

Systemic Inflammation Response Index (SIRI) as a Novel Predictor for All-Cause Mortality in Patients with Inflammatory Bowel Disease

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Abstract

Background

The global public health burden of inflammatory bowel disease (IBD) is rising steadily. The systemic inflammation response index (SIRI), as a promising indicator reflecting systemic inflammatory status, has unknown predictive value for mortality in IBD patients. This study evaluated SIRI's predictive capability for all-cause mortality in patients with IBD based on UK Biobank data.

Methods

Using UK Biobank data, we included 7,060 inflammatory bowel disease participants. SIRI was calculated based on baseline monocyte, neutrophil and lymphocyte counts. Associations and mechanistic pathways were explored via Cox regression, restricted cubic splines, and mediation analyses, after comprehensive covariates adjustment.

Results

After comprehensive covariate adjustment, elevated SIRI per unit was independently linked to a 5.4% increase in mortality hazard (HR = 1.054, 95% CI: 1.037–1.071). The highest SIRI quartile was associated with a 1.9-fold greater mortality hazard compared with the lowest SIRI quartile. A nonlinear relationship existed ($P < 0.001$), with risk rising sharply above SIRI 1.24. Handgrip strength, Red blood cell distribution width, and C-reactive protein served as partial mediators underlying this association.

Conclusion

Elevated systemic inflammation response index is independently linked to higher all-cause mortality in IBD patients in a non-linear manner. Derived from simple routine blood index, SIRI may help identify high-risk patients and guide clinical management.

Background

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are defined as long-term and recurrent gastrointestinal inflammatory illnesses¹. In recent years, its global incidence and prevalence have continued to increase, imposing a heavy burden on societies and healthcare systems worldwide^{2,3}. Beyond intestinal manifestations, IBDs are characterized by a pathophysiological cascade involving systemic inflammation^{4–6} triggered by persistent gut inflammation, such as cardiovascular events, malignancies, and thromboembolic complications, which contribute considerably to the excess mortality observed in IBD populations^{7–9}. Finding a reliable

prognostic indicator that predict all-cause mortality of IBD patients is critical to establishing standardized and effective clinical treatment to prevent fatal complications and potentially improve long-term prognosis¹⁰.

As an emerging inflammatory biomarker, the systemic inflammation response index (SIRI) can be applied to evaluate the overall inflammatory condition^{11–13}. Initially applied in pancreatic cancer prognosis, SIRI has been proven to predict poor survival and elevated mortality risk across multiple malignant and non-malignant critical diseases^{14–19}. Given that existing studies have identified SIRI as a standalone biomarker capable of predicting all-cause mortality and tumor-related death in other gastrointestinal diseases (including digestive system tumors)²⁰, we speculate that SIRI can also predict mortality risk in IBD patients. Though SIRI has been proven to be an effective indicator for evaluating the activity and severity of IBD²¹, studies directly linking SIRI to all-cause mortality of IBD patients are still very limited.

The present research intends to fill this gap in previous studies by evaluating how SIRI relates to overall mortality among IBD patients. Using data from UK Biobank (UKB), this study seeks to determine whether SIRI is able to be a novel, robust biomarker to predict mortality in IBD patients. Additionally, it may reveal biological mechanisms responsible for the relationship between systemic inflammation and adverse outcomes.

Methods

Study participants

We enrolled all study individuals from the UK Biobank, a large population-based cohort database. From 2006 to 2010, this project recruited more than 500,000 individuals aged 40–69 years at 22 research assessment centers spanning England, Wales, and Scotland. At recruitment, detailed information regarding sociodemographic, lifestyle, environmental, and health-related factors was collected from participants via screen questionnaires and face-to-face interviews. Concurrently, all individuals underwent physical examinations and provided biological specimens²². Of the 502,002 participants enrolled between 2006 and 2010, we included participants meeting the definition of IBD at baseline ($n = 7,948$). We first excluded individuals with missing SIRI or core demographic data ($n = 27$), leaving 7,921 subjects. We further excluded participants who died within the first year following recruitment²³, yielding a final analytical cohort of 7,060 patients.

Assessment of SIRI and IBD

Using blood test data from the UK Biobank, SIRI was calculated at baseline as neutrophil $\times$ monocyte / lymphocyte count⁶. Consistent with previous studies²⁴, IBD cases were identified by integrating self-

reported information, primary healthcare records, and hospitalization datasets using the 10th revision of the International Statistical Classification of Diseases (ICD-10, codes K50 and K51).

Assessment of outcome

Assessment of outcome

We examined all-cause mortality among participants. All UK Biobank volunteers signed informed consent allowing researchers to access national death registry data. Record linkage with the NHS Information Centre (covering England and Wales) and the NHS Central Register for Scotland enabled comprehensive retrieval of mortality data, including exact death dates and causes of death. The censoring date differed across regions: participants from England and Wales were censored on September 30, 2021, whereas the censoring endpoint for Scottish enrollees was set as October 31, 2021²⁵.

Assessment of covariates

The following covariates were included in our analysis: age, sex (female or male); Townsend deprivation index (TDI), where elevated values denote higher levels of socioeconomic deprivation; education (college degree or not); ethnicity (white or non-white); BMI (continuous); smoking habits (never, ever or current smoker); physical activity (met/week); and usage of medication (any use vs. no use of aspirin, ibuprofen, or laxatives). Handgrip strength, C-reactive protein (CRP), and red blood cell distribution width (RDW) were selected as mediators. Missing values were processed via multiple imputation to minimize statistical bias.

Statistical analysis

We used multivariate Cox proportional hazards regression to obtain hazard ratios (HRs) and 95% confidence intervals (CIs), where SIRI was modeled both continuously and as quartile-defined subgroups. A total of three regression models with hierarchical covariate adjustments were developed. Model 1 included no covariates. Age and sex were adjusted in Model 2, while Model 3 made further adjustments for ethnicity, BMI, TDI, education, physical activity, usage of medication, and smoking habits. We performed Schoenfeld residual diagnostics to test the proportional hazards assumption. No statistically significant violations were detected across all regression models (all $P > 0.05$).

The mediating effects of Handgrip strength, CRP, and RDW were examined via causal mediation analysis. Handgrip strength reflects physical function and systemic reserve, which may capture the pathway of muscle depletion and frailty. RDW and CRP reflect systemic inflammation and subclinical hematological changes linked to IBD activity^{26–31}, all of which may participate in the inflammatory cascade linking SIRI to mortality.

To test the correlation between SIRS changes and mortality risk across various populations, we conducted subgroup analysis according to age, gender, ethnicity, smoking status, physical activity, BMI, TDI and medication use. All models were adjusted according to Model 3. Restricted cubic spline (RCS) regression was adopted to quantify the nonlinear relationship of SIRS to all-cause mortality in patients confirmed with IBD.

We performed sensitivity analyses among participants with complete data, to test the robustness of our main findings.

Results

Baseline characteristics

Baseline characteristics of participants are presented in Table 1. We categorized participants by SIRS quartiles. Those with higher SIRS had a greater likelihood of being male and smokers. Participants with lower SIRS tended to have a more negative TDI and higher activity level. As SIRS increased, the proportion of participants with a college degree increased.

Table 1. Baseline characteristics of study participants by Systemic Inflammation Response Index quartiles

Characteristics	Q1 (Lowest)	Q2	Q3	Q4 (Highest)
n	1,765	1,765	1,765	1,765
SIRI	0.60 (0.48–0.70)	0.95 (0.87–1.14)	1.46 (1.34–1.59)	2.36 (1.95–2.97)
Age, years	58.0 (51.00–63.0)	59.0 (51.00–64.0)	59.0 (51.00–64.0)	60.0 (51.00–64.0)
Female, n (%)	1,193 (67.6)	974 (55.2)	798 (45.2)	592 (33.5)
White ethnicity, n (%)	1,617 (91.6)	1,685 (95.5)	1,701 (96.4)	1,697 (96.1)
BMI, kg/m ²	26.4 (23.8–29.5)	26.9 (24.3–29.9)	27.0 (24.4–30.0)	27.0 (24.3–30.2)
Townsend deprivation index	-2.06 (-3.60–0.75)	-1.96 (-3.63–0.83)	-1.93 (-3.49–0.76)	-1.81 (-3.38–1.13)
College degree, n (%)	424 (24.0)	462 (26.2)	486 (27.5)	476 (27.0)
Smoker, n (%)	779 (44.1)	880 (49.9)	885 (50.1)	959 (54.3)
Physical activity, MET/week	1860 (819–3732)	1777 (695–3786)	1670 (714–3546)	1572 (617–3399)
Neutrophil count, ×10 ⁹ /L	3.35 (2.71–3.96)	4.08 (3.50–4.80)	4.70 (4.04–5.50)	5.76 (4.75–6.87)
Monocyte count, ×10 ⁹ /L	0.34 (0.30–0.41)	0.44 (0.39–0.52)	0.50 (0.43–0.60)	0.60 (0.50–0.73)
Lymphocyte count, ×10 ⁹ /L	2.00 (1.60–2.40)	1.90 (1.52–2.30)	1.75 (1.40–2.20)	1.50 (1.10–1.90)
Medication use, n (%)	483 (27.4)	465 (26.3)	515 (29.2)	534 (30.3)
Handgrip strength, Kg	28.0 (19.5–38.0)	28.0 (19.0–38.0)	28.0 (21.0–38.0)	28.0 (21.0–38.0)
CRP, mg/L	1.75 (0.89–3.69)	1.63 (0.83–3.34)	1.70 (0.89–3.76)	1.89 (0.96–3.75)
RDW, %	13.6 (13.1–14.2)	13.6 (13.1–14.1)	13.6 (13.1–14.2)	13.6 (13.0–14.2)
Survival time, years	12.5 (6.4–19.1)	12.1 (6.1–19.0)	11.9 (6.0–19.0)	12.3 (6.3–19.0)

† Continuous variables are presented as mean ± SD or median (IQR); categorical variables are presented as n (%).

‡ SIRI, Systemic Inflammation Response Index; n, number of participants; kg/m², kilogram per square metre; BMI, body mass index; MET, metabolic equivalent of task; CRP, C-reactive protein; RDW, red blood cell distribution width.

Association between SIRI and all-cause mortality

Correlations between SIRI and all-cause mortality risk in IBD cohorts were quantified via Cox proportional hazards models. As presented in Table 2, elevated mortality risk was observed in each incremental rise in SIRI values. For the unadjusted model, the hazard ratio (HR) stood at 1.062 (95% CI 1.046-1.079, $P < 0.001$). Such positive association retained statistical significance in Model 2: HR = 1.044 (95% CI: 1.027-1.061, $P < 0.001$) and fully adjusted Model 3: HR = 1.054 (95% CI: 1.037-1.071, $P < 0.001$). Compared with individuals with the lowest SIRI, those falling into the top quartile presented the highest HR (HR = 1.768, 95% CI: 1.475-2.118 and HR = 1.910, 95% CI: 1.604-2.275 in Model 2 and 3, respectively).

Table 2. Association between systemic inflammation response index and all-cause mortality in Cox proportional hazards models

SIRI	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Per 1-unit increase	1.062 (1.046–1.079) ***	1.044 (1.027–1.061) ***	1.054 (1.037–1.071) ***
Q1 (Lowest)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.330 (1.099–1.609) **	1.202 (0.992–1.457)	1.272 (1.051–1.541) **
Q3	1.476 (1.226–1.778) ***	1.343 (1.111–1.622) **	1.373 (1.139–1.655) ***
Q4 (Highest)	2.071 (1.741–2.462) ***	1.768 (1.475–2.118) ***	1.910 (1.604–2.275) ***
P for trend	< 0.001	< 0.001	< 0.001

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

† HR, hazard ratio; CI, confidence interval. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, ethnicity, BMI, Townsend deprivation index, education, physical activity, smoking status, aspirin use, ibuprofen use, and laxative use.

Subgroup analysis

A further analysis was conducted on various subgroups including gender, age, ethnicity, BMI, smoking status, education, TDI, and medication use, to examine the prognostic link between SIRI and all-cause mortality (Table 3). Higher SIRI values predicted increased death risk throughout all subgroups, with significant interactions observed across gender, age, medication, and educational subgroups.

Table 3. Subgroup analysis of SIRI and all-cause mortality

Subgroup	n	HR (95% CI)	P for interaction
Sex			< 0.001
Female	3,557	1.29 (1.18–1.40)***	
Male	3,503	1.06 (1.03–1.09)***	
Age			0.046
≤59 years	3,720	1.16 (1.08–1.24)*	
>59 years	3,340	1.07 (1.04–1.09)*	
Ethnicity			0.179
White	6,700	1.08 (1.06–1.10)	
Non-White	360	1.39 (0.94–2.06)	
BMI			0.090
≤27 kg/m ²	3,532	1.13 (1.06–1.21)	
>27 kg/m ²	3,528	1.07 (1.05–1.10)	
Education			< 0.001
No college degree	5,207	1.20 (1.14–1.26)***	
College degree	1,853	1.06 (1.03–1.09)***	
TDI			0.006
> -1.94	3,530	1.07 (1.04–1.10)**	
≤ -1.94	3,530	1.18 (1.11–1.25)**	
Medication			0.004
No	5,055	1.16 (1.10–1.22)**	
Yes	2,005	1.06 (1.03–1.09)**	
Smoking			0.063
Never	3,603	1.14 (1.07–1.21)	
Former	3,457	1.07 (1.04–1.10)	

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

† All models are adjusted for covariates in Model 3 (age, sex, ethnicity, BMI, Townsend deprivation index, education, physical activity, smoking status, aspirin use, ibuprofen use, and laxative use); BMI = body mass index.

Kaplan-Meier survival analysis

Kaplan-Meier survival curves, stratified by SIRI quartiles, showed a clear dose-response pattern, with higher SIRI levels consistently linked to worse survival outcomes. Specifically, participants within the top quartile (Q4) exhibited the poorest survival outcome, whereas individuals from the bottom quartile (Q1) had the optimal survival outcome (Figure 1).

Non-linear relationship between SIRI and mortality

Restricted cubic spline (RCS) regression was implemented under the Cox regression framework to explore the nonlinear association between SIRI and the risk of all-cause mortality. Marked nonlinear associations were identified, with the P value less than 0.001. When SIRI was < 1.24, HR was below 1, indicating a reduced mortality risk; beyond SIRI = 1.24, the HR increased continuously with rising SIRI (Figure 2).

Mediation analysis

R software package mediation was applied to carry out causal mediation analysis, in which SIRI was included as an independent variable, death as a dependent variable. Handgrip strength, RDW, and CRP served as mediators in Model A, B and C, respectively. Gender, TDI, BMI, age, ethnicity, education, smoking status, and physical activity were set as covariates (Figure 3).

In Model A (mediator: Handgrip strength), SIRI was negatively correlated with Handgrip strength ($\beta = -0.271$, SE = 0.080). Higher Handgrip strength was linked to reduced mortality risk (OR = 0.972, 95%CI: 0.962–0.982), and the direct effect of SIRI on mortality remained robust (OR = 1.184, 95%CI: 1.106–1.266). The mediation effect of Handgrip strength was significant (ACME = 0.002, P = 0.004), indicating a partial mediating role.

In Model B (mediator: RDW), elevated SIRI was independently associated with higher all-cause mortality (OR = 1.149, 95%CI: 1.073–1.228). For the mediation pathway, SIRI positively predicted RDW ($\beta = 0.167$, SE = 0.013), and elevated RDW was significantly correlated with greater mortality odds (OR = 1.258, 95%CI: 1.185–1.335). A statistically significant average causal mediation effect (ACME = 0.004, P < 0.001) verified that RDW partially mediated the association between elevated SIRI and increased mortality risk.

For Model C with CRP as the mediator, SIRI significantly upregulated CRP levels ($\beta = 0.882$, SE = 0.059). Both the direct effect of SIRI on all-cause mortality (OR = 1.177, 95%CI: 1.097–1.261) and the effect of CRP on mortality (OR = 1.015, 95%CI: 1.002–1.027) reached statistical significance. The significant average causal mediation effect (ACME = 0.001, P < 0.001) demonstrated that CRP also served as a partial mediator in the relationship between SIRI and all-cause mortality.

Discussion

Based on prospective cohort data, this study assessed the ability of SIRI to predict mortality in IBD patients. Elevated SIRI was independently predictive of higher mortality risk, and a nonlinear correlation was validated by RCS analysis. Notably, the risk threshold was identified at a SIRI value of 1.24. Below this cutoff, the mortality risk remained relatively low, while it increased steadily as SIRI rose above this level. The potential biological mechanisms underlying the association between SIRI and mortality were further clarified using mediation analyses. We found that Handgrip strength, RDW and CRP partially mediated this relationship, which suggest that SIRI may influence prognosis at least partly through systemic inflammation and dysregulation of erythrocyte homeostasis. Importantly, results were consistent in different adjusted models and complete-case sensitivity analysis, supporting the stability of our core conclusions.

Neutrophils serve as key sentinel cells in the innate immune response³². In active inflammatory bowel disease (IBD), they are rapidly recruited to sites of intestinal inflammation, where they subsequently produce reactive oxygen species, neutrophil extracellular traps and proteases. While these mechanisms help eliminate pathogens, they also cause collateral tissue damage and help perpetuate a vicious cycle of chronic inflammation³³. Similarly, monocytes and their differentiated macrophages show marked infiltration into inflamed intestinal tissue in IBD³⁴. Among them, M1-type macrophages secrete pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). These cytokines drive Th1 and Th17 immune responses, further exacerbating mucosal damage³⁵. In contrast, lymphocytes—particularly regulatory T cells (Tregs)—act as important negative regulators of excessive intestinal inflammation by producing anti-inflammatory cytokines including IL-10 and transforming growth factor- β (TGF- β)³⁶. Accordingly, a SIRI value below 1.24 may reflect a relatively balanced immune state, with relatively low proinflammatory neutrophil and monocyte activation and relatively sufficient anti-inflammatory function, thereby mitigating intestinal inflammation and improving prognosis.

The association between SIRI and mortality may be driven by pathological pathways such as neutrophil-mediated tissue damage and monocyte-driven immune dysregulation³⁷, whereas CRP likely acts as a downstream effector marker of this inflammatory cascade³⁸. RDW exhibited a prominent mediating role. Chronic inflammation upregulates hepcidin via STAT3, causing functional iron deficiency and suppressed erythropoiesis³⁹. Additionally, malabsorption and blood loss in IBD lead to nutritional deficiencies (iron, folate, B₁₂)⁴⁰. Oxidative stress depletes erythrocyte antioxidant reserves, accelerating turnover of aged cells and release of immature reticulocytes⁴¹. This “ineffective hematopoiesis-oxidative injury-inflammation” loop may link elevated SIRI to poor prognosis.

Several limitations are acknowledged within the current analysis. Primarily, SIRI testing was restricted to the baseline, making it impossible to evaluate its long-term predictive ability for mortality. Second, although we adjusted for extensive confounding variables in the analysis, unmeasured indicators (e.g., intestinal disease activity, treatment compliance, and daily diet) may contribute to residual confounding bias. Third, our sample primarily consisted of White adult subjects, restricting the capacity to generalize

these outcomes to children or people with distinct ethnic identities. Future research should explore SIRI's time-dependent associations with prognosis and additional potential mediating pathways (e.g., gut microbiome, genetic susceptibility, epigenetic modifications), and evaluate whether SIRI-stratified anti-inflammatory intervention strategies improve long-term survival outcomes in IBD patients.

Conclusions

In this large prospective cohort study of IBD patients, elevated SIRI was independently associated with an increased risk of all-cause mortality, exhibiting a non-linear relationship with a threshold at 1.24. CRP and RDW partially mediated this association, with RDW contributing the largest proportion. Overall, these findings indicate that SIRI could serve as a practical and useful biomarker for risk stratification in patients with IBD.

Abbreviations

IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
SIRI	Systemic inflammation response index
UKB	UK Biobank
HR	Hazard ratio
CI	Confidence interval
OR	Odds ratio
TDI	Townsend deprivation index
BMI	Body mass index
CRP	C-reactive protein
RDW	Red blood cell distribution width
RCS	Restricted cubic spline
ACME	Average causal mediation effect
SE	Standard error
SD	Standard deviation
IQR	Interquartile range
MET	Metabolic equivalent of task
ICD-10	International Classification of Diseases, 10th revision
NHS	National Health Service
TNF-α	Tumor necrosis factor- α
IL-1β	Interleukin-1 β
IL-6	Interleukin-6
IL-10	Interleukin-10
TGF-β	Transforming growth factor- β
Th1	T helper type 1 cell
Th17	T helper type 17 cell
Tregs	Regulatory T cells
STAT3	Signal transducer and activator of transcription 3

Declarations

Ethics approval and consent to participate

UK Biobank was approved by the Northwest Multi-center Research Ethics Committee; participants provided written informed consent. This secondary analysis was conducted under UK Biobank Application Number 139541. All data collection and research use is in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

Data are not publicly available but can be requested via the UK Biobank application portal (<https://www.ukbiobank.ac.uk/researchers/>), subject to project approval.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Zifan Zhang and Rui Sun conceived the study, performed data extraction, completed the statistical analysis, interpreted the results, and drafted the original manuscript.

Yanpo Li provided critical intellectual guidance, supervised data analysis, and revised the manuscript.

Fan Wang participated in data cleaning, literature collection and manuscript revision.

Kangni Chen, Yupeng Chen, Jiayong Chen and Ruihao Zhang assisted with literature retrieval, data interpretation and manuscript polishing.

Yexi Chen and Zhiyang Li designed the research framework, supervised the whole project, critically reviewed and revised the manuscript.

All authors read and approved the final manuscript.

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Figures

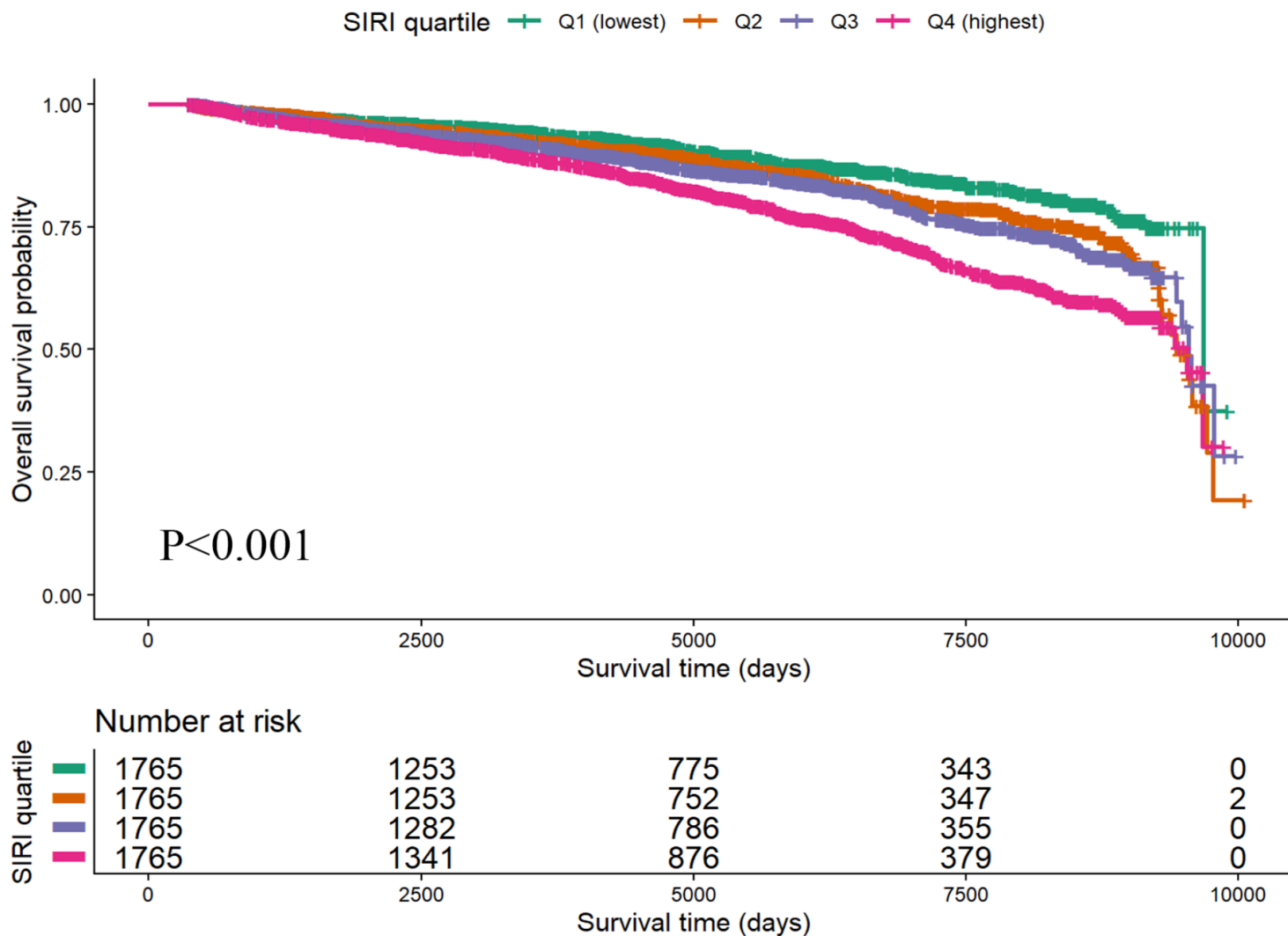


Figure 1

Kaplan-Meier survival curves for all-cause mortality according to systemic inflammation response index quartiles. Patients were stratified into four groups based on SIRI quartiles (Q1 to Q4). The log-rank test demonstrated statistically significant differences in survival across the four groups ($P < 0.001$). The number of patients at risk at each time point was shown below the x-axis.

Abbreviations: SIRI = systemic inflammation response index.

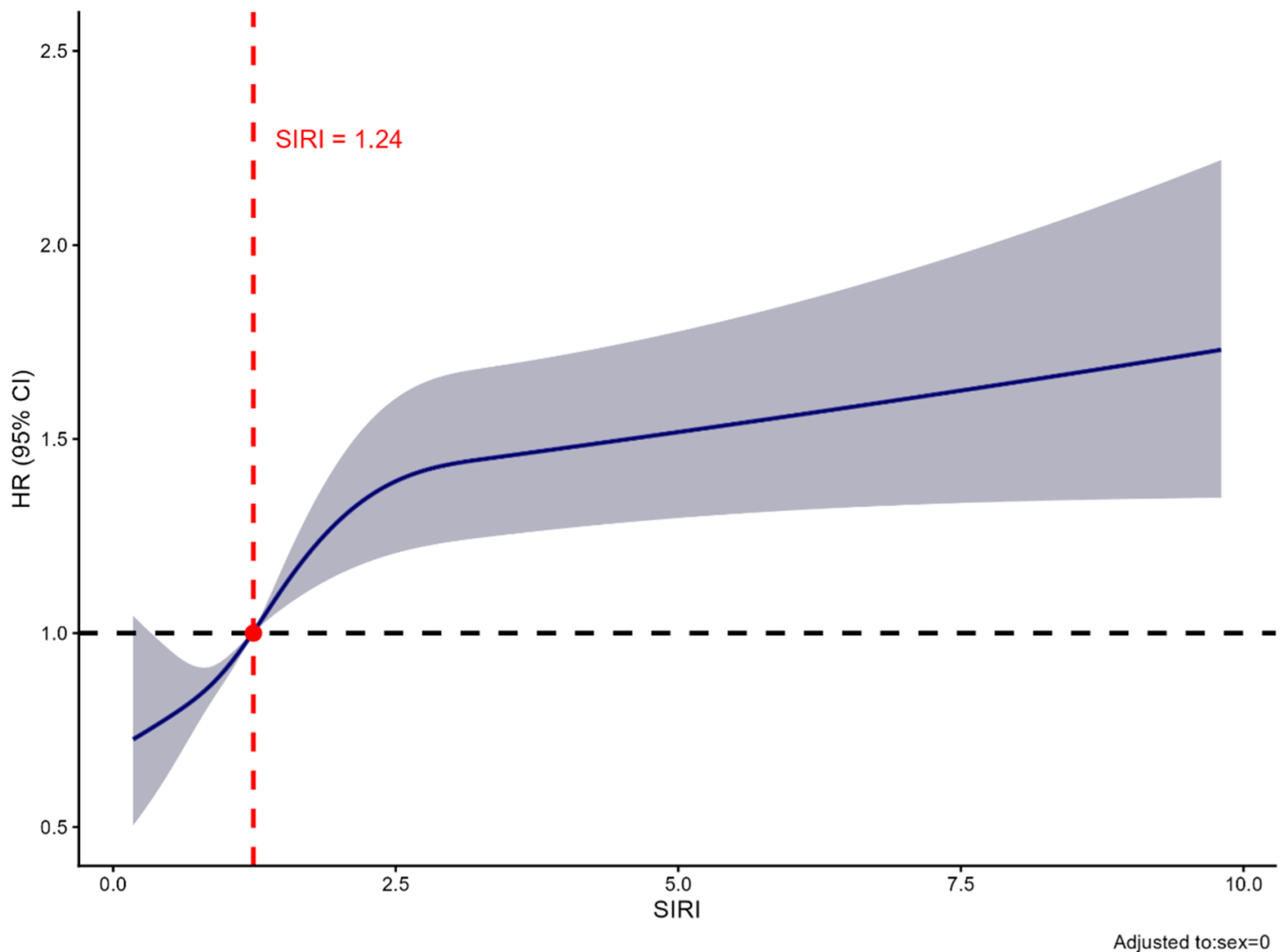


Figure 2

Restricted cubic spline analysis (knots at SIRS 10th, 25th, 75th, 90th percentiles of SIRS) for the non-linear SIRS–all-cause mortality association. Solid line = adjusted HR; shaded area = 95% CI (reference SIRS = 1.0). A threshold at SIRS = 1.24 was identified, with low risk below and progressively elevated risk above this value (P non-linearity < 0.001). The model was fully adjusted for age, sex, ethnicity, BMI, Townsend deprivation index, education, physical activity, smoking, aspirin, ibuprofen and laxative intake.

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; SIRS = systemic inflammation response index.

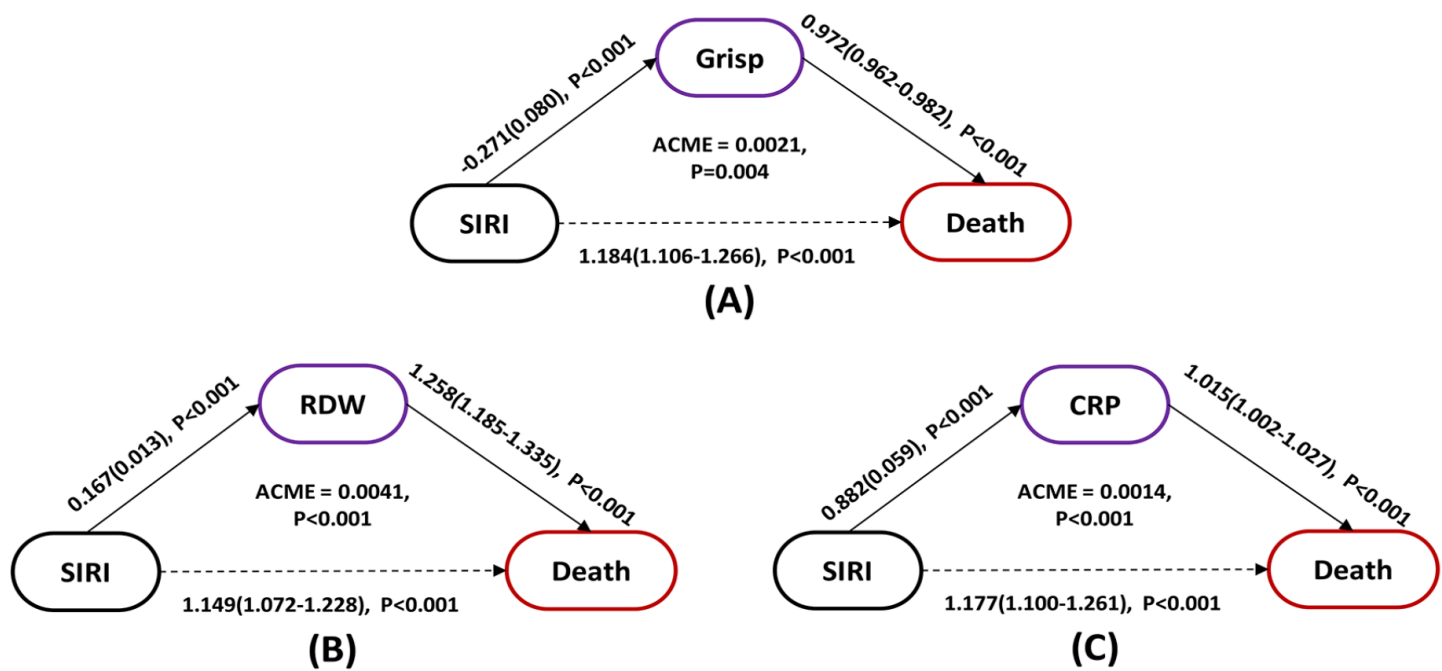


Figure 3

Mediation analysis of the association between systemic inflammation response index and all-cause mortality. Three separate mediation models were conducted with different mediators: (A) Handgrip strength, (B) Red blood cell distribution width, and (C) C-reactive protein. ACME, average causal mediation effect. Values along arrows are regression coefficients β (standard error, SE) or odds ratios (OR) with 95% confidence intervals (95% CI). All models were adjusted for age, sex, ethnicity, BMI, Townsend deprivation index, education, physical activity, smoking status, aspirin use, ibuprofen use, and laxative use.

Abbreviations: ACME = average causal mediation effect; BMI = body mass index; CRP = C-reactive protein; RDW = red blood cell distribution width; SIRS = systemic inflammation response index.