Association of systemic inflammatory response index with all-cause and malignant neoplasm mortality in patients with gastrointestinal disease

Peng Wang[1]^, Hongwei Zhu[1], Shuyuan Jiang[1], Xiaolei Liu[1], Bing Gao[1], Wanfu Bai[2], Wei Xie[1], Guo Shao[1,3]

[1]Department of Public Health, International College, Krirk University, Bangkok, Thailand; [2]Department of Pharmacy, Baotou Medical College, Baotou, China; [3]Center for Translational Medicine and Department of Laboratory Medicine, The Third People's Hospital of Longgang District, Shenzhen, China

Contributions: (I) Conception and design: S Jiang; (II) Administrative support: P Wang, G Shao; (III) Provision of study materials or patients: P Wang, H Zhu, S Jiang, X Liu, B Gao, W Bai; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: S Jiang, W Xie, G Shao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guo Shao, PhD. Department of Public Health, International College, Krirk University, No. 3 soi Ramintra 1, Ramintra Road, Anusaowaree, Bangkhen, Bangkok 10220, Thailand; Center for Translational Medicine and Department of Laboratory Medicine, The Third People's Hospital of Longgang District, No. 278 Songbai Road, Henggang Street, Longgang District, Shenzhen 518112, China. Email: shao.guo.china@gmail.com.

Background: Apart from being a primary cause of morbidity and mortality globally, gastrointestinal (GI) disorders also contribute significantly to the cost of healthcare. In patients with GI diseases, the systemic inflammatory response index (SIRI) is not often used as a marker of systemic immune inflammation to assess mortality-associated risk from malignant neoplasms or all causes. Therefore, the objective of this study was to elaborate on the link between SIRI and all causes and malignant neoplasm mortality in patients with GI disorders.

Methods: Retrospective analysis was performed using National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2018. Restricted cubic spline (RCS) plots and multivariate Cox proportional hazards regression were used to examine the relationship between SIRI and GI patient mortality from malignant neoplasms and all causes. Data on survival were shown using Kaplan-Meier (KM) survival curves, and these correlations were further explored by subgroup and interaction analyses. Receiver operating characteristic (ROC) curves were generated to evaluate the specificity and sensitivity of SIRI in predicting mortality among patients with GI diseases.

Results: This study included 4,137 GI patients who were followed comprehensively over 20 years, during which 165 malignant neoplasm mortality and 713 all-cause mortalities were recorded. A nonlinear association between all-cause mortality and SIRI was observed, whereas in GI patients, a linear relationship was identified between SIRI and cancer-related death. The hazard ratio (HR) was 1 at a SIRI level of 1.114, indicating the low-to-high mortality risk change. Participants in the highest quartile (Q4) in the fully adjusted model (model 3) showed a significantly greater likelihood of death from both malignant neoplasms and all-cause relative to those in the lowest quartile (Q1). The mortality HR for malignant neoplasms was 1.74 [95% confidence interval (CI): 1.08–2.82], whereas the HR for all-cause mortality was 2.50 (95% CI: 1.95–3.20). Furthermore, subgroup analysis revealed that higher SIRI was linked with a higher malignant neoplasm mortality risk among male, low-income, smoking, and drinking GI patients. Comparing SIRI to the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), the ROC curve analysis showed that SIRI had better diagnostic effectiveness. Interaction study verified that SIRI is an independent variable that significantly increases the probability of

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^ ORCID: 0009-0005-8528-1044.

death from both all-cause and malignant neoplasms.

Conclusions: The nonlinear positive correlation between the SIRI and the mortality from malignant neoplasms and all-cause in GI patients is highlighted by this study. Elevated SIRI levels were significantly linked to a higher mortality rate from GI disorders, including malignant neoplasms and all-cause. Thus, in GI patients, SIRI can be used as a prognostic marker for mortality and long-term health outcomes prediction.

Keywords: Gastrointestinal (GI); systemic inflammatory response index (SIRI); malignant neoplasm; all-cause; mortality

Introduction

Background

The gastrointestinal (GI) tract is a vital organ system responsible for key physiological functions such as digestion, absorption, and metabolism (1). A broad spectrum of disorders or conditions of the digestive system would affect the GI tract. These disorders constitute a significant cause of the overall healthcare burden worldwide and contribute to a considerable number of morbidity and mortality. The global occurrence and frequency of gastritis and duodenitis in 2019 were 0.38% and 0.52%, respectively, with women experiencing higher rates at 0.42% and 0.57%, respectively (2). In the United States (US), annual GI healthcare expenditures reach $119.6 billion, with over 36.8 million outpatient visits due to GI symptoms. Moreover, research funding for GI-related studies reaches $3.1 billion (3). Annually, GI malignancies are responsible for around 3.4 million fatalities worldwide (4). Furthermore, in 2019, diseases related to the digestive system constituted over 33% of epidemic cases and about one-fifth of acute ailments, underscoring the urgent need to address this public health challenge (5).

Rationale and knowledge gap

Prior research has highlighted a significant correlation between systemic inflammation and the risk of cancer in individuals with GI diseases despite the complexity of the etiology of these conditions (6). Extensive research has been conducted on the systemic inflammatory response index (SIRI) to diagnose rectal cancer and predict complications following gastric cancer surgery (7,8). Therefore, SIRI has become a valuable tool for evaluating the risk of all-cause mortality, specifically from cancer, in patients with GI conditions. This biomarker offers advantages such as ease of sample collection, rapid results, affordability, and high efficiency, and can be readily obtained through routine blood tests. According to recent research, SIRI has a better predictive value than other markers, such as neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) in patients with early pyloric stenosis of gastric cancer undergoing radical resection (9). However, the knowledge regarding the link between SIRI levels and mortality from malignant neoplasms or all-cause in GI patients is scarce. Therefore, the current study was undertaken to explore any possible relationship between SIRI as a systemic inflammatory marker and mortality in GI patients. The objective is to provide clinicians with a reliable and accurate tool for providing novel perspectives on the prognosis of GI patients.

Objective

The present research assessed the relationship between SIRI and all-cause and malignant neoplasm-associated mortality in GI patients using data from a large national sample of patients obtained from the National Health and Nutrition Examination Survey (NHANES; https://www.cdc.gov/nchs/nhanes/) database. The NHANES is a nationally representative cross-sectional survey developed to determine the health and nutritional status of the US population. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.

amegroups.com/article/view/10.21037/tcr-24-1491/rc).

Methods

Study participants and inclusion/exclusion criteria

This research used data from NHANES to conduct a retrospective cohort analysis. The NHANES program has an intricate, multistage, stratified design, with mobile examination centers (MECs) employed for home examinations and interviews. The National Center for Health Statistics (NCHS) oversees data collection and quality control and maintains the NHANES database as a public resource. Data were gathered for this study from 1999 to 2018, including 101,316 individuals. A total of 16,683 records with incomplete GI disease questionnaires were excluded. The data from 77,244 participants without

GI diseases were also excluded. Moreover, 3,248 participants with undisclosed death records under the age of 18 years and 4 records ineligible for follow-up were also excluded. Lastly, the final analysis included 4,137 individuals (*Figure 1*).

Since NHANES is a publicly accessible database including anonymized personal data, no further informed permission or ethical clearance was necessary. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Furthermore, to safeguard the security and privacy of human participants, this study closely adhered to all institutional and data management rules.

Data of GI disease and SIRI

GI disease diagnosis was determined through a questionnaire, including questions such as "Did you have a stomach or intestinal illness with vomiting or diarrhea that started during those 30 days?" (HSQ510), with response options of "yes" or "no". Numerous NHANES studies have made extensive use of this diagnostic method (10,11).

At MECs, blood samples were examined using Beckman Coulter MAXM analyzers (Fullerton, USA), yielding information on each participant's blood cell distribution. Blood sample processing and editing were conducted at NHANES MECs. Using Beckman Coulter's counting and sizing technology—which includes an automated dilution and mixing unit for sample processing and a single-beam photometer for hemoglobin determination—the complete blood count (CBC) parameters were determined. White blood cell (WBC) differentials were assessed using volume-conductivity-scatter (VCS) technology.

The formula was utilized to compute the SIRI: SIRI = (neutrophil count × monocyte count)/lymphocyte count. The study participant was divided into four groups to investigate SIRI levels: Q1 (<0.730), Q2 (0.730 to <1.100), Q3 (1.100 to <1.667), and Q4 (≥1.667).

Acquisition of mortality data

Using the respondent sequence number that NHANES participants were given during their survey, NCHS collected mortality follow-up data (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). For all-cause mortality or deaths from any cause, the ucode_leading code range in the NCHS 2019 Public Use Linked Mortality File Codebook is 001-010. The ucode_leading code for mortality due to malignant diseases is 002.

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┌─────────────────────────┐
│   NHANES [1999–2018]    │
│      (n=101,316)        │
└─────────────────────────┘
            │         ┌──────────────────────────────┐
            │────────▶│ Cases with missing data for  │
            │         │ gastrointestinal diseases    │
            ▼         │ were excluded (n=16,683)     │
┌─────────────────────────┐ └────────────────────────┘
│    Dependent variable   │
│      (n=84,633)         │
└─────────────────────────┘
            │         ┌──────────────────────────────┐
            │────────▶│ Negative gastrointestinal data│
            │         │ were excluded (n=77,244)     │
            ▼         └──────────────────────────────┘
┌─────────────────────────┐
│   Gastrointestinal data │
│      (n=7,389)          │
└─────────────────────────┘
            │         ┌──────────────────────────────┐
            │────────▶│ Excluded:                     │
            │         │ Under age 18 years and not   │
            │         │ available for public release │
            │         │ (n=3,248);                    │
            ▼         │ Ineligible for mortality (n=4)│
┌─────────────────────────┐ └────────────────────────┘
│    Study participants   │
│      (n=4,137)          │
└─────────────────────────┘
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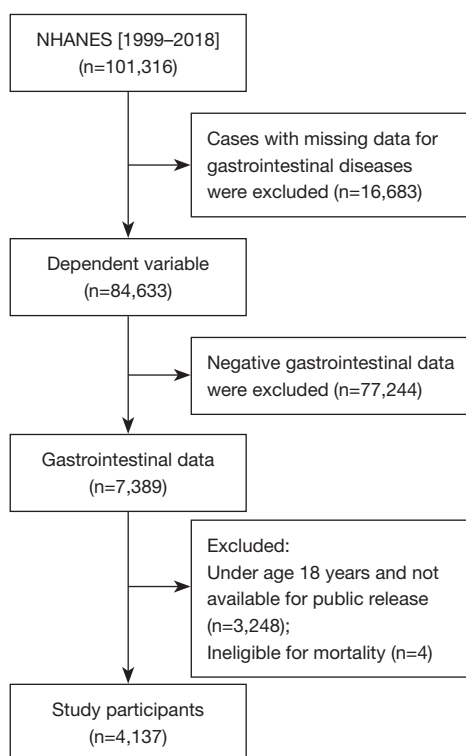
Figure 1 Diagram of the population screening process and inclusion/exclusion criteria. NHANES, National Health and Nutrition Examination Survey.

Selection of covariates

The data on eosinophils (EO), basophils (BASO), red cell distribution width (RDW), total cholesterol (TC), platelets (PLT), high-density lipoprotein (HDL) cholesterol, and WBC were acquired from the laboratory records. Various health-related metrics were obtained from questionnaire data, including blood pressure (BP) (BPQ020), thyroid conditions (MCQ160I, MCD160M, MCQ160M), cancer or malignancy (MCQ220), and heart disease (MCQ160E). Smoking status was derived from SMQ020. Based on the diabetes mellitus (DM) questionnaire, DIQ010 was obtained. Alcohol consumption data were obtained from ALQ100, ALQ101, and ALQ121. Dietary data were used to determine total polyunsaturated fatty acids (TPFA), cholesterol levels, total monounsaturated fatty acids (TMFA), and total saturated fatty acids (TSFA). Moreover, covariates such as ethnicity, gender, age, marital status, household income, in the household, and education level were included to enrich the present analysis.

Statistical analyses

Since the data distribution was skewed, categorical variables were shown as counts and frequencies, while continuous variables were shown as medians with interquartile ranges. To compare categorical data, the Chi-squared test was utilized, and Shapiro-Wilk tests were used for non-normally distributed continuous data to compare baseline characteristics between the two groups. The mean ± standard deviation (SD) was used to represent continuous variables having a normal distribution.

To evaluate the effect of SIRI on survival in patients with GI disorders, hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. After testing the proportional hazards assumption for Cox regression models, models were constructed using Cox regression to assess the correlation between SIRI and survival, accounting for multiple confounders: Model 1 was unadjusted. Model 2 was adjusted for education level, marital status, in the household, household income, and poverty income ratio (PIR). Model 3 incorporated further modifications for the variables in Model 2, along with EO, BASO, TSFA, BP, PLT, HDL, WBC, heart disease, alcohol, and diabetes.

Subgroup analyses were conducted to explore the relationship of SIRI with mortality risk among eight subgroups (in the household, household income, education level, gender, BP, marital status, PIR, alcohol, ethnicity, and smoking status. Moreover, Kaplan-Meier (KM) survival curves were established to assess the survival results of various SIRI groups. To further investigate any possible correlations between these eight subgroups and mortality risk, interaction studies were also performed.

The specificity and sensitivity of SIRI to predict the risk of mortality among patients with GI disorders were evaluated using receiver operating characteristic (ROC) curves. A widely recognized method for investigating potential nonlinear relationships between two variables—restricted cubic spline (RCS) analysis—was utilized. Restricted splines were employed in the Cox regression model to visually represent the possible nonlinear relationship of SIRI with the risk of mortality. To further explain the connection between SIRI and mortality and to establish the threshold level, the threshold analysis was performed. For most covariates, the rate of missing data was <10.0% (BP 0.22%, DM 2.18%, education level 3.94%, household income 4.28%, marital status 4.81%, RDW 4.98%, WBC 5%, PLT 5%, neutrophil count 5.29%,

basophil count 5.29%, eosinophil count 5.29%, monocyte count 5.29%, lymphocyte count 5.29%, smoke 5.68%, HDL 6.14%, TC 6.14%, cancer 6.91%, alcohol 6.94%, heart disease 7.03%, thyroid disease 7.11%, and PIR 7.9%). However, 12.8% of participants had missing dietary data, including TSFA, TMFA, TPFA, and cholesterol. To minimize the sample size reduction caused by missing variables as much as possible, multiple imputation was used. we employed the mice package for addressing missing data via multiple imputation in the R program. Initially, we identified patterns of missing data within our dataset and subsequently utilized the Random Forest method for imputation. This approach utilizes the robust algorithm of mice and the capability of Random Forest to capture complex data relationships, thereby generating multiple complete datasets. This method significantly improves the validity and reliability of our findings.

R program (v.4.3.3) was employed for data analysis. The P values less than 0.05 were considered statistically significant in all two-sided analyses.

Results

Baseline characteristics of the participants

From the 1999–2018 NHANES cohort, 101,316 participants were initially extracted. Following the application of inclusion and exclusion criteria, 4,137 individuals with GI disorders were found to be eligible for the research. *Table 1* presents the baseline characteristics of the participants. In 713 individuals, the condition was shown to have developed over a mean follow-up time of 122 months. Among all-cause deaths, 165 were attributed to malignant tumors. Higher SIRI levels were predominantly observed in women (58.8%), individuals under 60 years old (70.4%), and non-Hispanic Blacks (45.9%). Furthermore, the prevalence of these levels was higher among those with lower incomes and those with more sick family members (64.9% and 85.1%, respectively). The results of education level, TMFA, marital status, TC, TPFA, cholesterol, TSFA, and alcohol consumption were all non-significant.

Hazards model and analysis of KM survival curves

As indicated in *Table 2*, three models were developed to assess the independent role of SIRI and its correlation with all-cause mortality and malignancies. Thorough revisions were conducted to perform adjustments for any potential confounding factors.

No covariates were adjusted in Model 1. PIR, household income, education level, marital status, and the household were adjusted in Model 2. Further adjustments were made for heart disease, alcohol, DM, EO, BASO, TSFA, BP, PLT, HDL, and WBC in Model 3. Greater SIRI levels were linked to a higher mortality risk, according to Cox regression results (Q4 *vs.* Q1). Individuals in the fourth quartile of SIRI had a 2.48-fold higher risk of all-cause death and a 2.08-fold greater death risk from malignant tumors as compared to those in the first quartile.

According to the data shown in *Figure 2*, the KM curve results confirmed these findings. The study showed that among the all-cause death population, individuals exhibiting greater SIRI scores had a significantly decreased survival during the 20-year follow-up in comparison to those with lower SIRI scores (P<0.001). Similarly, among the population that died from malignant neoplasm, higher SIRI scores were associated with a significant decrease in survival during the 20-year follow-up in comparison to those with lower SIRI scores (P=0.002).

Correlation of SIRI with all-cause mortality and malignant neoplasm mortality

RCS regression analysis was conducted to determine the precise association between SIRI and HR (*Figure 3*). SIRI and HR were shown to have a nonlinear correlation (nonlinear P=0.001, P<0.001) when the link between the two variables was examined for all-cause mortality. This suggests that a significant nonlinear relationship exists between SIRI and HR. Thus, to elucidate this correlation, nonlinear models were employed. The value of SIRI equals 1.114 when HR is 1. Within a certain range, an increase in SIRI reduces the risk of all-cause death when it is less than 1.114. However, the risk of all-cause death increases at SIRI >1.114, and the HR for all-cause mortality levels off progressively as SIRI increases further. Conversely, SIRI and HR showed a linear relationship (nonlinear P=0.96) for death from malignant neoplasms. As SIRI increases, HR also increases a trend that persists until SIRI exceeds the threshold of 1.114, where the HR surpasses 1.0.

Subgroup and interaction analysis

Subgroup analyses were conducted in connection to many factors, such as gender, in the household, education level, BP, marital status, PIR, alcohol, ethnicity, and smoking,

Table 1 Baseline characteristics of the 4,137 participants

Variables	Total (n=4,137)	Quartiles of SIRI				P value
		Q1 (n=1,034)	Q2 (n=1,030)	Q3 (n=1,046)	Q4 (n=1,027)	
Gender						<0.001
Female	2,434 (58.8)	680 (65.8)	612 (59.4)	584 (55.8)	558 (54.3)	
Male	1,703 (41.2)	354 (34.2)	418 (40.6)	462 (44.2)	469 (45.7)	
Age (years)						<0.001
Old (≥60)	1,225 (29.6)	248 (24.0)	262 (25.4)	321 (30.7)	394 (38.4)	
Young (<60)	2,912 (70.4)	786 (76.0)	768 (74.6)	725 (69.3)	633 (61.6)	
Ethnicity						<0.001
Mexican American	1,089 (26.3)	265 (25.6)	289 (28.1)	276 (26.4)	259 (25.2)	
Non-Hispanic Black	1,900 (45.9)	341 (33.0)	471 (45.7)	544 (52.0)	544 (53.0)	
Non-Hispanic White	839 (20.3)	342 (33.1)	189 (18.3)	153 (14.6)	155 (15.1)	
Other ethnicity	309 (7.5)	86 (8.3)	81 (7.9)	73 (7.0)	69 (6.7)	
Education level						0.06
High school	1,965 (47.5)	478 (46.2)	518 (50.3)	509 (48.7)	460 (44.8)	
< High school	2,172 (52.5)	556 (53.8)	512 (49.7)	537 (51.3)	567 (55.2)	
Marital status						0.51
No partner	1,825 (44.1)	455 (44.0)	436 (42.3)	466 (44.6)	468 (45.6)	
Partner	2,312 (55.9)	579 (56.0)	594 (57.7)	580 (55.4)	559 (54.4)	
In the household						0.001
More people	3,522 (85.1)	903 (87.3)	897 (87.1)	884 (84.5)	838 (81.6)	
One people	615 (14.9)	131 (12.7)	133 (12.9)	162 (15.5)	189 (18.4)	
Household income						<0.001
High	1,451 (35.1)	383 (37.0)	417 (40.5)	360 (34.4)	291 (28.3)	
Low	2,686 (64.9)	651 (63.0)	613 (59.5)	686 (65.6)	736 (71.7)	
PIR						<0.001
High	1,397 (33.8)	340 (32.9)	402 (39.0)	351 (33.6)	304 (29.6)	
Less	2,740 (66.2)	694 (67.1)	628 (61.0)	695 (66.4)	723 (70.4)	
Cholesterol (mg)	216 (125, 374)	208 (120, 344)	216 (127, 363)	214 (125, 374)	224 (127, 418)	0.06
TSFA (g)	21.7 (13.9, 32.5)	21.2 (13.1, 31.3)	21.3 (14.1, 32.8)	22.1 (14.2, 32.6)	22.3 (14.3, 33.7)	0.052
TMFA (g)	23.9 (15.5, 36.0)	23.6 (14.9, 34.7)	23.7 (15.9, 36.6)	24.3 (15.8, 36.3)	24.0 (15.7, 36.8)	0.34
TPFA (g)	13.9 (8.59, 21.6)	13.6 (8.25, 21.3)	13.7 (8.96, 22.1)	14.1 (8.60, 20.9)	14.0 (8.52, 21.8)	0.68
TC (mg/dL)	189 (162, 218)	189 (162, 218)	191 (165, 220)	191 (160, 218)	186 (161, 216)	0.053
HDL (mg/dL)	49.0 (40.0, 61.0)	51.0 (41.0, 62.0)	49.0 (40.0, 60.0)	47.0 (40.0, 59.0)	49.0 (40.0, 62.0)	<0.001
EO (1,000 cells/μL)	0.20 (0.10, 0.30)	0.10 (0.10, 0.20)	0.20 (0.10, 0.20)	0.20 (0.10, 0.30)	0.20 (0.10, 0.30)	<0.001
BASO (1,000 cells/μL)	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.10 (0.00, 0.10)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=4,137)	Quartiles of SIRI				P value
		Q1 (n=1,034)	Q2 (n=1,030)	Q3 (n=1,046)	Q4 (n=1,027)	
RDW (%)	12.9 (12.3, 13.8)	12.9 (12.3, 13.6)	12.8 (12.2, 13.5)	12.9 (12.3, 13.8)	13.2 (12.5, 14.1)	<0.001
PLT (1,000 cells/µL)	254 (214, 305)	249 (208, 294)	252 (217, 300)	259 (218, 308)	260 (213, 312)	0.001
WBC (1,000 cells/µL)	7.20 (5.90, 8.80)	5.70 (4.90, 6.90)	6.80 (5.80, 8.00)	7.65 (6.60, 8.90)	9.00 (7.70, 10.5)	<0.001
BP						<0.001
Yes	1,626 (39.3)	367 (35.5)	361 (35.0)	431 (41.2)	467 (45.5)	
No	2,511 (60.7)	667 (64.5)	669 (65.0)	615 (58.8)	560 (54.5)	
Thyroid disease						0.04
Yes	507 (12.3)	126 (12.2)	108 (10.5)	123 (11.8)	150 (14.6)	
No	3,630 (87.7)	908 (87.8)	922 (89.5)	923 (88.2)	877 (85.4)	
Heart disease						<0.001
Yes	252 (6.1)	46 (4.4)	48 (4.7)	64 (6.1)	94 (9.2)	
No	3,885 (93.9)	988 (95.6)	982 (95.3)	982 (93.9)	933 (90.8)	
Cancer						<0.001
Yes	474 (11.5)	84 (8.1)	96 (9.3)	138 (13.2)	156 (15.2)	
No	3,663 (88.5)	950 (91.9)	934 (90.7)	908 (86.8)	871 (84.8)	
Smoke						<0.001
Yes	2,087 (50.4)	469 (45.4)	483 (46.9)	548 (52.4)	587 (57.2)	
No	2,050 (49.6)	565 (54.6)	547 (53.1)	498 (47.6)	440 (42.8)	
DM						<0.001
Yes	643 (15.5)	144 (13.9)	130 (12.6)	171 (16.3)	198 (19.3)	
No	3,494 (84.5)	890 (86.1)	900 (87.4)	875 (83.7)	829 (80.7)	
Alcohol						0.14
Yes	2,970 (71.8)	716 (69.2)	760 (73.8)	752 (71.9)	742 (72.2)	
No	1,167 (28.2)	318 (30.8)	270 (26.2)	294 (28.1)	285 (27.8)	
Time (months)	122±69.0	126±66.7	127±66.8	124±69.8	112±71.7	<0.001
All-cause mortality						<0.001
Yes	713 (17.2)	124 (12.0)	141 (13.7)	178 (17.0)	270 (26.3)	
No	3,424 (82.8)	910 (88.0)	889 (86.3)	868 (83.0)	757 (73.7)	
Malignant neoplasm mortality						0.01
Yes	165 (4.0)	31 (3.0)	43 (4.2)	34 (3.3)	57 (5.6)	
No	3,972 (96.0)	1,003 (97.0)	987 (95.8)	1012 (96.7)	970 (94.4)	

The data are presented as median values accompanied by interquartile ranges (in parentheses), or as the percentage (%) of individuals within each group ("Yes" or "No"). SIRI, systemic inflammatory response index; PIR, poverty income ratio; TSFA, total saturated fatty acids; TMFA, total monounsaturated fatty acids; TPFA, total polyunsaturated fatty acids; TC, total cholesterol; HDL, high-density lipoprotein; EO, eosinophils number; BASO, basophils number; RDW, red cell distribution width; PLT, platelet; WBC, white blood cell; BP, blood pressure; DM, diabetes mellitus.

Table 2 Prognostic value of SIRI in mortality using multivariate Cox regression

Model	SIRI continuity		Quartiles of SIRI								P for trend
			Q1 (<0.730)	Q2 (0.730–<1.100)		Q3 (1.100–<1.667)		Q4 (≥1.667)			
	HR (95% CI)	P value	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value		
All-cause mortality											
Model 1	1.30 (1.24–1.36)	<0.001	1 (Ref)	1.14 (0.89–1.45)	0.30	1.45 (1.15–1.82)	0.002	2.48 (2.01–3.07)	<0.001		<0.001
Model 2	1.28 (1.22–1.35)	<0.001	1 (Ref)	1.15 (0.90–1.46)	0.26	1.40 (1.11–1.76)	0.004	2.31 (1.86–2.85)	<0.001		<0.001
Model 3	1.38 (1.29–1.47)	<0.001	1 (Ref)	1.29 (1.01–1.65)	0.04	1.50 (1.18–1.90)	0.001	2.50 (1.95–3.20)	<0.001		<0.001
Malignant neoplasm mortality											
Model 1	1.31 (1.19–1.43)	<0.001	1 (Ref)	1.39 (0.87–2.20)	0.17	1.11 (0.68–1.80)	0.69	2.08 (1.35–3.23)	0.001		0.003
Model 2	1.29 (1.17–1.42)	<0.001	1 (Ref)	1.39 (0.88–2.21)	0.16	1.07 (0.65–1.73)	0.80	1.94 (1.25–3.01)	0.003		<0.001
Model 3	1.35 (1.17–1.54)	<0.001	1 (Ref)	1.39 (0.87–2.22)	0.17	1.00 (0.61–1.66)	0.99	1.74 (1.08–2.82)	0.02		<0.001

Model 1: without covariant; Model 2: adjusted education level, marital status, in the household, household income, PIR; Model 3: adjusted education level, marital status, in the household, household income, PIR, EO, BASO, TSFA, BP, PLT, HDL, WBC, heart disease, alcohol, DM. SIRI, systemic inflammatory response index; HR, hazard ratio; CI, confidence intervals; PIR, poverty income ratio; EO, eosinophils number; BASO, basophils number; TSFA, total saturated fatty acids; BP, blood pressure; PLT, platelet; HDL, high-density lipoprotein; WBC, white blood cell; DM, diabetes mellitus.
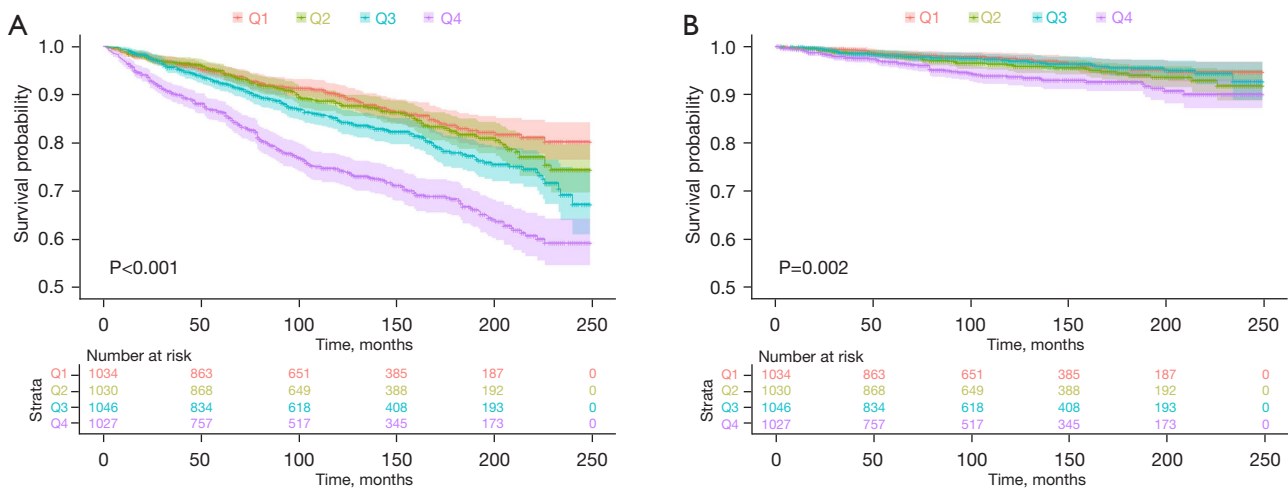

Figure 2 Kaplan-Meier survival curves of SIRI levels: (A) all-cause mortality; (B) malignant neoplasm mortality. SIRI, systemic inflammatory response index.
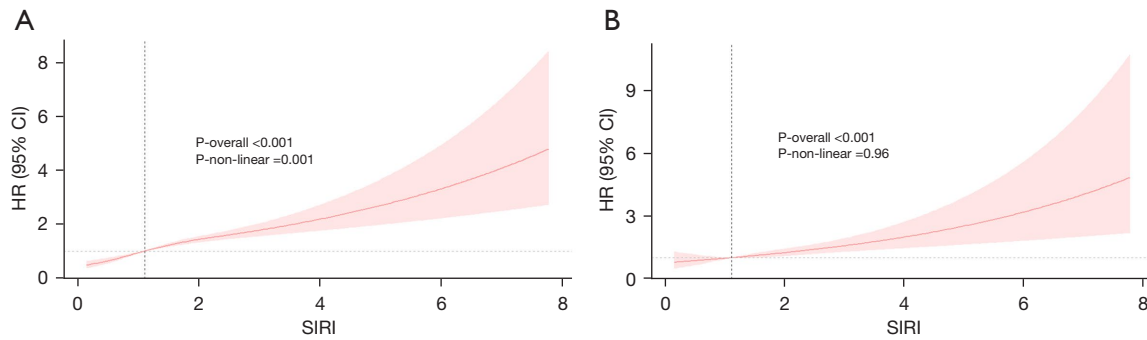
Figure 3 Relationship between all-cause (A) and malignant neoplasm (B) mortality in participants with GI. The red shadow represents their 95% CIs. Nonlinear relationships were observed in (A). HR, hazard ratio; CI, confidence interval; SIRI, systemic inflammatory response index; GI, gastrointestinal.
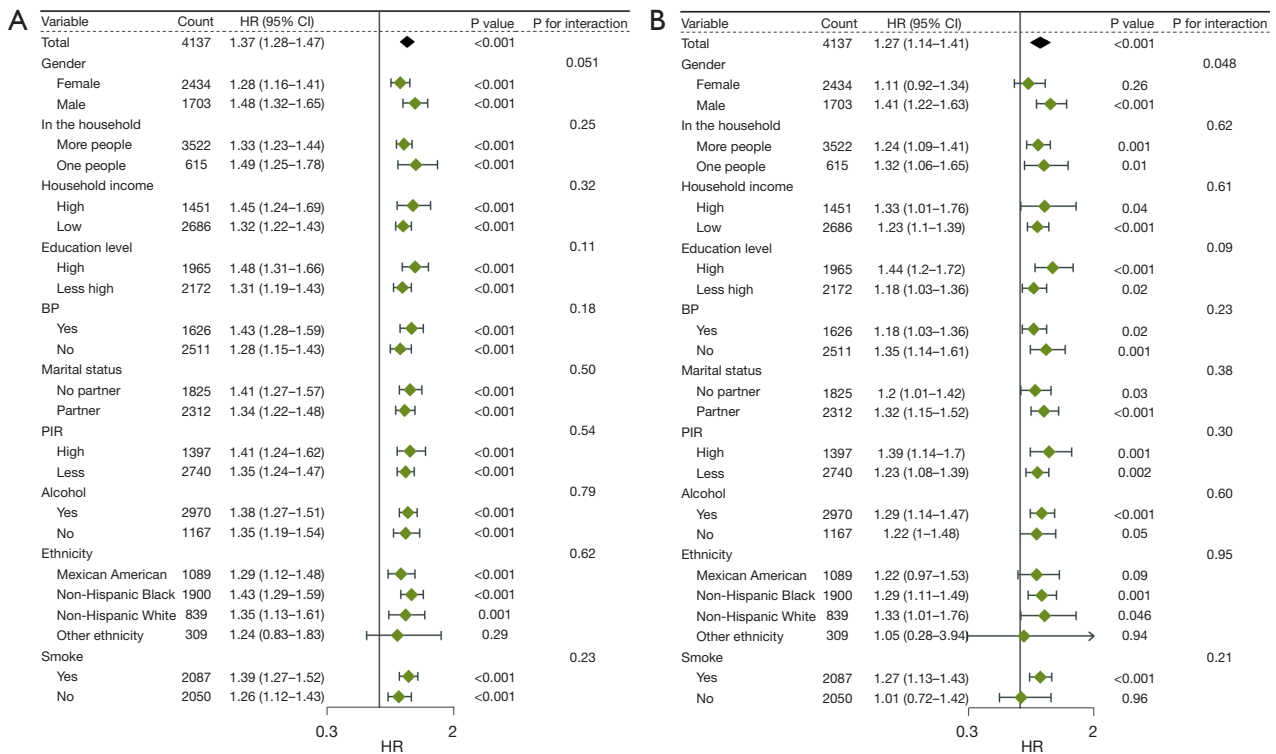

Figure 4 Subgroup analysis of the relationship between SIRI and mortality: (A) all-cause mortality; (B) malignant neoplasm mortality. The adjustments included gender, in the household, household income, education level, BP, marital status, PIR, alcohol, ethnicity, and smoking. SIRI, systemic inflammatory response index; BP, blood pressure; PIR, poverty income ratio; HR, hazard ratio; CI, confidence interval.

to assess the consistency of the link between SIRI and mortality in various subgroups (*Figure 4*). The results demonstrated that in GI patients, SIRI remained an independent risk factor for all-cause mortality. However, heightened SIRI is linked to a higher risk of malignant neoplasm-related mortality in male patients, and these

individuals frequently have drinking and smoking habits. Interaction analysis showed that SIRI did not interact with any of the eight factors (in the household, education level, BP, marital status, PIR, alcohol, ethnicity, and smoking habit) in collectively affecting all-cause mortality or mortality from malignant neoplasm. This suggests that
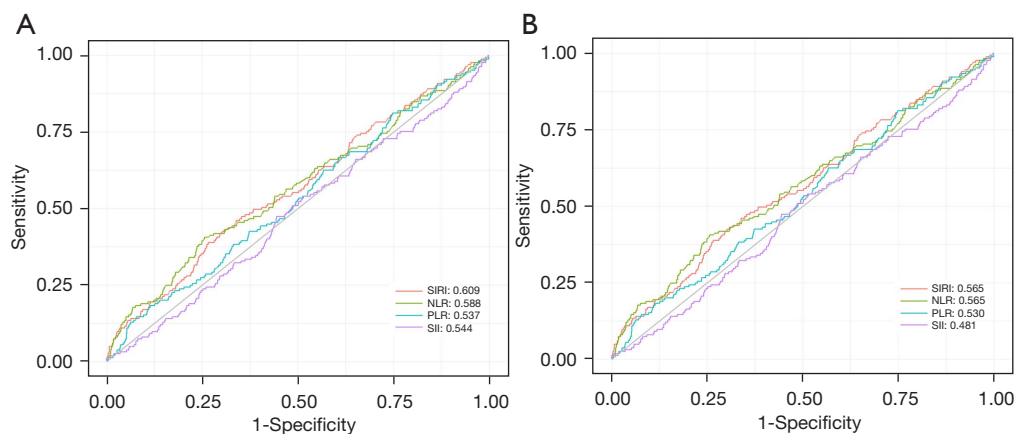
Figure 5 ROC analysis of SIRI, NLR, PLR and SII for mortality in gastrointestinal. (A) All-cause mortality. SIRI: AUC =0.609, 95% CI: 0.586–0.632; PLR: AUC =0.537, 95% CI: 0.512–0.561; NLR: AUC =0.588, 95% CI: 0.564–0.613; SII: AUC =0.544, 95% CI: 0.520–0.568. (B) Malignant neoplasm mortality. SIRI: AUC =0.565, 95% CI: 0.518–0.611; PLR: AUC =0.530, 95% CI: 0.484–0.576; NLR: AUC =0.565, 95% CI: 0.516–0.613; SII: AUC =0.481, 95% CI: 0.436–0.527. SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

the higher risk of both outcomes is caused by SIRI, an independent factor.

Sensitivity and specificity analysis

To assess the sensitivity and specificity of the SIRI as a GI mortality prediction tool, ROC curves were established (*Figure 5*). The area under the curve (AUC) for SIRI was 0.609 (95% CI: 0.586–0.632), indicating that it may be used to predict all-cause mortality. Similarly, 0.565 (95% CI: 0.518–0.611) was the AUC for SIRI's prognostic ability in malignant neoplasm mortality. However, SIRI performed better than the NLR, platelet-to-lymphocyte ratio (PLR), and SII in terms of prognostic value for both all-cause and malignant neoplasm mortality in GI patients.

Discussion

Key findings

Accounting for almost a quarter of all cancer cases and one-third of all cancer-associated fatalities globally, GI malignancies are a leading source of both mortality and morbidity (12). Tumors in the rectum, colon, pancreas, stomach, and liver are the most common types of these malignancies. According to global cancer statistics, gastric cancer (GC) ranks fifth, and colorectal cancer is the second

most prevalent cause of cancer-related mortality worldwide. Public health has been substantially impacted by the high mortality rates linked to these GI cancers (13). Moreover, the incidence of colorectal, pancreatic, and gallbladder cancer is rising among younger populations. This study found that a significant percentage of individuals with GI disorders were under 60 years old. Modifiable risk factors for GI cancer commonly include smoking, alcohol usage, dietary choices, a sedentary lifestyle, obesity, and metabolic disorders. Therefore, it is essential to mitigate the impact of GI cancer by promoting healthy lifestyles that target these risk factors (14).

Strengths and limitations

There are several significant strengths in this study. First, a sizable sample of 4,137 individuals with complete clinical data and survival information was assessed. Second, a threshold for SIRI levels was linked to a lower risk of both all-cause and malignant neoplasm mortality in GI patients. However, there are significant limitations in the present research. The first drawback of this study is its cross-sectional design with the absence of dynamic follow-up data, which can provide various insights over time. Furthermore, the NCHS' survival data are restricted to 2019 and before, making it unable to get more current follow-up data. Lastly, some statistical uncertainty may

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be introduced by the 4,137 individuals' comparatively low percentage of fatalities attributable to cancer. Larger cohort studies are thus required to support and corroborate these results in the future.

Comparison with similar researches

The link between inflammation and cancer is well-established, and chronic inflammation is considered an important risk factor for various malignancies, including GC. Chronic gastritis, frequently triggered by *Helicobacter pylori* infection, advances to atrophic gastritis, intestinal metaplasia, and ultimately, GC (15). The risk of colitis-associated colorectal cancer steadily increases with the duration and severity of colitis (16). Tumor-associated inflammation has been recognized as a hallmark of cancer development. Systemic inflammatory reactions have been shown in clinical research to be predictive of a poor prognosis in patients with a variety of malignancies, including gastric cancer (17,18). Growing data in recent years have demonstrated that immunological responses and host inflammation are key factors in the progression of cancer and the response of the disease to therapy (19). One of the primary agents of the innate immune response, neutrophils perform a multitude of immunological-related tasks, including phagocytosis, degranulation, formation of reactive oxygen species (ROS), and the generation of neutrophil extracellular traps (NETs) (20,21). NETs—altered by histones and neutrophil granules—were first explained as a way for neutrophils to capture and eliminate infections (22). According to recent research, NETs have a role in the development and spread of GI malignancies, such as pancreatic, liver, colon, and stomach cancers (23). Neutrophils are an important type of infiltrating immune cell in the tumor microenvironment (24). The biological characteristics of various cancers are intimately linked to NETs. When NETs break down into soluble nucleosomes, granulocyte proteins and pieces of DNA are released into the peripheral blood circulation. The formation of NETs has been observed in the tissue microenvironment and peripheral blood of gastric cancer patients. The number of NETs and neutrophil accumulation gradually decreases from tumor tissue to peritumoral tissue. Moreover, NETs have outperformed carbohydrate antigens 19-9 and carcinoembryonic antigens in the diagnostic value of gastric cancer (25). There is a significant correlation between NET levels in peripheral blood and neutrophil counts and the NLR. According to clinical research, NETs are more prevalent in metastatic lesions and invade the primary GI cancer tissues (26). There is a correlation between the number of NETs in peripheral blood and the advancement of the clinical tumor stage. Neutrophils undergo nuclear deformation, chromatin loosening, nuclear and granule membrane separation, and release NETs into the extracellular compartment when appropriately stimulated. However, nucleated neutrophils, despite producing NETs, preserve their intact cell membranes and continue to exhibit physiological traits such as phagocytosis (27).

Explanations of findings

Based on this knowledge, several parameters in blood tests have been explored as biomarkers for the survival of cancer patients, such as the NLR (28), PLR (29), and SII (30). Clinicians have recently shown significant interest in a novel biomarker called the SIRI. SIRI is a novel inflammatory marker derived from neutrophil, monocyte, and lymphocyte counts (31,32). Moreover, various research studies show that comprehensive inflammation scores uncover more profound and intricate associations between these indicators and cancer outcomes (33,34). A strong correlation between SIRI levels and the probability of mortality from both malignant neoplasms and all-cause in individuals with GI disorders was identified in this nationwide survey. Higher SIRI levels were linked to a higher chance of all-cause and malignant neoplasm mortality. These results provide compelling evidence in favor of the notion that SIRI is important in predicting mortality rates for this group of patients. The nonlinear positive relationship between the inflammatory biomarker SIRI and the malignant neoplasms and all causes of mortality in individuals with GI disorders was further explored in this study. This association was more pronounced in female individuals younger than 60 years. Furthermore, a critical SIRI threshold of 1.114 was also identified, at which patients with GI disorders had a significantly higher chance of death. The reliability and utility of SIRI in clinical applications can be further affirmed through large-scale, multi-center trials encompassing various GI diseases, long-term patient follow-ups, and evaluations of SIRI's association with prognosis and treatment outcomes. This may provide greater application prospects for SIRI.

Implications and actions needed

Factors that affect mortality in patients with GI diseases

include smoke, alcohol, education level, income, and lifestyle choices (35). For instance, in European individuals, weekly alcohol intake has been causally related to an estimated 56.5% higher risk of colorectal cancer (36). Promoting physical activity and reducing sedentary behavior are also important strategies for preventing various upper and lower GI diseases, as well as hepatobiliary and pancreatic disorders (37). Three Cox proportional hazard models were used to account for various confounding factors and establish the association between high SIRI levels and mortality risk to reduce the impact of these variables. According to the present research, higher SIRI continued to be an independent risk factor for both all-cause and malignant neoplasm mortality in patients with GI disorders, regardless of adjusting for these confounders. Subgroup analysis further demonstrated that elevated SIRI was independently linked with higher risks of both all-cause and malignant neoplasm mortality. Moreover, SIRI's potential as a reliable prognostic marker was highlighted by its higher predictive capacity on the ROC curve in comparison to PLR, NLR, and SII. The RCS analysis was used to further elaborate the correlation between HR and SIRI (*Figure 3*). According to the present research, there is a nonlinear relationship between SIRI and the risk of malignant neoplasm in GI disorders. Patients with SIRI levels higher than 1.114 had a significantly greater probability of dying from malignant neoplasms.

Conclusions

The present research emphasized the nonlinear positive correlation between the SIRI and all-cause and malignant neoplasm mortality in individuals with GI conditions. The results of the current study showed that higher levels of SIRI are strongly associated with a higher risk of mortality from both GI disorders and malignant neoplasms. SIRI was proved to be a valuable predictor of long-term health outcomes and mortality in GI populations.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1491/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1491/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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