p=0.027), while no correlation was observed with logALI. Except for logPNI and logALI, the trends of other inflammatory indicators remained consistent after adjusting for age, gender, race, education, and PIR in Model 2, as well as history of smoking, alcohol consumption, hypertension, hyperlipidemia, and diabetes mellitus in Model 3. No correlation was observed between logPNI and physical activity after adjusting for factors such as age and gender.

Table. 4. Correlation between PA and logPBIMs in 3 models.

	Low PA(Reference)	High PA (β (95%CI))					
LogPBIMs		**Model1**	***p***	**Model2**	***p***	**Model3**	***p***
LogSII	0.00	-0.10 (-0.15 - -0.05)	<.001	-0.08 (-0.14 - -0.02)	0.009	-0.08 (-0.14 - -0.02)	0.008
LogCALLY	0.00	0.39 (0.27-0.52)	<.001	0.28 (0.16 - 0.41)	<.001	0.16 (0.02 - 0.30)	0.031
LogMLR	0.00	-0.07 (-0.11- -0.03)	<.001	-0.06 (-0.10 - -0.03)	0.001	-0.07 (-0.11 - -0.03)	0.002
LogNLR	0.00	-0.09 (-0.14 - -0.04)	0.001	-0.07 (-0.13 - -0.02)	0.012	-0.09 (-0.15 - -0.03)	0.002
LogNPAR	0.00	-0.05 (-0.07- -0.03)	<.001	-0.03 (-0.06 - -0.01)	0.002	-0.03 (-0.05 - -0.01)	0.006
LogPNI	0.00	0.02 (0.01- 0.03)	0.027	0.01 (-0.00 - 0.02)	0.163	0.01 (-0.01 - 0.02)	0.323
LogALI	0.00	0.05 (-0.01- 0.10)	0.109	0.03 (-0.03 - 0.09)	0.318	0.07 (0.01 - 0.13)	0.028

Model 1 unadjusted.
Model 2 adjusted for age, sex, race, education,poverty-income ratio, marital status.
Model 3 adjusted for age,sex, race, education, poverty-income ratio, marital status, smoking, alcohol use, diabetes, hypertension, and hyperlipidemia.
PA: Physical Activity.

3.5. Associations of PBIMs with Mortality

Having identified several inflammatory markers as being responsive to physical activity levels, we therefore investigated their individual prognostic value for all-cause and cause-specific mortality. We first explored the shape of the association between logPBIM levels and all-cause mortality using restricted cubic spline (RCS). In adjusted Model 3, the results indicate that these immune indicators tend to exhibit a nonlinear association with the mortality risk of cancer survivors (Figure 3).

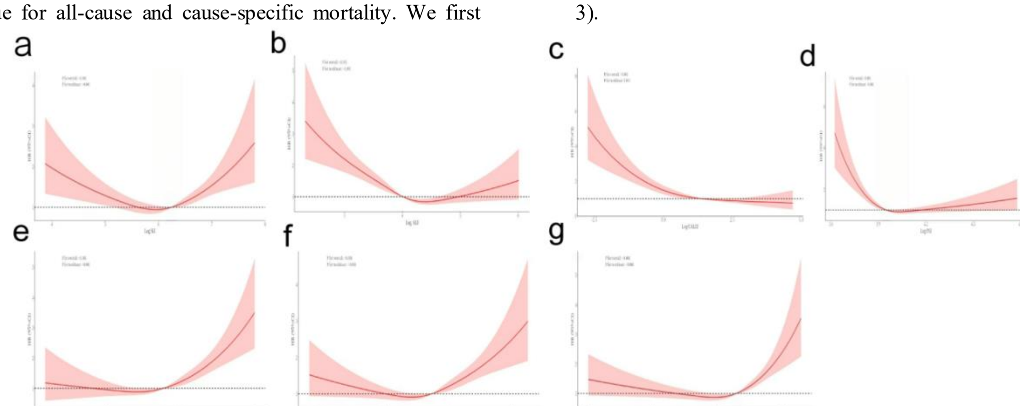

Fig. 3. Restricted cubic spline analysis of peripheral blood immune/inflammatory markers and all-cause mortality. The association was evaluated using multivariable-adjusted restricted cubic spline (RCS) analysis (four knots at the 5th, 35th, 65th, and 95th percentiles). The solid red line represents the estimated hazard ratios (HRs), and the shaded area denotes the 95% confidence interval. The model was adjusted for age, gender, race, education, marital status, poverty-income ratio (PIR), smoking status, alcohol use, diabetes, hypertension, and hyperlipidemia.

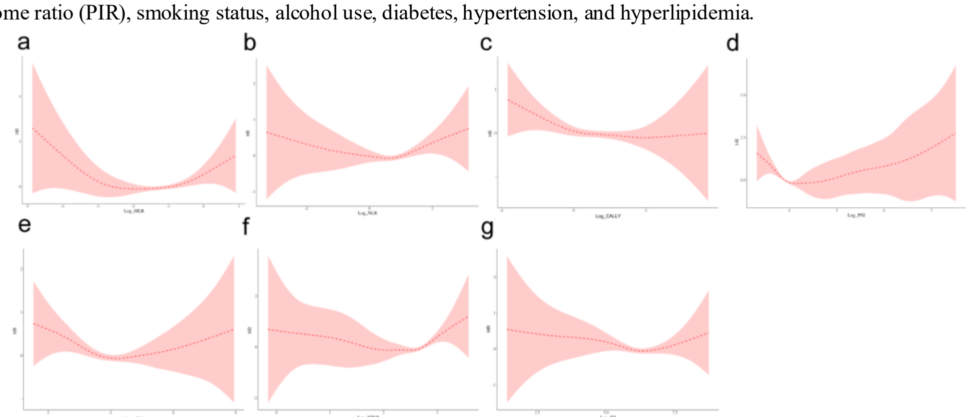

Fig. 4. The threshold curves illustrate the associations between seven immune/inflammatory markers indices and all-cause mortality.

Based on the confirmed nonlinear dynamics, we characterized the threshold effects of three salient markers through piecewise regression analysis. logNPAR demonstrated an exceptionally strong J-shaped association, with levels above its inflection point (2.561) associated with a dramatic 953% increased mortality risk per unit (HR=10.53; 95% CI: 5.33-20.81). logMLR showed the second-strongest effect with a 126% elevated risk beyond its threshold. In contrast, the emerging marker logCALLY exhibited a protective association with an inflection point at 0.055; values below this threshold were associated with a significant 34% risk reduction (HR=0.66; 95% CI: 0.54-0.82), while above it, a more modest 13% risk reduction was observed (HR=0.87; 95% CI: 0.79-0.95). These quantified risk relationships are visually represented in the threshold effect diagrams (Figure 4). The complete threshold analysis results for all inflammatory markers are presented in (Table 5).

Table. 5. Threshold effect of log PBIMs on all-cause mortality.

Inflammatory Mediator	Inflection Point	Segment	HR (95% CI)	*p*-value	*p* for Nonlinearity
LogSII	6.204	Below	0.80 (0.66 - 0.97)	0.027	<.001
		Above	1.98 (1.54 - 2.56)	<.001	
LogNLR	0.582	Below	0.81 (0.61 - 1.08)	0.153	<.001
		Above	2.13 (1.69 - 2.68)	<.001	
LogMLR	-1.58	Below	0.63 (0.36 - 1.12)	0.114	<.001
		Above	2.26 (1.78 - 2.87)	<.001	
LogNPAR	2.561	Below	0.61 (0.40 - 0.94)	0.026	<.001
		Above	10.53 (5.33 - 20.81)	<.001	
LogALI	4.317	Below	0.45 (0.37 - 0.54)	<.001	<.001
		Above	1.34 (0.97 - 1.85)	0.073	
LogCALLY	0.055	Below	0.66 (0.54 - 0.82)	<.001	0.014
		Above	0.87 (0.79 - 0.95)	0.002	
LogPNI	3.932	Below	0.01 (0.00 - 0.02)	<.001	<.001
		Above	1.47 (0.89 - 2.45)	0.134	

3.6. Mediation Analysis of PBIMs on Associations of PA with Mortality

We further evaluated the mediating effects of PBIMs in the association between physical activity and survival of cancer patients. After adjusting for all covariates, log-transformed logCALLY and logMLR exerted a relatively strong mediating effect: the mediation proportion of logCALLY was 8.95%, and that of logMLR was 10.49%. logNPAR and logNLR also showed significant mediation, accounting for 7.29% and 8.53% of the total effect. In contrast, no significant mediating effects were observed for logSII and logPNI.

4. Discussion

In this large, nationally representative cohort of U.S. cancer survivors, we confirmed a significant inverse association between higher levels of physical activity and risks of all-cause and cardiovascular mortality. More importantly, this study provides novel mechanistic insights by identifying specific peripheral blood inflammatory markers—most notably the CALLY index and the MLR—as significant partial mediators of this protective association. To our knowledge, this is the first study to examine the role of PBIMs in the association between physical activity and survival outcomes in a large, nationally representative cohort of cancer survivors. These findings illuminate a potential biological mechanism through which physical activity may confer survival benefits in this vulnerable population.

Our primary finding—that higher physical activity is associated with reduced all-cause mortality—is well aligned with a robust body of epidemiological and clinical evidence. This conclusion is strongly reinforced by the landmark CHALLENGE trial, which established structured exercise as a cornerstone therapy capable of improving both disease-free and overall survival in colon cancer patients [17]. Furthermore, meta-analyses of randomized controlled trials confirm that exercise significantly reduces mortality risk among cancer survivors [3, 7, 18, 19]. The consistency of this association across all demographic and clinical subgroups in our study, with no significant interaction effects detected, strengthens the validity and generalizability of these findings. Notably, while we observed significant reductions in all-cause and cardiovascular mortality, the association with cancer-specific mortality did not retain statistical significance after full adjustment. This finding differs from some previous studies and may be attributed to the heterogeneous study population and the specific covariate selection in our analytical model. Moving beyond confirming this established relationship, our study provides novel insights into the potential biological mechanisms—specifically, the role of systemic inflammation and its modulation through exercise.

The most salient finding of our study is the identification of CALLY and MLR as significant mediators, with NLR and NPAR also contributing to the mediation effect. These mediators can be conceptually divided into those that incorporate nutritional status and those that primarily reflect immune cell balance. Firstly, the CALLY index, which integrates nutritional status (albumin), immune competence (lymphocytes), and systemic inflammation (C-reactive protein), emerged as a key biological intermediary. Involuntary weight loss is a significant concern for cancer patients, often serving as a predictor of poor prognosis [20]. Direct evidence that exercise boosts albumin synthesis is lacking; however, our study identifies albumin-related metrics as mediators between physical activity and survival in cancer patients. A multi-center cohort study based on the INSCOC project demonstrated that CALLY serves as an independent positive prognostic factor for overall survival in patients with esophageal cancer, exhibiting superior predictive accuracy and clinical utility compared to the NLR, PLR, SII, and PNI [21]. Our finding is supported by accumulating evidence that CALLY serves as a robust prognostic indicator across various cancer types, with higher values consistently predicting better survival outcomes [22-26]. This suggests that the survival benefit of physical activity may be partially explained by its ability to improve a composite state of low-grade inflammation and nutritional health. This aligns with the known physiology: exercise has been shown to reduce systemic CRP levels [27] and modulate lymphocyte populations. Specifically, exercise mobilizes and activates cytotoxic T lymphocytes (CTLs) [8, 27, 28], and natural killer (NK) cells [29], increasing their recruitment to the tumor microenvironment. Similarly, the NPAR, another marker incorporating albumin, demonstrated a significant mediating effect. The consistent involvement of albumin in both CALLY and NPAR underscores the potential role of exercise in mitigating cancer-related malnutrition and cachexia, conditions tightly linked to systemic inflammation and poor prognosis.

Previous studies have demonstrated that lower lymphocyte-to-monocyte ratio (LMR) levels are often associated with poorer prognosis and increased risks of tumor recurrence [30, 31]. We investigated its inverse, the monocyte-to-lymphocyte ratio (MLR), and characterized its nonlinear relationship with survival in cancer survivors. We found that the risk of all-cause mortality increased significantly with rising MLR levels, a finding that is consistent with the established prognostic value of LMR. Furthermore, we identified a significant inverse association between physical activity and MLR, suggesting that exercise may improve survival outcomes, at least in part, by reducing this inflammatory ratio. As for NLR, its elevation has also been shown to be associated with poor prognosis in cancer patients [32, 33]. Our database study has also revealed this result. Furthermore, we found a significant negative correlation between physical activity and MLR as well as NLR, which has shown a similar trend observed in a previous study on exercise and immune inflammation based on the NHANES database [34]. It suggests that physical activity can enhance survival outcomes by lowering inflammatory ratios.

The findings of this study have important clinical implications. The CALLY, NPAR, NLR, and MLR—readily available and cost-effective blood-based biomarkers—show promise for integration into long-term follow-up systems for cancer survivors. Since these indices are derived from routine blood tests, they require no additional healthcare spending, rendering them a fiscally sustainable option for public health and insurance systems. These biomarkers could be used to evaluate inflammatory and nutritional status, thus helping to guide the design of personalized physical activity interventions. Moving forward, clinicians may consider incorporating these indicators as auxiliary tools for prognostic evaluation. Their simplicity and accessibility make them particularly advantageous in resource-limited healthcare settings.

This study possesses several notable strengths. First, the utilization of the NHANES database, a nationally representative cohort with a complex sampling design, enhances the generalizability of our findings to the non-institutionalized US population of cancer survivors. Second, the application of formal mediation analysis allowed us to move beyond establishing association to quantifying the specific proportion of the survival benefit explained by objective, routinely collected inflammatory biomarkers, thus providing valuable insight into the potential biological mechanism. Finally, the concurrent evaluation of a panel of novel and established peripheral blood inflammatory markers (PBIMs), coupled with an examination of their non-linear relationships with mortality, provides a more mechanistic understanding of the "physical activity-survival" relationship.

This study has several limitations that should be considered when interpreting the results. First, the lack of detailed information on cancer stage, histology, and specific treatment regimens precluded a more nuanced analysis. Second, physical activity was self-reported, which is susceptible to recall and social desirability bias. Employing objective measures, such as accelerometers, in future studies would provide more accurate exposure assessment. Finally, as an observational study, the findings cannot establish causality, despite our use of mediation analysis and extensive adjustment for confounders. Randomized controlled trials (RCTs) prescribing physical activity interventions are warranted to confirm the causal pathways suggested herein.

5. Conclusion

Based on an analysis of a large, nationally representative cohort in the United States, this study found that higher levels of physical activity significantly reduced all-cause and cardiovascular mortality among cancer survivors. More importantly, through mediation analysis, we revealed for the first time that peripheral blood inflammatory markers—particularly the CALLY index and the MLR—play significant mediating roles in this protective association. These easily accessible inflammatory markers provide a novel perspective for understanding the biological mechanisms through which physical activity improves prognosis in cancer survivors, and they hold promise as practical assessment tools and guidance for personalized interventions in long-term survivorship care.

Data Availability

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

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Ethical Approval

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

Conflicts of Interest

None.

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