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Prognostic Effect of the Aggregate Index of Systemic Inflammation (AISI) on All-cause, Cardiovascular Mortality and Cause-Specific Mortality in Adult Cancer Patients

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Abstract

Background: Cancer is a leading global health concern, being the second top cause of death worldwide. This study examines the association between the Aggregate Index of Systemic Inflammation (AISI) and mortality in adult cancer patients. Methods: Data from the National Health and Nutrition Examination Survey (NHANES) were utilized to conduct Cox proportional-hazards models and generate Kaplan-Meier plots, facilitating the derivation of endpoint data and the identification of diverse survival patterns among participants diagnosed with cancer. Restricted cubic spline (RCS) transformations were employed to evaluate the dose-response relationship between the AISI and mortality in cancer patients. Subgroup interaction analysis was conducted to ascertain the predictive validity of the AISI within specific populations. Logistic regression analysis, along with stratification analysis, was applied to assess the association between the AISI and all-cause mortality among cancer patients. Results: A total of 2 253 subjects were included in this study from 1999 to 2018. Our results demonstrate that elevated quartiles of the AISI are significantly correlated with an increased risk of all-cause mortality and cardiovascular mortality (P<0.001). The predictive capability of AISI for both all-cause and cardiovascular mortality was substantiated, with c-indices of 0.82 and 0.81, respectively. AISI was positively associated with increased risk of all-cause mortality in cancer patients when combined with synergistic factors such as age, race, education, and history of diabetes. Conclusions: AISI is significantly associated with all-cause and cardiovascular mortality in cancer patients, highlighting systemic inflammation's role in prognosis. AISI could be a valuable prognostic marker, meriting further research into its mechanisms and implications for managing cancer patients.

Keywords Cancer; AISI; mortality; inflammation; prognosis

1 Introduction

Cancer constitutes a major global health challenge, consistently ranking as a leading cause of morbidity and mortality worldwide[1-2, 5]. Despite significant progress in treatment modalities such as surgery,

chemotherapy, and radiation therapy, the prognosis for many patients remains unfavorable, particularly in advanced stages[3-4, 6-7] . Existing therapeutic paradigms often fail to adequately address the inherent heterogeneity of the disease, leading to suboptimal patient management, significant adverse effects that compromise quality of life, and high mortality rates [8–9]. This underscores the urgent necessity for continued research to identify novel biomarkers and therapeutic targets. A comprehensive understanding of the underlying biological mechanisms is imperative for developing more effective strategies and improving patient outcomes.

The relationship between systemic inflammation and cancer outcomes has received considerable scholarly attention in recent years [10]. The Aggregate Index of Systemic Inflammation (AISI) has been introduced as a comprehensive metric for systemic inflammation, incorporating various inflammatory biomarkers to evaluate an individual's inflammatory status. Xie et al. demonstrated that AISI has predictive value for mortality risk in prostate cancer. Wang et al. further elaborated that a higher AISI score was associated with a worse prognosis in cancer patients [11-12]. Prior research has indicated that elevated levels of inflammatory markers are associated with reduced survival rates in cancer patients, implying that inflammation may play a critical role in cancer progression and mortality [13]. Additionally, variables such as age, sex, race, and comorbidities can affect both inflammation and cancer outcomes, highlighting the need for a multifaceted approach to understanding these interactions [14-15]. Yang et al. found that elevated AISI levels were associated with increased all-cause and cardiovascular mortality in women with cancer, but their study lacked comprehensive assessment of demographic data, physical examination findings, and past medical history for the entire study population, including men and women [16]. Our study fills this gap by comprehensively combining demographics, laboratory tests, physical examination findings, and disease history to elucidate the relationship between AISI and cancer patient prognosis and mortality. We seek to elucidate the association between AISI and all-cause mortality, cardiovascular mortality, and cancer-specific mortality among adult cancer patients, thereby contributing to the expanding body of literature on the prognostic importance of inflammation in cancer.

This study employs data from the National Health and Nutrition Examination Survey (NHANES) to examine the association between AISI and mortality rates among cancer patients. Utilizing a range of analytical techniques, including the Cox proportional hazards model, Kaplan-Meier survival analysis, and logistic regression, this research endeavors to elucidate the potential prognostic value of AISI in clinical settings. By systematically analyzing the relationship between AISI and overall mortality, cardiovascular mortality, and cancer-specific mortality, the study aims to provide insights that could enhance the understanding of the role of inflammation in cancer outcomes and inform improved patient management strategies.

2 Materials and Methods

2.1 Data sources

This cross-sectional study utilized data from the NHANES, conducted by the Centers for Disease Control and Prevention (CDC) from 1999 to 2018. The NHANES database is a nationally representative survey designed to evaluate the nutritional and health status of the United States population through a stratified multistage probability sampling method.

To evaluate the link between AISI metrics and all-cause, cardiovascular, and cancer-specific mortality in adult cancer patients, only those diagnosed with cancer were included in the analysis. The study began with 101,316 participants from 10 interview cycles spanning 1999 to 2018. After excluding participants under 18 years old, 59,204 remained. Further exclusion of 54,038 participants without a cancer diagnosis resulted in 5,166 adult cancer patients. Subsequently, 2,874 participants with incomplete or missing data

for essential covariates (including education, marital status, poverty income ratio, diabetes, hypertension, smoking, alcohol use, physical measurements, and metabolic dysfunction) were removed, leaving 2,292 adult cancer participants. Finally, participants with missing mortality data and those excluded for specific reasons (e.g., unexpected death, n=39) were removed, resulting in 2,253 participants with complete follow-up data for the current analysis (Fig. 1).

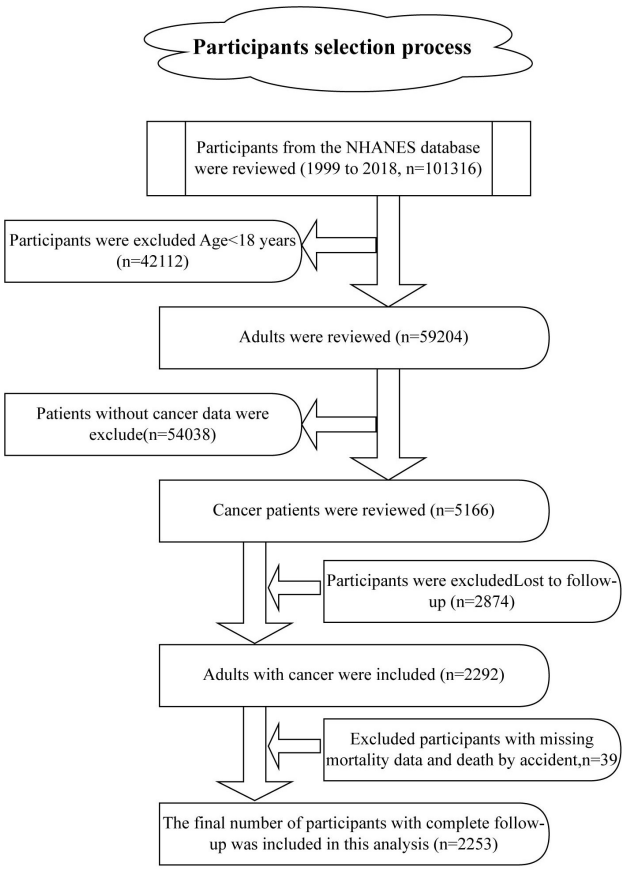

Figure 1: Study flow chart

2.2 Definition of Cancer

We characterized a history of cancer or malignancy based on participants' responses in the NHANES database to the question, "Have you ever been informed by a doctor or other health professional that you/he/she have cancer or any type of malignancy?" These questions were administered using a computer-assisted personal interview system by trained interviewers in the participants' homes. The system is equipped with built-in consistency checks to minimize errors associated with data entry.

2.3 Definitions of AISI and covariates

AISI is a composite measure of various inflammation-related biomarkers, frequently employed to comprehensively assess individual inflammation levels. It is also utilized in clinical research and disease detection to provide a holistic reflection of the body's systemic inflammatory state. The formula is as follows:

$$\text{AISI} = \frac{\text{absolute neutrophil count} \times \text{absolute platelet count} \times \text{absolute monocyte count}}{\text{absolute lymphocyte count}}$$

The counts are expressed as 1000 cells/μL.

In this study, the demographic characteristics of adult cancer patients were extracted from the NHANES database, with consideration given to various potential covariates as identified in the extant literature. The socioeconomic variables encompassed age (categorized into 10-year intervals ranging from 18 to 80 years), gender (male versus female), race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and other races), educational attainment (college degree or higher, high school diploma or equivalent, and less than high school), marital status (married, unmarried, or cohabiting), and poverty income ratio (PIR) ($<$1.3, 1.3-1.8, and $>$1.8). Additionally, lifestyle behaviors and comorbid conditions were assessed, including alcohol consumption (classified as never, moderate, or heavy), smoking status (never, current, or former smoker), presence of sleep disorders (no, yes), frequency of weekly physical activity (never, occasionally, or often), and the presence of comorbidities such as diabetes mellitus, hypertension, osteoporosis, bone cancer, cardiovascular disease (CVD), and chronic kidney disease (CKD) (no, yes).

The study encompasses both physical and laboratory assessments, including measurements of weight, height, waist circumference, and body mass index (BMI), as well as evaluations of energy intake (calculated as the average kilocalories from two 24-hour dietary recall interviews), serum albumin levels, alanine aminotransferase, aspartate aminotransferase, high-density lipoprotein, triglycerides, total cholesterol, glomerular filtration rate, glycated hemoglobin, and C-reactive protein.

2.4 Outcome measurements

The primary outcome of this investigation is the all-cause mortality rate among cancer patients. Secondary outcomes include the cardiovascular mortality rate and cancer-specific mortality rate within this population. The classification of causes of death adheres to the International Classification of Diseases, 10th Revision (ICD-10). Mortality data from 1999 to 2018 were extracted from the NHANES follow-up cohort. These data are available in the NHANES public use mortality data file up to December 31, 2019.

2.5 Statistical analysis

According to the NHANES database, recommended weights were utilized to calculate group-specific weights (https://wwwn.cdc.gov/nchs/nhanes/tutorials/weighting.aspx). This study employed sample weights, clustering, and stratification to accurately estimate variance, thereby ensuring national representation of the adult cancer population in the United States. The normality of each variable was assessed using histogram distributions, Q-Q plots, and Kolmogorov-Smirnov tests. Comparisons of continuous variables between survivors and non-survivors were conducted using the Kruskal-Wallis test. Categorical variables were compared using the chi-square test. As all continuous variables were not normally distributed, they are presented as medians with interquartile ranges. Categorical variables are presented as numbers with weighted percentages.

The Cox proportional hazards model was employed to estimate the association between AISI and various mortality outcomes, including all-cause, cardiovascular, and cancer-specific mortality, among cancer patients. The selection of covariates for this analysis was informed by prior literature on survival in cancer patients [17]. Three models were developed: Model 1 was unadjusted; Model 2 included adjustments for gender, age, and race; Model 3 was fully adjusted for age, gender, race, marital status, education, poverty income ratio, energy intake, smoking status, alcohol consumption, physical activity, sleep disorders, hypertension, osteoporosis, diabetes, CKD, CVD, serum albumin, alanine aminotransferase, aspartate aminotransferase, high-density lipoprotein, C-reactive protein, and glomerular filtration rate. The consistency index (C-index) [18] was utilized to evaluate the predictive accuracy of AISI for mortality. Kaplan-Meier (KM) curves were employed to illustrate the survival data and to compare survival patterns across different quartiles of AISI among cancer patients. A restricted cubic spline (RCS) transformation was employed

to evaluate the dose-response relationship between AISI and outcomes such as all-cause mortality, cardiovascular mortality, and cancer mortality among cancer participants. The determination of RCS curve knots was informed by the minimization of Akaike' s Information Criterion (AIC). Additionally, subgroup interaction analyses were performed, stratified by variables including age, race, education, marital status, poverty income ratio, body mass index (BMI), hypertension, diabetes, smoking status, alcohol consumption, and gender. These analyses aimed to further substantiate the association between AISI and all-cause mortality in cancer patients, as well as to assess the predictive significance of AISI within specific demographic and clinical subpopulations.

Finally, we assessed the area under the curve (AUC) of the receiver operating characteristic (ROC) curve across multiple logistic regression models—namely, the unadjusted Model 1, the partially adjusted Model 2, and the fully adjusted Model 3—to verify the method's validity and accuracy. The calibration curve, featuring both the fitted curve and the diagonal line, was employed to evaluate the concordance between predicted and actual values in the logistic regression models. In the fully adjusted Model 3, stratified analyses were conducted across various subgroups based on age, race, and gender to explore potential differences in the association between AISI and all-cause mortality among cancer patients. Statistical analyses were executed using R software (version 4.4.3, https://www.r-project.org/).

3 Results

3.1 Baseline characteristics of adult Cancer patients

Between 1999 and 2018, a total of 2,253 participants were enrolled in this study. The median age of the cohort was 64 years (53.0–75.0), with a median weight of 78.3 kg, a median height of 166.5 cm, a median waist circumference of 99.5 cm, a BMI of 27.48 kg/m^2, and a median daily caloric intake of 1,801 Kcal. Female participants constituted a larger proportion of the study population, comprising 1,213 individuals (59.3%), compared to male participants, who numbered 1,040 (40.7%). The majority of the adult cancer patients were non-Hispanic whites, totaling 1,564 individuals (85.7%), while non-Hispanic blacks represented 5.6% (296 individuals) of the cohort. Furthermore, 68% (1,692 individuals) of the participants had attained a high school education or higher. Among the participants, 37.2% (894 individuals) were current smokers, and 24.9% (545 individuals) were current drinkers. Regarding comorbidities, 638 participants (30.6%) reported a history of sleep disorders, and 582 participants (31.2%) did not engage in weekly physical activity. Additionally, 18% of the participants had diabetes mellitus, 61.6% had hypertension, 10.9% had osteoporosis, 15.9% had CVD, and 19.3% had CKD. Notably, 0.7% of these cancer patients also had comorbid bone cancer. The median AISI was recorded at 270.9. The median duration of follow-up was 107 months, during which 812 cases of all-cause mortality, 175 cases of cardiovascular-related mortality, and 245 cases of cancer-related mortality were documented. Non-survivors were predominantly characterized by being male, older, more educated, married, having a moderate income, having comorbid hypertension, consuming alcohol, being current smokers, not participating in physical activity, having a lower BMI, and presenting a higher AISI compared to survivors (all $P < 0.05$) (Table 1).

Table 1: The demographic characteristics of adults with cancer in the present study

Variables	Total (n=2253)	Survivors (n=1435, 74.1%)	Non-survivors (n=818, 25.9%)	*p*
Age (years), n (%)	64.0 (53.0–75.0)	60.0 (49.0–70.0)	75.0 (67.0–80.0)	<0.001
18–29	52 (3.0)	48 (3.6)	4 (1.4)	
30–39	101 (6.6)	99 (8.7)	2 (0.6)	

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Variables	Total (n=2253)	Survivors (n=1435, 74.1%)	Non-survivors (n=818, 25.9%)	*p*
40–49	164 (10.5)	145 (13.1)	19 (2.7)	
50–59	289 (17.9)	247 (21.7)	42 (6.9)	
60–69	542 (25.6)	395 (27.6)	147 (19.9)	
70–80	1105 (36.5)	501 (25.3)	604 (68.4)	
Gender, n (%)				<0.001
Male	1040 (40.7)	582 (37.4)	458 (50.0)	
Female	1213 (59.3)	853 (62.6)	360 (50.0)	
Race/Ethnicity, n (%)				0.266
Hispanic	294 (5.4)	232 (5.9)	62 (4.0)	
Non-Hispanic white	1564 (85.7)	920 (85.1)	644 (87.5)	
Non-Hispanic black	296 (5.6)	197 (5.2)	99 (6.7)	
Other races	99 (3.3)	86 (3.8)	13 (1.9)	
Education status, n (%)				<0.001
More than high school	1063 (39.7)	599 (34.9)	464 (53.4)	
High school or equivalent	629 (28.3)	434 (29.2)	195 (25.7)	
Less than high school	558 (31.9)	400 (35.8)	158 (20.9)	
Not recorded	3 (0.1)	2 (0.1)	1 (0.1)	
Marital status, n (%)				<0.001
Married	1306 (64.1)	865 (67.7)	441 (53.7)	
Not married	852 (31.6)	502 (27.9)	350 (42.1)	
Living with partner	83 (3.9)	65 (4.3)	18 (2.9)	
Not recorded	12 (0.4)	3 (0.1)	9 (1.3)	
Poverty-income ratio, n (%)				<0.001
<1.3	496 (14.3)	294 (11.6)	202 (22.0)	
1.3–1.8	835 (34.1)	488 (30.8)	347 (43.7)	
>1.8	725 (43.8)	530 (49.8)	195 (26.9)	
Not recorded	197 (7.7)	123 (7.8)	74 (7.4)	
Daily alcohol drinking status, n (%)				<0.001
Non-drinkers	289 (10.6)	175 (9.1)	114 (14.7)	
Moderate-drinkers	285 (11.1)	184 (10.7)	101 (12.3)	
Heavy-drinkers	260 (13.8)	204 (16.1)	56 (7.3)	
Not recorded	1419 (64.5)	872 (64.1)	547 (65.6)	
Smoking, n (%)				<0.001
Never	1013 (46.3)	696 (49.0)	317 (38.8)	
Now	894 (37.2)	504 (34.2)	390 (45.6)	
Ever	343 (16.4)	232 (16.7)	111 (15.6)	
Not recorded	3 (0.1)	3 (0.1)	0 (0.0)	
Sleep disorder, n (%)				<0.001
No	1615 (69.4)	966 (66.3)	649 (78.1)	
Yes	638 (30.6)	469 (33.7)	169 (21.9)	
Physical activity, n (%)				<0.001
Inactive	582 (31.2)	384 (26.7)	198 (54.4)	
Less active or Active	888 (68.8)	737 (73.3)	151 (45.6)	

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Variables	Total (n=2253)	Survivors (n=1435, 74.1%)	Non-survivors (n=818, 25.9%)	*p*
History of diabetes, n (%)				0.001
No	1703 (82.0)	1114 (83.9)	589 (76.7)	
Yes	550 (18.0)	321 (16.1)	229 (23.3)	
History of hypertension, n (%)				<0.001
No	712 (38.4)	544 (44.5)	168 (20.9)	
Yes	1541 (61.6)	891 (55.5)	650 (79.1)	
History of osteoporosis, n (%)				<0.001
No	2001 (89.1)	1294 (91.1)	707 (83.7)	
Yes	252 (10.9)	141 (8.9)	111 (16.3)	
Bone cancer, n (%)				0.044
No	2233 (99.3)	1427 (99.5)	806 (98.7)	
Yes	20 (0.7)	8 (0.5)	12 (1.3)	
CVD, n (%)				<0.001
No	1783 (84.1)	1213 (88.8)	570 (70.7)	
Yes	453 (15.9)	212 (11.2)	241 (29.3)	
CKD, n (%)				<0.001
No	1697 (80.7)	1144 (84.8)	553 (69.2)	
Yes	556 (19.3)	291 (15.2)	265 (30.8)	
Weight (kg)	78.3 (66.1–92.3)	79.2 (66.8–92.5)	75.1 (63.9–91.2)	0.003
Standing height (cm)	166.5 (160.0–174.7)	166.4 (160.4–174.7)	166.9 (159.3–174.6)	0.643
Waist circumference (cm)	99.9 (88.9–110.7)	99.8 (88.5–110.7)	100.1 (89.6–110.9)	0.611
BMI (kg/m^2), n (%)	27.5 (24.1–32.3)	27.7 (24.2–32.9)	26.9 (23.8–31.3)	0.005
<25	655 (31.2)	374 (29.6)	281 (35.9)	
25–30	759 (32.2)	494 (33.2)	265 (29.3)	
>30	787 (34.8)	552 (36.1)	235 (31.2)	
Not recorded	52 (1.7)	15 (1.1)	37 (3.6)	
Daily energy (kcal)	1801.0 (1335.0–2286.0)	1821.0 (1396.0–2309.0)	1665.0 (1120.0–2203.0)	<0.001
ALB (g/L)	20.0 (16.0–27.0)	20.0 (16.0–28.0)	19.0 (15.0–24.0)	<0.001
ALT (U/L)	42.0 (40.0–44.0)	42.0 (40.0–44.0)	41.0 (39.0–44.0)	<0.001
AST (U/L)	23.0 (19.0–27.0)	23.0 (19.0–27.0)	23.0 (20.0–28.0)	0.050
HDL (mg/dL)	54.0 (45.0–65.0)	54.0 (45.0–65.0)	54.0 (45.0–67.0)	0.631
TR (mmol/L)	1.28 (0.89–1.84)	1.23 (0.87–1.81)	1.39 (0.98–1.95)	<0.001
TC (mmol/L)	5.04 (4.40–5.79)	5.07 (4.42–5.82)	4.97 (4.27–5.66)	0.014
eGFR (mL/min/1.73 m^2)	82.01 (67.34–95.45)	84.64 (70.48–97.78)	71.63 (54.06–85.03)	<0.001
Glycohemoglobin (%)	5.6 (5.3–5.9)	5.5 (5.3–5.9)	5.7 (5.4–6.0)	<0.001
CRP (mg/dL)	0.28 (0.12–0.83)	0.26 (0.10–0.83)	0.28 (0.15–0.83)	<0.001
AISI	270.9 (169.2–419.3)	245.5 (158.1–386.9)	332.8 (216.0–515.7)	<0.001

Notes. M, median; Q, quartile; AISI, the Aggregate Index of Systemic Inflammation; PIR, poverty income ratio; CVD, cardiovascular disease; CKD, chronic kidney disease; BMI, body mass index; ALB, serum albumin levels; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; TR, triglycerides; TC, total cholesterol; eGFR, glomerular filtration rate; CRP, C-reactive protein. Non-normally distributed variables are shown as median (Q1, Q3). Categorical variables are shown as number (percentage). Bold values indicate statistical significance ($p < 0.05$).

3.2 Association between AISI and mortality outcome in adult Cancer patients

When compared to participants in the low quartile subgroup, those in the high quartile of AISI exhibited significantly elevated rates of all-cause mortality (Fig. 2A), cardiovascular mortality (Fig. 2C), and cancer mortality (Fig. 2E) among unweighted participants ($P < 0.001$). Similarly, weighted participants in the high quartile of AISI also demonstrated significantly higher rates of all-cause mortality (Fig. 2B), cardiovascular mortality (Fig. 2D), and cancer mortality (Fig. 2F) compared to those in the low quartile subgroup ($P < 0.001$). A multivariate-adjusted Cox regression analysis revealed that the fourth quartile of AISI was significantly associated with an increased risk of all-cause mortality, with an adjusted hazard ratio (aHR) of 1.369 (95% confidence interval [CI]: 1.051–1.782, $P = 0.020$) (Fig. 3A). Furthermore, a high quartile level of AISI was significantly correlated with cardiovascular mortality in adult cancer patients, as indicated by an aHR of 1.37 (95% CI: 1.058–1.774, $P = 0.017$) (Fig. 3B). However, no significant association was observed between the high quartile level of AISI and cancer mortality, with an aHR of 1.219 (95% CI: 0.727–2.045, $P = 0.452$) (Fig. 3C). The c-index for AISI in predicting all-cause mortality was 0.585, while for cardiovascular mortality, it was 0.644, and for cancer mortality, it was 0.564. When AISI was combined with other clinical factors, the c-index for predicting all-cause mortality increased to 0.821, and for predicting cardiovascular mortality, it rose to 0.814.

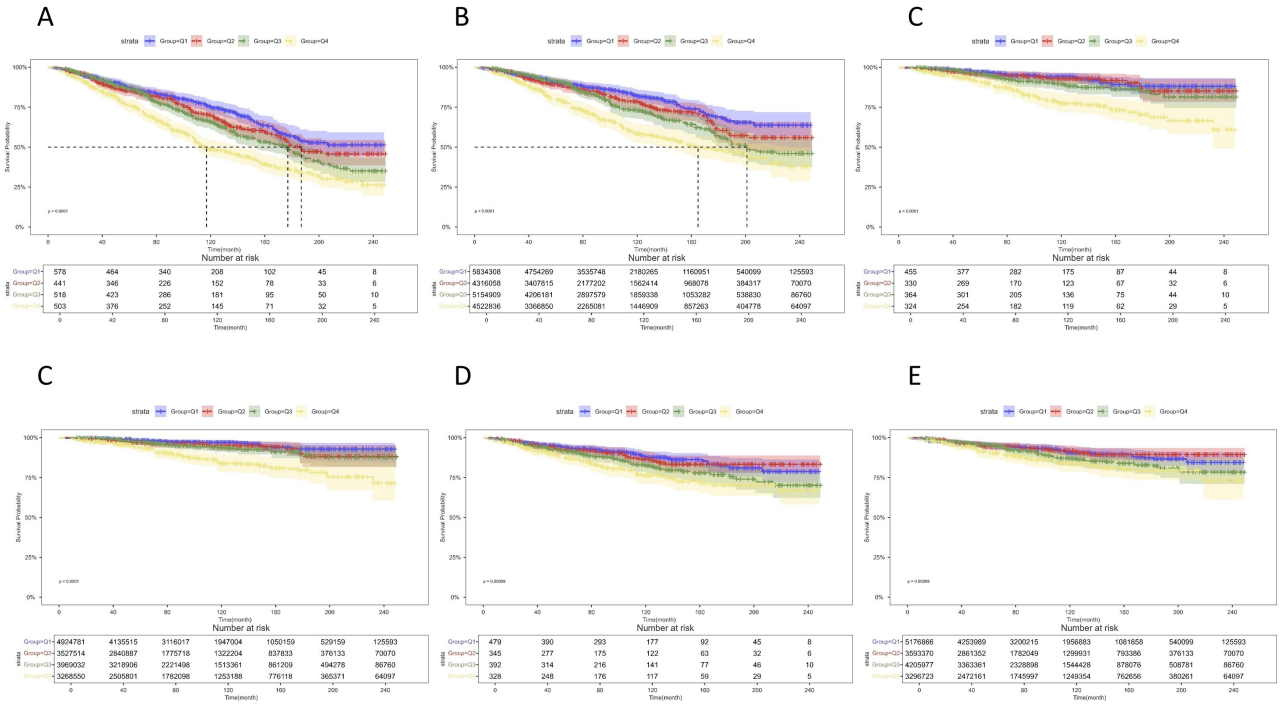

Figure 2: Kaplan-Meier curves show the survival patterns of adult cancer patients at different AISI quartile levels. A (unweighted) -B (weighted) are all-cause mortality for adult cancer patients at different quartile levels of AISI. C (unweighted) -D (weighted) is the cardiovascular mortality of adult cancer patients at different quartile levels of AISI. E (unweighted) -F (weighted) is the cancer mortality of adult cancer patients at different quartile levels of AISI. Q, quartile; AISI, the Aggregate Index of Systemic Inflammation.

3.3 Linear trend of AISI related measures and mortality outcomes in adult Cancer patients

AISI demonstrates a linear association with both all-cause and cardiovascular mortality rates in cancer patients (P for overall effect < 0.005, P for nonlinearity > 0.05) (Fig. 4A and 4B). Conversely, the RCS plot, adjusted for multiple covariates, indicates that AISI does not exert a statistically significant impact on the cancer-specific mortality rate among cancer patients (P for overall effect = 0.195, P for nonlinearity = 0.121) (Fig. 4C). This suggests that elevated levels of AISI are correlated with a marked increase in the risk of all-cause and cardiovascular mortality in this patient population.

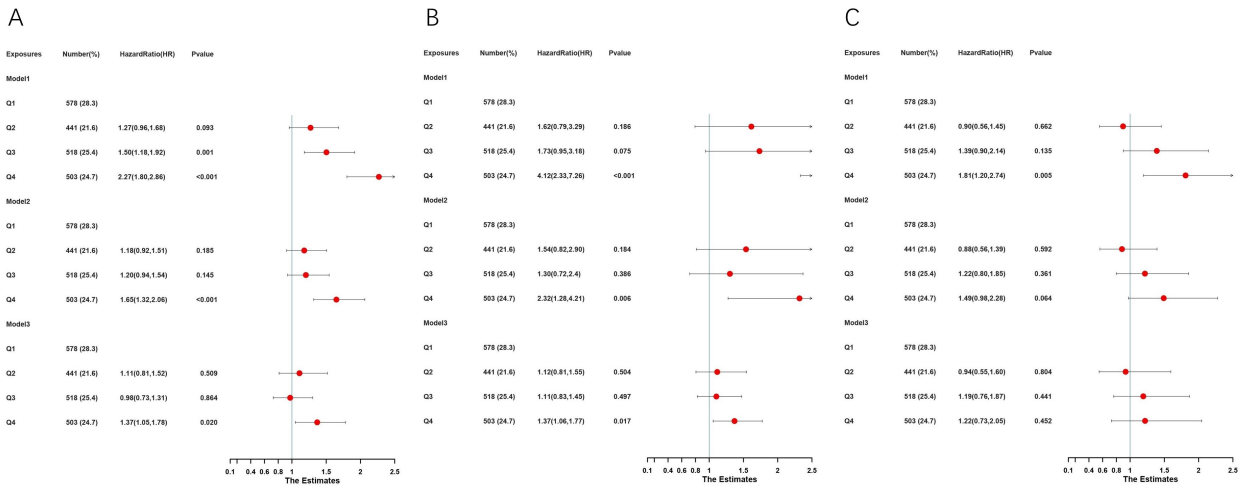

Figure 3: Forest plot A shows the association between AISI and all-cause mortality in adult cancer patients. Forest plot B shows the association between AISI and cardiovascular mortality in adult cancer patients. Forest plot C shows the association between AISI and cancer mortality in adult cancer patients. Model 1: unadjusted; Model 2: adjusted for age, gender, race; Model 3: adjusted for gender, age, race, education, marital status, PIR, energy intake, smoking status, alcohol consumption, physical activity, sleep disorders, hypertension, osteoporosis, diabetes, CKD, CVD, ALB, ALT, AST, HDL, CRP, and eGFR. AISI, the Aggregate Index of Systemic Inflammation; PIR, poverty income ratio; CVD, cardiovascular disease; CKD, chronic kidney disease; ALB, serum albumin levels; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; CRP, C-reactive protein; eGFR, glomerular filtration rate.

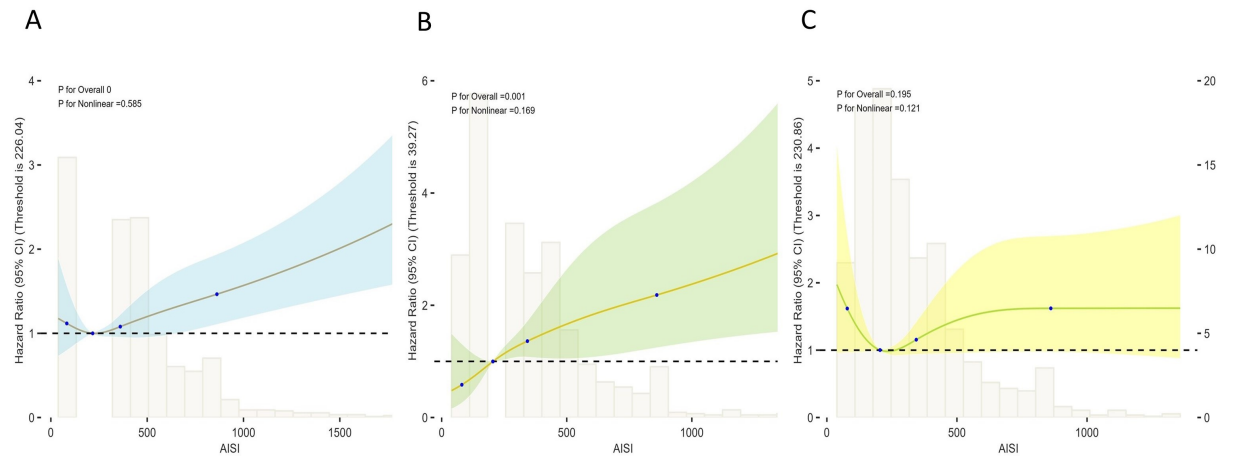

Figure 4: Restricted cubic splines reflect the dose-response relationship between AISI and all-cause mortality in adult cancer patients. B: Restricted cubic splines reflect the dose-response relationship between AISI and cardiovascular mortality in adult cancer patients. C: Restricted cubic splines reflect the dose-response relationship between AISI and cancer mortality in adult cancer patients. AISI, the Aggregate Index of Systemic Inflammation.

3.4 Subgroup interaction analysis

Stratified analyses indicated no significant differences in outcomes related to marital status, poverty-to-income ratio, BMI, hypertension, alcohol history, smoking history, and gender interaction. Nonetheless, with an interaction *P*-value of less than 0.05, the predictive efficacy of AISI was notably enhanced within specific subpopulations, particularly among individuals aged 60 to 69 years, non-Hispanic Black individuals, those with a high school education, and individuals with a history of diabetes. This finding suggests that the integration of AISI with these four synergistic factors is positively correlated with an increased risk of all-cause mortality among cancer patients (Figure 5).

Supplementary Figure S1 illustrates that the AUC, as evaluated by the ROC curve in the logistic regression models (Model 1, Model 2, Model 3), exceeds 0.5. As the number of adjusted covariates increases from Model 1 to Model 2 and Model 3, there is a corresponding increase in the AUC values, thereby enhancing the validity of the method and improving the accuracy rate.

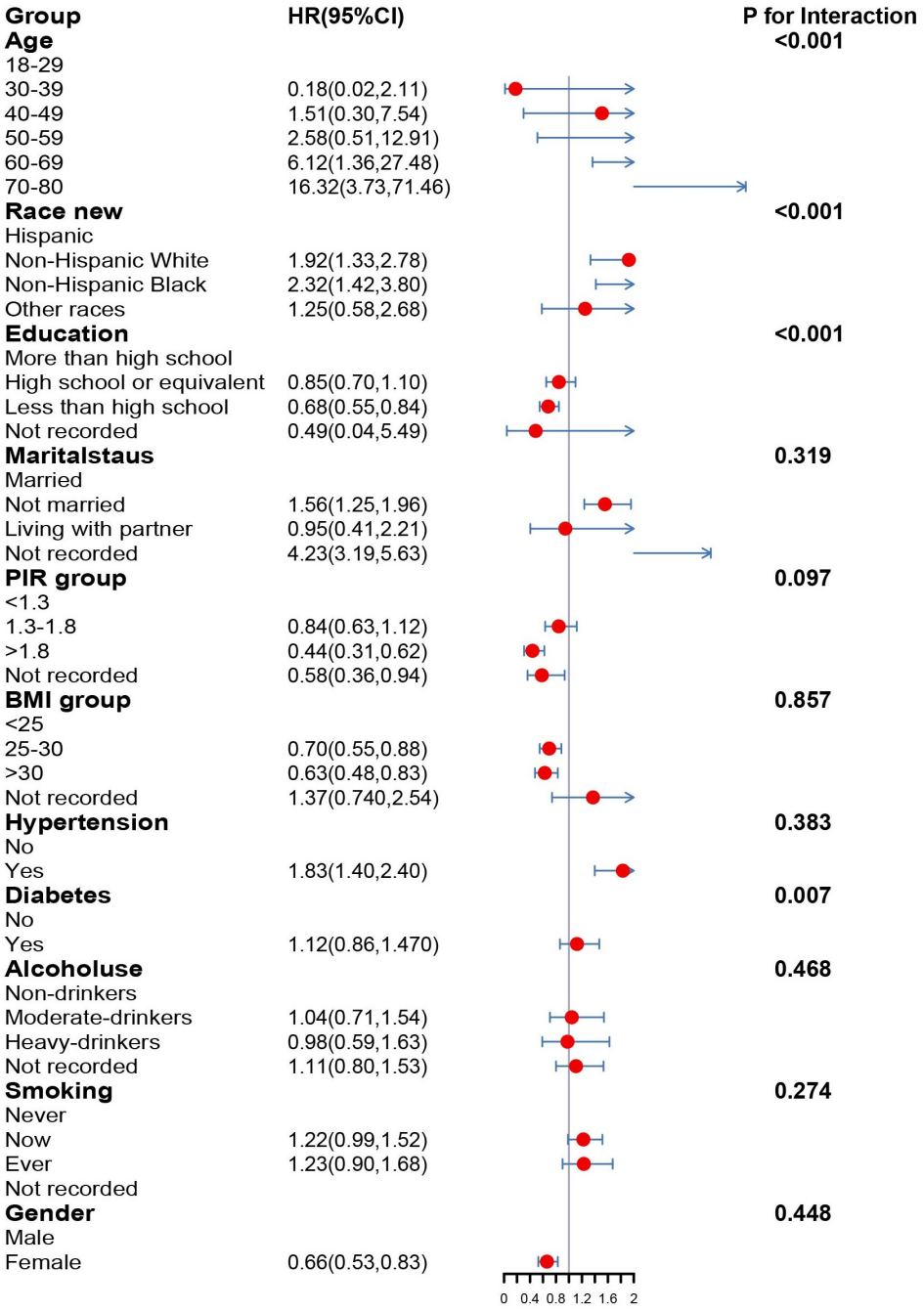

Figure 5: Subgroups were defined according to age, race, education, marital status, PIR, BMI, hypertension, diabetes, smoking, alcohol consumption, and gender. To investigate the association between AISI and all-cause mortality in different subgroups of adult cancer patients. PIR, poverty income ratio; BMI, body mass index; AISI, the Aggregate Index of Systemic Inflammation.

Figure S2 demonstrates that in the calibration curve assessment of these logistic regression models, the fitted curves for the partially adjusted Model 2 and the fully adjusted Model 3 progressively align with the diagonal line. This alignment indicates that the predicted and actual incidence rates are converging, with the predictions of the fully adjusted Model 3 closely approximating the actual values. In Model 3, which is fully adjusted, stratified analyses by age, race, and gender were performed to evaluate potential differences in the association between AISI and all-cause mortality among cancer patients, as depicted in Figure S3. In the age subgroup analysis, significant interactions were identified in both the 18-49 and 50+ age categories, with odds ratios (OR) and their corresponding 95% confidence intervals exceeding 1 ($P < 0.001$). This suggests a significant positive correlation between AISI and the risk of all-cause mortality among cancer patients. Notably, the OR value for the 18-49 age group was higher, indicating a marginally increased risk in this cohort. In contrast, within the race subgroup analysis, no significant interactions were detected

among Hispanic and non-Hispanic white groups. However, significant interactions were observed in the non-Hispanic black and other race categories, with OR values and 95% confidence intervals both exceeding 1 ($P < 0.001$). The findings suggest a significant positive correlation between AISI and the risk of all-cause mortality among cancer patients in these groups. Notably, the OR is higher in the "other race" group, indicating an elevated risk. Within the gender subgroups, no significant interactions were detected among females. However, significant interactions were observed in the male subgroup, as evidenced by OR values and their 95% confidence intervals exceeding 1 ($P = 0.021$). This underscores a significant positive correlation between AISI and the risk of all-cause mortality in male cancer patients.

4 Discussion

In the present study, we found that an elevated AISI was significantly correlated with mortality outcomes in cancer patients. Specifically, cancer patients in the fourth quartile of AISI exhibited a 1.37-fold increase in both all-cause and cardiovascular mortality. Furthermore, AISI demonstrated superior predictive capability for all-cause and cardiovascular mortality among cancer patients when combined with clinical factors, with C-index values of 0.821 and 0.814, respectively. A linear relationship was observed between AISI and both all-cause and cardiovascular mortality in this population. When AISI was combined with synergistic factors such as age, race, education, and a history of diabetes, it was positively associated with an increased risk of all-cause mortality in cancer patients. The AUC of the ROC, as assessed by the logistic regression models, surpassed 0.5, thereby confirming the study's validity. In the analysis of age subgroups, significant interactions were identified within the 18–49 years and 50 years and older cohorts, as well as among non-Hispanic Black and other racial subgroups, and male subgroups. These findings underscore a significant positive correlation between AISI and the risk of all-cause mortality in cancer patients.

Nooh et al. illustrated that multiple inflammatory markers, including AISI, were associated with poor survival in adult COVID-19 cancer patients [19]. Feier et al. found a significant increase in AISI in gastric cancer patients who experienced recurrence [20]. Shen et al. clarified that AISI is a risk factor for distant metastasis in patients with colorectal cancer [21]. Bai et al. found that AISI was associated with all-cause and cardiovascular mortality in patients with congestive heart failure [17]. In contrast to prior research, which predominantly concentrated on isolated risk factors, our study innovatively incorporates AISI as an integrative measure of inflammation, offering a more comprehensive perspective on its influence on cancer outcomes. This study elucidates the substantial association between AISI and both all-cause and cardiovascular mortality among cancer patients, thereby underscoring the pivotal role of inflammation in cancer prognosis. The findings indicate that elevated AISI levels are correlated with heightened mortality risks, highlighting the necessity for further investigation into inflammatory pathways in the context of cancer management.

Statistical analyses utilizing the NHANES database demonstrate that individuals with elevated AISI levels experience significantly higher rates of all-cause and cardiovascular mortality compared to those with lower levels. Moreover, the data indicate that this association persists across diverse demographic subgroups, including variations in age, race, and comorbid conditions. These findings underscore the importance of inflammation, as measured by AISI, as a critical prognostic factor in cancer patients, thereby highlighting its relevance in clinical evaluations and therapeutic planning.

The current study showed that elevated AISI was significantly and positively associated with all-cause and cardiovascular mortality in cancer patients, indicating that inflammation is a key factor affecting the survival of these individuals [22]. In similar findings involving patients with depression and asthma, a higher frailty index was associated with increased all-cause and cardiovascular mortality [23–24]. These studies collectively underscore systemic inflammation as an important prognostic factor in various patient populations [25]. The present findings add to the expanding body of evidence that underscores the significance of inflammation in cancer prognosis [28–30]. Variations in findings across studies may result from differences in the patient populations examined and the inflammatory markers evaluated [26–27]. This highlights the necessity for further research to elucidate the mechanisms underlying these associations and to investigate potential therapeutic interventions that target inflammation in cancer management [31–32].

The association between AISI and mortality among cancer patients was examined through the application of diverse statistical models, aiming to thoroughly investigate the relationship between this exposure and the pertinent outcomes. The study utilized Cox proportional hazards models alongside multivariable logistic regression analyses to evaluate the effect of AISI on all-cause mortality, cardiovascular mortality, and cancer-specific mortality in adult cancer patients. In the multivariable logistic regression analysis, a significant positive association was observed between elevated levels of AISI and increased all-cause mortality. This finding suggests that individuals in the highest quartile of AISI exhibited a substantially higher risk of mortality compared to those in the lowest quartile. Furthermore, the Cox regression analysis corroborated the significant association between AISI and cardiovascular mortality, whereas no significant correlation was identified for cancer-specific mortality. The concordance of results across these statistical methodologies strengthens the validity of the findings, as both the Cox model and logistic regression demonstrated a linear relationship between AISI and mortality outcomes. Employing multiple models facilitated a comprehensive analysis of the data, demonstrating that elevated AISI levels correlate with an increased risk of mortality. This finding provides robust evidence supporting the role of systemic inflammation in cancer prognosis. The study highlights the significance of AISI as a potential biomarker for evaluating mortality risk in cancer patients, indicating that interventions targeting the reduction of

systemic inflammation could enhance patient outcomes.

Increased AISI levels were associated with decreased survival rates, suggesting that specific inflammatory cell populations may play a role in the immunosuppressive characteristics of the tumor microenvironment, thereby affecting the efficacy of therapeutic interventions [33-34]. Future research should aim to identify the key transcription factors governing these cell subtypes, as elucidating their functions could offer insights into potential inflammatory therapeutic targets for cancer [35-37]. This study examines the association between AISI and various mortality outcomes, including all-cause, cardiovascular, and cancer-specific mortality, in adult cancer patients. Prior research demonstrates that systemic inflammation is a critical factor in cancer progression and patient survival [38]. Elevated levels of inflammatory markers have been linked to poorer prognoses across different cancer types, suggesting that inflammation may significantly contribute to cancer pathophysiology and its associated complications [39-41]. Moreover, socioeconomic factors like income and educational attainment influence both cancer outcomes and inflammatory responses, emphasizing the complex interactions among these variables [42-43]. By exploring the relationship between AISI and mortality, this study aims to clarify the role of systemic inflammation as a prognostic indicator, aiding in the creation of personalized treatment strategies.

5 Strength and Limitations

Our study presents significant findings regarding the association between a high quartile of the AISI and overall mortality as well as cardiovascular mortality in cancer patients. We explored the prognostic impact of the AISI on postoperative outcomes in adult carcinoma patients and its clinical value in the management of cancer patients. Secondly, the sample size of the study is robust, and the follow-up time is sufficient to observe mortality rate outcomes. In addition, we controlled for a series of covariates to determine the independent association between AISI-related indicators and mortality outcomes in cancer patients. Finally, we conducted a logistic regression multi-model calibration curve to assess how closely the predicted values of the fully adjusted model align with the actual values.

Nevertheless, several limitations must be acknowledged in this study. Firstly, the absence of wet laboratory experiments constrains the validation of the AISI as a reliable biomarker in clinical contexts. Furthermore, the lack of clinical validation analyses raises concerns regarding the robustness of our findings. Potential batch effects arising from multiple datasets could also introduce variability that may confound the results, necessitating caution in their interpretation.

In summary, our results suggest that a high AISI is significantly associated with increased mortality risks in cancer patients, underscoring its potential as a prognostic tool. The capacity of the AISI to function as a marker of inflammation highlights its relevance in predicting patient outcomes. Future research should focus on larger, more diverse cohorts and incorporate clinical validation to enhance the applicability of the AISI in clinical practice.

6 Conclusions

The study highlights the substantial association between the AISI and both all-cause and cardiovascular mortality among cancer patients, underscoring the importance of systemic inflammation in cancer prognosis. These findings indicate that AISI has the potential to be a valuable prognostic marker in clinical practice, thereby justifying further research into its underlying mechanisms and implications for the management of cancer patients.

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Ethics statement The study protocol received approval from the National Center for Health Statistics (NCHS) Research Ethics Review Board and complied with the Declaration of Helsinki. Secondary analyses of this study adhered to the STROBE guidelines for cross-sectional studies and did not require additional institutional review board approval. Further details regarding the NHANES database can be accessed on the CDC website as of May 21, 2025 (https://www.cdc.gov/nchs/nhanes/).

Informed Consent Statement All adult participants provided written informed consent.

Data Availability Statement The datasets generated or analyzed in this study are available in the National Health and Nutrition Examination Survey repository.

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Conflict of interest To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

Generative AI statement The authors declare that no generative AI has been used in the creation of this manuscript.

Abbreviations

AISI	Aggregate Index of Systemic Inflammation
NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
NCHS	National Center for Health Statistics
RCS	Restricted Cubic Spline
PIR	Poverty Income Ratio
CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
BMI	Body Mass Index
ICD-10	International Classification of Diseases, 10th Revision
C-index	Consistency Index
KM	Kaplan-Meier
AIC	Akaike’s Information Criterion
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic
aHR	Adjusted Hazard Ratio
OR	odds ratios
ALB	Serum Albumin Levels
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
HDL	High-Density Lipoprotein
TR	Triglycerides
TC	Total Cholesterol
eGFR	Glomerular Filtration Rate
CRP	C-Reactive Protein

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References

[1] Siegel, R. L., Kratzer, T. B., Giaquinto, A. N., et al. (2025). Cancer statistics, 2025. *CA Cancer J Clin*, 75(1), 10-45. doi:10.3322/caac.21871.

[2] Barnes, J. M., Johnson, K. J., Osazuwa-Peters, N., et al. (2023). Changes in cancer mortality after Medicaid expansion and the role of stage at diagnosis. *J Natl Cancer Inst*, 115(8), 962-970. doi:10.1093/jnci/djad094.

[3] Nguyen, N. P., Sallah, S., Karlsson, U., et al. (2002). Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. *Cancer*, 94(4), 1131-1141. doi:10.1002/cncr.10257.

[4] Elmqvist, M. A., Jordhøy, M. S., Bjordal, K., et al. (2009). Health-related quality of life during the last three months of life in patients with advanced cancer. *Support Care Cancer*, 17(2), 191-198. doi:10.1007/s00520-008-0477-2.

[5] Sancho-Albero, M., Encinas-Giménez, M., Sebastián, V., et al. (2022). Transfer of photothermal nanoparticles using stem cell derived small extracellular vesicles for in vivo treatment of primary and multinodular tumours. *J Extracell Vesicles*, 11(3), e12193. doi:10.1002/jev2.12193.

[6] Panchal, N. K., & Sabina, E. P. (2020). A serine/threonine protein PIM kinase as a biomarker of cancer and a target for anti-tumor therapy. *Life Sci*, 255, 117866. doi:10.1016/j.lfs.2020.117866.

[7] Brown, G. (2021). Oncogenes, proto-oncogenes, and lineage restriction of cancer stem cells. *Int J Mol Sci*, 22(18), 9667. doi:10.3390/ijms22189667.

[8] Roessler, S., Budhu, A., & Wang, X. W. (2014). Deciphering cancer heterogeneity: the biological space. *Front Cell Dev Biol*, 2, 12. doi:10.3389/fcell.2014.00012.

[9] Pei, L., Liu, Y., Liu, L., et al. (2023). Roles of cancer-associated fibroblasts (CAFs) in anti- PD-1/PD-L1 immunotherapy for solid cancers. *Mol Cancer*, 22(1), 29. doi:10.1186/s12943-023-01731-z.

[10] Roxburgh, C. S., & McMillan, D. C. (2014). Cancer and systemic inflammation: treat the tumour and treat the host. *Br J Cancer*, 110(6), 1409-1412. doi:10.1038/bjc.2014.90.

[11] Xie, W., Xu, Z., Qiu, Y., et al. (2023). A novel nomogram combined the Aggregate Index of Systemic Inflammation and PIRADS score to predict the risk of clinically significant prostate cancer. *Biomed Res Int*, 2023, 9936087. doi:10.1155/2023/9936087.

[12] Wang, H. K., Wei, Q., Yang, Y. L., et al. (2023). Clinical usefulness of the lymphocyte-to-monocyte ratio and aggregate index of systemic inflammation in patients with esophageal cancer: a retrospective cohort study. *Cancer Cell Int*, 23(1), 13.

doi:10.1186/s12935-023-02856-3.
[13] Giannetta, E., La Salvia, A., Rizza, L., et al. (2021). Are markers of systemic inflammatory response useful in the management of patients with neuroendocrine neoplasms?. *Front Endocrinol (Lausanne)*, 12, 672499. doi:10.3389/fendo.2021.672499.
[14] Yao, J., Chen, X., Meng, F., et al. (2024). Combined influence of nutritional and inflammatory status and depressive symptoms on mortality among US cancer survivors: Findings from the NHANES. *Brain Behav Immun*, 115, 109-117. doi:10.1016/j.bbi.2023.10.002.
[15] Zhao, T., Zhao, H., Zhang, X., et al. (2024). Combined effects of nutrition, inflammatory status, and sleep quality on mortality in cancer survivors. *BMC Cancer*, 24(1), 1456. doi:10.1186/s12885-024-13181-x.
[16] Yang, Y., Hu, Z., Ye, Y., et al. (2025). Association of aggregate index of systemic inflammation with increased all-cause and cardiovascular mortality in female cancer patients. *Front Oncol*, 15, 1552341. doi:10.3389/fonc.2025.1552341.
[17] Bai, X., Cheng, L., Wang, H., et al. (2025). The aggregate index of systemic inflammation (AISI) and the risk of all-cause, cardiovascular, and cardio-cerebrovascular mortality in congestive heart failure patients: results from NHANES 1999-2018. *Sci Rep*, 15(1), 18282. doi:10.1038/s41598-025-01196-8.
[18] Liu, L., Xiao, Y., Wei, D., et al. (2024). Development and validation of a nomogram for predicting suicide risk and prognostic factors in bladder cancer patients following diagnosis: A population-based retrospective study. *J Affect Disord*, 347, 124-133. doi:10.1016/j.jad.2023.11.086.
[19] Nooh, H. A., Abdellateif, M. S., Refaat, L., et al. (2021). The role of inflammatory indices in the outcome of COVID-19 cancer patients. *Med Oncol*, 39(1), 6. doi:10.1007/s12032-021-01605-8.
[20] Feier, C. V. I., Muntean, C., Faur, A. M., et al. (2024). An exploratory assessment of pre-treatment inflammatory profiles in gastric cancer patients. *Diseases*, 12(4), 78. doi:10.3390/diseases12040078.
[21] Shen, X., Xiang, M., Tang, J., et al. (2024). Evaluation of peripheral blood inflammation indexes as prognostic markers for colorectal cancer metastasis. *Sci Rep*, 14(1), 20489. doi:10.1038/s41598-024-68150-y.
[22] Feier, C. V. I., Muntean, C., Faur, A. M., et al. (2024). An exploratory assessment of pre-treatment inflammatory profiles in gastric cancer patients. *Diseases*, 12(4), 78. doi:10.3390/diseases12040078.
[23] Tian, T. L., Qu, X. K., Zhang, H. B., et al. (2025). Association between advanced lung cancer inflammation index and all-cause and cause-specific mortality among asthma patients: a cohort study. *Front Nutr*, 12, 1519271. doi:10.3389/fnut.2025.151927.
[24] Liu, X., Wang, Y., Huang, Y., et al. (2025). Association between frailty index and mortality in depressed patients: results from NHANES 2005-2018. *Sci Rep*, 15(1), 3305. doi:10.1038/s41598-025-87691-4.
[25] Sever, N., Yıldırım, S., Gurbuz, A. F., et al. (2025). The effect of systemic inflammation and clinicopathologic features on survival in malignant pleural mesothelioma: A multicenter analysis. *Medicina (Kaunas)*, 61(1), 144. doi:10.3390/medicina61010144.
[26] Sánchez-Lázaro, I. J., Almenar-Bonet, L., Reganon-Salvador, E., et al. (2011). Are there differences in acute phase inflammation markers regarding the type of heart failure? *Heart Int*, 6(2), e17. doi:10.4081/hi.2011.e17.
[27] Neamți, L., Drugan, T. C., Drugan, C., et al. (2024). Assessing seasonal variations of biomarkers in inflammatory bowel disease. *Eur J Gastroenterol Hepatol*, 36(8), 993-999. doi:10.1097/MEG.0000000000002795.
[28] Roxburgh, C. S., & McMillan, D. C. (2010). Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*, 6(1), 149-163. doi:10.2217/fon.09.136.
[29] Paik, K. Y., Lee, I. K., Lee, Y. S., et al. (2014). Clinical implications of systemic inflammatory response markers as independent prognostic factors in colorectal cancer patients. *Cancer Res Treat*, 46(1), 65-73. doi:10.4143/crt.2014.46.1.65.
[30] Murphy, J., O'Sullivan, G. C., Lee, G., et al. (2000). The inflammatory response within Dukes' B colorectal cancers: implications for progression of micrometastases and patient survival. *Am J Gastroenterol*, 95(12), 3607-3614. doi:10.1111/j.1572-0241.2000.03377.x.
[31] Anwar, F., Naqvi, S., Shams, S., et al. (2023). Nanomedicines: intervention in inflammatory pathways of cancer. *Inflammopharmacology*, 31(3), 1199-1221. doi:10.1007/s10787-023-01217-w.
[32] Peebles, K. A., Lee, J. M., Mao, J. T., et al. (2007). Inflammation and lung carcinogenesis: applying findings in prevention and treatment. *Expert Rev Anticancer Ther*, 7(10), 1405-1421. doi:10.1586/14737140.7.10.1405.
[33] Sun, X., Xia, J., Jiang, H., et al. (2025). Single-cell and spatial transcriptome profiling identifies cellular heterogeneity and immunosuppressive tumor microenvironment in inflammatory breast cancer. *J Adv Res*. Advance online publication. doi:10.1016/j.jare.2025.05.061.
[34] Zhao, F., Jiang, X., Li, Y., et al. (2025). Characterizing tumor biology and immune microenvironment in high-grade serous ovarian cancer via single-cell RNA sequencing: insights for targeted and personalized immunotherapy strategies. *Front Immunol*, 15, 1500153. doi:10.3389/fimmu.2024.1500153.
[35] Horvath, L., Lang, C., Boettiger, K., et al. (2024). Potential subtype-specific therapeutic approaches in small cell lung cancer. *Curr Opin Oncol*, 36(1), 51-56. doi:10.1097/CCO.0000000000001005.
[36] Song, Q., Wang, Y., & Liu, S. (2024). Subtype-specific transcription factors affect polyamine metabolism and the tumor microenvironment in breast cancer. *Cancer Innov*, 4(1), e138. doi:10.1002/cai2.138.

[37] Feng, M., Matoso, A., Epstein, G., et al. (2024). Identification of lineage-specific transcriptional factor-defined molecular subtypes in small cell bladder cancer. *Eur Urol*, 85(6), 523-526. doi:10.1016/j.eururo.2023.05.023.
[38] Yu, L. C., Wang, C. A., Hu, C. Y., et al. (2024). Preoperative systemic inflammation response index enhances the prognostic value of tumor multifocality in upper tract urothelial carcinoma. *Oncol Lett*, 28(3), 436. doi:10.3892/ol.2024.14569.
[39] Xiao, L., Cao, T., Ou, J., et al. (2022). Clinical characteristics and prognostic analysis of multiple primary malignant neoplasms in female patients with breast cancer or genitalia malignancies. *PeerJ*, 10, e13528. doi:10.7717/peerj.13528.
[40] Worapongpaiboon, R., Siranart, N., Pajareya, P., et al. (2025). Inflammatory markers in predicting survival in pancreatic cancer: A systematic review and meta-analysis. *Pancreatology*, 25(3), 385-395. doi:10.1016/j.pan.2025.02.014.
[41] Strzelec, B., Chmielewski, P. P., & Kielan, W. (2024). Esophageal cancer: current status and new insights from inflammatory markers - a brief review. *Pol Przegl Chir*, 96(3), 83-87. doi:10.5604/01.3001.0054.4523.
[42] Akkala, S., Zuber, M., Atta, J. A., et al. (2025). Socioeconomic status and breast cancer treatment in the United States: Results from a systematic literature review. *Cancer Control*, 32, 10732748251341520. doi:10.1177/10732748251341520.
[43] Hvidberg, L., Wulff, C. N., Pedersen, A. F., et al. (2015). Barriers to healthcare seeking, beliefs about cancer and the role of socio-economic position. A Danish population-based study. *Prev Med*, 71, 107-113. doi:10.1016/j.ypmed.2014.12.007.[1] Siegel, R. L., Kratzer, T. B., Giaquinto, A. N., et al. (2025). Cancer statistics, 2025. *CA Cancer J Clin*, 75(1), 10-45. doi:10.3322/caac.21871.
[2] Barnes, J. M., Johnson, K. J., Osazuwa-Peters, N., et al. (2023). Changes in cancer mortality after Medicaid expansion and the role of stage at diagnosis. *J Natl Cancer Inst*, 115(8), 962-970. doi:10.1093/jnci/djad094.
[3] Nguyen, N. P., Sallah, S., Karlsson, U., et al. (2002). Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. *Cancer*, 94(4), 1131-1141. doi:10.1002/cncr.10257.
[4] Elmqvist, M. A., Jordhøy, M. S., Bjordal, K., et al. (2009). Health-related quality of life during the last three months of life in patients with advanced cancer. *Support Care Cancer*, 17(2), 191-198. doi:10.1007/s00520-008-0477-2.
[5] Sancho-Albero, M., Encinas-Giménez, M., Sebastián, V., et al. (2022). Transfer of photothermal nanoparticles using stem cell derived small extracellular vesicles for in vivo treatment of primary and multinodular tumours. *J Extracell Vesicles*, 11(3), e12193. doi:10.1002/jev2.12193.
[6] Panchal, N. K., & Sabina, E. P. (2020). A serine/threonine protein PIM kinase as a biomarker of cancer and a target for anti-tumor therapy. *Life Sci*, 255, 117866. doi:10.1016/j.lfs.2020.117866.
[7] Brown, G. (2021). Oncogenes, proto-oncogenes, and lineage restriction of cancer stem cells. *Int J Mol Sci*, 22(18), 9667. doi:10.3390/ijms22189667.
[8] Roessler, S., Budhu, A., & Wang, X. W. (2014). Deciphering cancer heterogeneity: the biological space. *Front Cell Dev Biol*, 2, 12. doi:10.3389/fcell.2014.00012.
[9] Pei, L., Liu, Y., Liu, L., et al. (2023). Roles of cancer-associated fibroblasts (CAFs) in anti- PD-1/PD-L1 immunotherapy for solid cancers. *Mol Cancer*, 22(1), 29. doi:10.1186/s12943-023-01731-z.
[10] Roxburgh, C. S., & McMillan, D. C. (2014). Cancer and systemic inflammation: treat the tumour and treat the host. *Br J Cancer*, 110(6), 1409-1412. doi:10.1038/bjc.2014.90.
[11] Xie, W., Xu, Z., Qiu, Y., et al. (2023). A novel nomogram combined the Aggregate Index of Systemic Inflammation and PIRADS score to predict the risk of clinically significant prostate cancer. *Biomed Res Int*, 2023, 9936087. doi:10.1155/2023/9936087.
[12] Wang, H. K., Wei, Q., Yang, Y. L., et al. (2023). Clinical usefulness of the lymphocyte-to-monocyte ratio and aggregate index of systemic inflammation in patients with esophageal cancer: a retrospective cohort study. *Cancer Cell Int*, 23(1), 13. doi:10.1186/s12935-023-02856-3.
[13] Giannetta, E., La Salvia, A., Rizza, L., et al. (2021). Are markers of systemic inflammatory response useful in the management of patients with neuroendocrine neoplasms?. *Front Endocrinol (Lausanne)*, 12, 672499. doi:10.3389/fendo.2021.672499.
[14] Yao, J., Chen, X., Meng, F., et al. (2024). Combined influence of nutritional and inflammatory status and depressive symptoms on mortality among US cancer survivors: Findings from the NHANES. *Brain Behav Immun*, 115, 109-117. doi:10.1016/j.bbi.2023.10.002.
[15] Zhao, T., Zhao, H., Zhang, X., et al. (2024). Combined effects of nutrition, inflammatory status, and sleep quality on mortality in cancer survivors. *BMC Cancer*, 24(1), 1456. doi:10.1186/s12885-024-13181-x.
[16] Yang, Y., Hu, Z., Ye, Y., et al. (2025). Association of aggregate index of systemic inflammation with increased all-cause and cardiovascular mortality in female cancer patients. *Front Oncol*, 15, 1552341. doi:10.3389/fonc.2025.1552341.
[17] Bai, X., Cheng, L., Wang, H., et al. (2025). The aggregate index of systemic inflammation (AISI) and the risk of all-cause, cardiovascular, and cardio-cerebrovascular mortality in congestive heart failure patients: results from NHANES 1999-2018. *Sci Rep*, 15(1), 18282. doi:10.1038/s41598-025-01196-8.
[18] Liu, L., Xiao, Y., Wei, D., et al. (2024). Development and validation of a nomogram for predicting suicide risk and prognostic factors in bladder cancer patients following diagnosis: A population-based retrospective study. *J Affect Disord*, 347, 124-133. doi:10.1016/j.jad.2023.11.086.
[19] Nooh, H. A., Abdellateif, M. S., Refaat, L., et al. (2021). The role of inflammatory indices in the outcome of COVID-19 cancer patients. *Med Oncol*, 39(1), 6. doi:10.1007/s12032-021-01605-8.

[20] Feier, C. V. I., Muntean, C., Faur, A. M., et al. (2024). An exploratory assessment of pre-treatment inflammatory profiles in gastric cancer patients. *Diseases*, 12(4), 78. doi:10.3390/diseases12040078.
[21] Shen, X., Xiang, M., Tang, J., et al. (2024). Evaluation of peripheral blood inflammation indexes as prognostic markers for colorectal cancer metastasis. *Sci Rep*, 14(1), 20489. doi:10.1038/s41598-024-68150-y.
[22] Feier, C. V. I., Muntean, C., Faur, A. M., et al. (2024). An exploratory assessment of pre-treatment inflammatory profiles in gastric cancer patients. *Diseases*, 12(4), 78. doi:10.3390/diseases12040078.
[23] Tian, T. L., Qu, X. K., Zhang, H. B., et al. (2025). Association between advanced lung cancer inflammation index and all-cause and cause-specific mortality among asthma patients: a cohort study. *Front Nutr*, 12, 1519271. doi:10.3389/fnut.2025.151927.
[24] Liu, X., Wang, Y., Huang, Y., et al. (2025). Association between frailty index and mortality in depressed patients: results from NHANES 2005-2018. *Sci Rep*, 15(1), 3305. doi:10.1038/s41598-025-87691-4.
[25] Sever, N., Yıldırım, S., Gurbuz, A. F., et al. (2025). The effect of systemic inflammation and clinicopathologic features on survival in malignant pleural mesothelioma: A multicenter analysis. *Medicina (Kaunas)*, 61(1), 144. doi:10.3390/medicina61010144.
[26] Sánchez-Lázaro, I. J., Almenar-Bonet, L., Reganon-Salvador, E., et al. (2011). Are there differences in acute phase inflammation markers regarding the type of heart failure? *Heart Int*, 6(2), e17. doi:10.4081/hi.2011.e17.
[27] Neamți, L., Drugan, T. C., Drugan, C., et al. (2024). Assessing seasonal variations of biomarkers in inflammatory bowel disease. *Eur J Gastroenterol Hepatol*, 36(8), 993-999. doi:10.1097/MEG.0000000000002795.
[28] Roxburgh, C. S., & McMillan, D. C. (2010). Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*, 6(1), 149-163. doi:10.2217/fon.09.136.
[29] Paik, K. Y., Lee, I. K., Lee, Y. S., et al. (2014). Clinical implications of systemic inflammatory response markers as independent prognostic factors in colorectal cancer patients. *Cancer Res Treat*, 46(1), 65-73. doi:10.4143/crt.2014.46.1.65.
[30] Murphy, J., O'Sullivan, G. C., Lee, G., et al. (2000). The inflammatory response within Dukes' B colorectal cancers: implications for progression of micrometastases and patient survival. *Am J Gastroenterol*, 95(12), 3607-3614. doi:10.1111/j.1572-0241.2000.03377.x.
[31] Anwar, F., Naqvi, S., Shams, S., et al. (2023). Nanomedicines: intervention in inflammatory pathways of cancer. *Inflammopharmacology*, 31(3), 1199-1221. doi:10.1007/s10787-023-01217-w.
[32] Peebles, K. A., Lee, J. M., Mao, J. T., et al. (2007). Inflammation and lung carcinogenesis: applying findings in prevention and treatment. *Expert Rev Anticancer Ther*, 7(10), 1405-1421. doi:10.1586/14737140.7.10.1405.
[33] Sun, X., Xia, J., Jiang, H., et al. (2025). Single-cell and spatial transcriptome profiling identifies cellular heterogeneity and immunosuppressive tumor microenvironment in inflammatory breast cancer. *J Adv Res*. Advance online publication. doi:10.1016/j.jare.2025.05.061.
[34] Zhao, F., Jiang, X., Li, Y., et al. (2025). Characterizing tumor biology and immune microenvironment in high-grade serous ovarian cancer via single-cell RNA sequencing: insights for targeted and personalized immunotherapy strategies. *Front Immunol*, 15, 1500153. doi:10.3389/fimmu.2024.1500153.
[35] Horvath, L., Lang, C., Boettiger, K., et al. (2024). Potential subtype-specific therapeutic approaches in small cell lung cancer. *Curr Opin Oncol*, 36(1), 51-56. doi:10.1097/CCO.0000000000001005.
[36] Song, Q., Wang, Y., & Liu, S. (2024). Subtype-specific transcription factors affect polyamine metabolism and the tumor microenvironment in breast cancer. *Cancer Innov*, 4(1), e138. doi:10.1002/cai2.138.
[37] Feng, M., Matoso, A., Epstein, G., et al. (2024). Identification of lineage-specific transcriptional factor-defined molecular subtypes in small cell bladder cancer. *Eur Urol*, 85(6), 523-526. doi:10.1016/j.eururo.2023.05.023.
[38] Yu, L. C., Wang, C. A., Hu, C. Y., et al. (2024). Preoperative systemic inflammation response index enhances the prognostic value of tumor multifocality in upper tract urothelial carcinoma. *Oncol Lett*, 28(3), 436. doi:10.3892/ol.2024.14569.
[39] Xiao, L., Cao, T., Ou, J., et al. (2022). Clinical characteristics and prognostic analysis of multiple primary malignant neoplasms in female patients with breast cancer or genitalia malignancies. *PeerJ*, 10, e13528. doi:10.7717/peerj.13528.
[40] Worapongpaiboon, R., Siranart, N., Pajareya, P., et al. (2025). Inflammatory markers in predicting survival in pancreatic cancer: A systematic review and meta-analysis. *Pancreatology*, 25(3), 385-395. doi:10.1016/j.pan.2025.02.014.
[41] Strzelec, B., Chmielewski, P. P., & Kielan, W. (2024). Esophageal cancer: current status and new insights from inflammatory markers - a brief review. *Pol Przegl Chir*, 96(3), 83-87. doi:10.5604/01.3001.0054.4523.
[42] Akkala, S., Zuber, M., Atta, J. A., et al. (2025). Socioeconomic status and breast cancer treatment in the United States: Results from a systematic literature review. *Cancer Control*, 32, 10732748251341520. doi:10.1177/10732748251341520.
[43] Hvidberg, L., Wulff, C. N., Pedersen, A. F., et al. (2015). Barriers to healthcare seeking, beliefs about cancer and the role of socio-economic position. A Danish population-based study. *Prev Med*, 71, 107-113. doi:10.1016/j.ypmed.2014.12.007.