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Association of Systemic Inflammatory Response Index with the cardiometabolic multimorbidity among US adults: A population-based study

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Abstract:

BACKGROUND: Chronic inflammation plays an essential role in the occurrence and progression of cardiometabolic diseases (CMDs). We aim to examine the association between a novel inflammatory biomarker Systemic Inflammatory Response Index (SIRI) and different cardiometabolic multimorbidity (CMM) statuses.

METHODS: This was a cross-sectional study that includes general participants of the National Health and Nutrition Examination Survey database from 1999 to 2018. SIRI was calculated as neutrophil count × lymphocyte count/monocyte count. The CMDs were defined as a series of diseases including diabetes mellitus (DM), heart disease (HD), and stroke. We explored the association of SIRI with outcomes with weighted multivariable logistic regression models weighted restricted cubic spline. The diagnostic value of SIRI was evaluated using weighted receiver operating characteristic (ROC) curves.

RESULTS: A total of 43,345 participants were enrolled with a mean age of 45.86 years. The weighted prevalence of CMD and CMM was 17.14% and 2.94%, respectively. Compared to those without CMD, the adjusted odds ratios (95% confidence interval) for each unit increase in SIRI were 1.14 (1.09–1.19) for DM, 1.13 (1.07–1.19) for HD, 1.11 (1.04–1.19) for stroke, 1.17 (1.12–1.22) for CMD, and 1.16 (1.10–1.23) for CMM, according to the weighted multivariable logistic regression. Elevated SIRI level was independently associated with increased CMM. There was no interaction found in subgroup analysis. According to the ROC analysis, SIRI had a superior diagnostic ability to neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and monocyte–lymphocyte ratio for CMD (area under the curve [AUC] =0.581) and CMM (AUC = 0.633).

CONCLUSIONS: Elevated level of SIRI was positively associated with the prevalence of DM, coronary artery disease, stroke, CMD, and CMM, suggesting that SIRI could be a potential noninvasive biomarker for CMD and CMM.

Keywords:

Cardiometabolic multimorbidity, chronic inflammation, National Health and Nutrition Examination Survey, Systemic Inflammatory Response Index

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Introduction

Cardiometabolic diseases (CMDs), including diabetes mellitus (DM), heart disease (HD), and stroke, are leading causes of morbidity and mortality worldwide, contributing to a significant portion of global health burdens.[1,2] These diseases often coexist, a condition known as cardiometabolic multimorbidity (CMM), increasing the complexity of clinical management and leading to poorer health outcomes. CMM is characterized by the coexistence of more than two CMDs within an individual,

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and participants with CMM experience a 2.1–6.9-fold increased risk of all-cause mortality compared to those without CMDs, thereby imposing immense economic and healthcare burdens.[3,4]

It is well established that chronic inflammation plays an essential role in the occurrence and progression of CMDs.[5,6] A growing body of research has demonstrated the positive association between blood inflammatory biomarkers and CMDs, including DM, HD, and stroke.[7-10] Despite these insights, there is a paucity of research specifically exploring the relationship between inflammatory indicators and CMM. An effective noninvasive estimation of inflammatory status for the prediction and clinical management of CMDs is urgently needed.

The Systemic Inflammatory Response Index (SIRI) has emerged as a novel biomarker that serves as a surrogate indicator of the body's chronic inflammatory state. Originally, it was reported in predicting the prognosis of cancers.[11-14] Then, it has been well documented to be associated with the incidence and poor outcome of hypertension,[15] stroke,[16-19] HD,[10,20,21] and metabolic syndrome.[10] However, the relationship between SIRI and CMM is still under discussion.

Therefore, this study aims to explore the association between SIRI and different CMM statuses among a representative sample of the US general population. Our hypothesis is that an increased SIRI level would be positively associated with the prevalence of CMM.

Methods

Study population

Data for this study were derived from the National Health and Nutrition Examination Survey (NHANES) database, which collected information on the health and nutritional status of US noninstitutional civilians. The complex stratified, multistage, multistage probability cluster design makes it representative of the US population. The questionnaires are collected by interviews during the home visit, while the physical examinations and the collection of biological samples are conducted in the Mobile Examination Centers. Detailed information about the collection and testing of samples is available at https://wwwn.cdc.gov/nchs/nhanes/.

The NHANES survey was approved by the National Center for Health Statistics ethics review board. Written informed consents were signed by all participants. This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

We first enrolled 59,204 adults aged 18 years or older from NHANES (1999–2018). Participants who were pregnant (n = 1,670), with incomplete data on CMD (n = 4,403) and SIRI (n = 5,386) and with cancer (n = 4,400) were excluded from our research. Finally, a total of 43,345 participants with available information were included in our study [Figure 1].

Calculation of Systemic Inflammatory Response Index

The complete blood counts were derived using the Beckman Coulter MAXM instrument, while the white blood cell differentials were obtained using Volume, Conductivity, and Scatter (VCS) technology. Neutrophil, lymphocyte, and monocyte counts were presented as 10^9 cells/L. We calculated SIRI as neutrophil count × lymphocyte count/monocyte count based on previous studies.[22]

Collection of cardiometabolic markers

The cardiometabolic risk factors are as follows: systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, HbA1c, fasting plasma glucose, 2 h oral glucose tolerance test (OGTT) plasma glucose, total cholesterol high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). HOMA-IR = fasting glucose (mmol/L) × fasting insulin (uU/mL)/22.5, as previously described.[23]

Assessment of cardiometabolic diseases

CMDs included DM, coronary artery disease (CAD; heart attack, angina, and coronary HD), and stroke.[24] DM was diagnosed with the following criteria: (1) diagnosed by physician, (2) glycohemoglobin HbA1c (%) >6.5, (3) fasting glucose (mmol/L) ≥7.0, (4) random blood glucose (mmol/L) ≥11.1, (5) 2-h OGTT blood glucose (mmol/L) ≥11.1, and (6) use of diabetes medication or insulin. CAD and stroke were determined

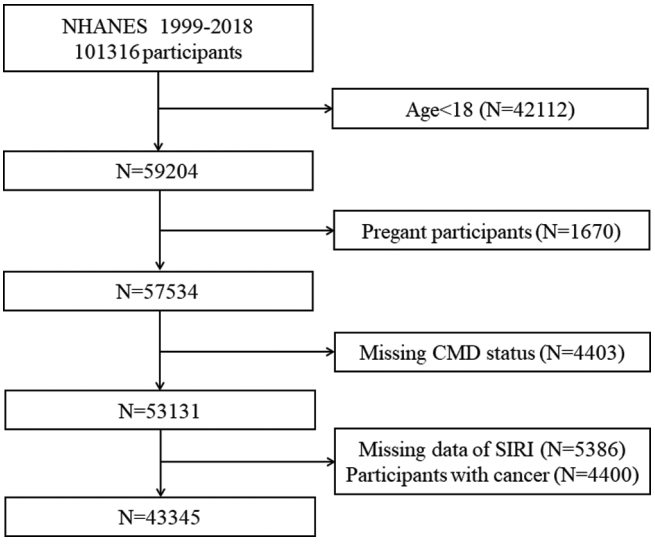

Figure 1: Flowchart of participants' enrollment

based on the self-reported diagnosis from the physician. Individuals who answered "yes" to the question "Has a doctor or other health professional ever told you that you had a heart attack/congestive heart failure/coronary HD/angina/stroke?" were considered to have CAD or stroke. Further, we grouped participants who had more than two cardiometabolic comorbidities into the CMM group to examine the association between SIRI and different cardiometabolic comorbidity statuses.

Covariates

Covariates were selected based on previous studies including age, sex (male/female), race (non-Hispanic white/non-Hispanic black/others), educational level (<high school/high school/>high school), family to poverty ratio, body mass index (BMI), smoking status (current/former/never), hypertension (yes/no), and hyperlipidemia (yes/no).[15]

BMI was calculated as the ratio of body weight (kg) to the square of height (m) and expressed as kg/m^2. It was then further categorized as <25, 25–30, or ≥30 kg/m^2, which represented normal weight, overweight, and obese, respectively. Hypertension was diagnosed as follows: (1) SBP ≥140 mmHg or DBP ≥90 mmHg, (2) previous diagnosis from the physician, and (3) prescription of antihypertensive medications. Individuals with self-reported diagnosis from doctors or prescription of antidyslipidemia medications were defined to have hyperlipidemia.

Statistical analysis

The analyses were conducted according to the guidelines of the Centers for Disease Control and Prevention, and proper sample weights were utilized with R (R Foundation for Statistical Computing, Vienna, Vienna, Austria) "survey" to meet the complex multistage methodology. All covariates were distributed normally. We performed one-way ANOVA (for continuous variates) and χ^2 test (for categorical variates) to compare the differences across quartiles of SIRI. The results were presented as means (standard error) and proportions (95% confidence interval [95% CI]) for continuous and categorical variables, respectively.

Weighted multivariable logistic regression models were conducted to explore the association between SIRI and CMD or CMM. The odds ratios (ORs) and 95% CIs were calculated for each 1-SD increment in SIRI level. Besides, we divided SIRI into quartiles, and the group of the lowest SIRI quartile representing the lowest inflammatory status was set as the reference. Three models were performed in this study: model 1 was crude model; Model 2 was adjusted for age, sex, and race; and Model 3 was further adjusted for BMI, education level, income-to-poverty ratio, smoking status, hypertension, and hyperlipidemia. We also plot 4 knots (5th, 35th, 65th, and 95th percentiles) weighted restricted cubic spline (RCS) with covariates adjusted. The likelihood ratio test was used to examine nonlinearity.

In addition, to elucidate the predictive ability of SIRI, we performed a weighted receiver operating curve (ROC) analysis and calculated the area under the curve (AUC) of SIRI along with several other blood inflammatory biomarkers including neutrophil–lymphocyte ratio (NLR), monocyte–lymphocyte ratio (MLR), and Systemic Immune-Inflammation Index (SII). NLR was calculated as neutrophils/lymphocytes. MLR was calculated as monocytes/lymphocytes. SII was calculated as neutrophils × platelets/lymphocytes.[22]

Subgroup analyses were conducted to examine the association of SIRI with CMD and CMM stratified by the main confounding factors including age, sex, BMI, hypertension, and hyperlipidemia. The age was divided into <60 or ≥60 years in the analysis. The interaction effects were examined using the product terms in the fully adjusted model. In the sensitivity analysis, we repeated our main analysis when excluding 5591 participants with abnormal white cell counts (<4 × 10^9/L or > 10 × 10^9/L) to avoid the influence of acute infection status. The missing data rate for any variable was <5%. Missing values were input based on the random forest algorithm with R package "missForest."[25] All statistical analyses were performed using R 3.6.1, and $P < 0.05$ was considered statistically significant (Department of Neurointervention, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China).

Clinical trial registry

No clinical trials were involved.

Results

The weighted baseline characteristics of study population across quartiles of SIRI are shown in Table 1. This study represented 179,908,057 US citizens, of whom 50.71% were male, with a mean age of 45.86 years. The weighted prevalence of CMD and CMM in our study was 17.14% and 2.94%, respectively. Participants with higher quartiles of SIRI were more likely to be older, male, and had a higher BMI as well as a higher proportion of hypertension, hyperlipidemia, DM, CAD, stroke, CMD, and CMM. Both the weighted prevalence of CMD and CMM increased from Q1 to Q4 significantly.

The SIRI ranged from 0.02 to 24.60. Table 2 displays the distribution of participants' cardiometabolic biomarkers. The mean levels of all factors were significantly different across SIRI quartiles. Basically, the increasing

Table 1: Weighted baseline characteristics of participants according to Systemic Inflammatory Response Index quartiles

Characteristics	Quartiles of the SIRI				*P*
	Q1 (*n*=10,861) 0.02–0.69	Q2 (*n*=10,822) 0.69–1.01	Q3 (*n*=10,831) 1.01–1.47	Q4 (*n*=10,831) 1.47–24.6	
Age	43.73 (0.26)	44.83 (0.25)	46.09 (0.24)	48.44 (0.30)	<0.0001
Sex					
Female	58.06 (0.65)	53.08 (0.60)	48.58 (0.68)	44.23 (0.73)	<0.0001
Male	41.94 (0.65)	46.92 (0.60)	51.42 (0.68)	55.77 (0.73)	
Race/ethnicity					
Black	11.42 (0.01)	22.67 (1.12)	10.40 (0.61)	7.71 (0.49)	<0.0001
White	66.27 (0.02)	51.47 (1.47)	65.72 (1.24)	70.97 (1.22)	
Others	22.31 (0.01)	25.86 (1.05)	23.88 (1.00)	21.33 (1.02)	
Educational level					
< High school	17.23 (0.56)	15.77 (0.59)	16.50 (0.65)	17.61 (0.69)	<0.0001
High school	21.30 (0.68)	23.15 (0.66)	23.81 (0.62)	27.24 (0.64)	
> High school	61.47 (0.90)	61.09 (0.92)	59.69 (0.88)	55.15 (0.95)	
Poverty	2.96 (0.03)	3.06 (0.04)	3.03 (0.04)	2.89 (0.04)	<0.0001
BMI (kg/m^2)	27.82 (0.11)	28.47 (0.10)	29.29 (0.11)	29.87 (0.12)	<0.0001
Smoking status					
Current	16.83 (0.54)	19.05 (0.62)	22.22 (0.63)	27.41 (0.70)	<0.0001
Former	20.55 (0.67)	23.31 (0.55)	23.34 (0.60)	25.61 (0.68)	
Never	62.62 (0.79)	57.64 (0.77)	54.44 (0.65)	46.99 (0.85)	
DM	10.17 (0.39)	10.18 (0.39)	12.72 (0.41)	17.43 (0.54)	<0.0001
HD	2.97 (0.22)	3.66 (0.24)	5.18 (0.30)	8.21 (0.37)	<0.0001
Stroke	1.93 (0.17)	1.85 (0.14)	2.52 (0.23)	3.95 (0.23)	<0.0001
Hypertension	29.55 (0.70)	32.02 (0.63)	36.03 (0.74)	44.42 (0.79)	<0.0001
Hyperlipidemia	65.06 (0.80)	68.30 (0.60)	70.99 (0.69)	71.48 (0.70)	<0.0001
CMD	13.24 (0.48)	13.65 (0.47)	17.32 (0.47)	23.71 (0.62)	<0.0001
CMM	1.67 (0.14)	1.85 (0.16)	2.80 (0.20)	5.23 (0.27)	<0.0001

BMI: Body mass index, DM: Diabetes mellitus, HD: Heart disease, CMD: Cardiometabolic disease, CMM: Cardiometabolic multimorbidity, SIRI: Systemic Inflammatory Response Index

Table 2: Weighted mean of cardiovascular risk factors according to quartiles of the Systemic Inflammatory Response Index

Characteristics	Quartiles of the SIRI				*P*
	Q1 (*n*=10,861) 0.02–0.69	Q2 (*n*=10,822) 0.69–1.01	Q3 (*n*=10,831) 1.01–1.47	Q4 (*n*=10,831) 1.47–24.6	
SBP (mmHg)	119.47 (0.24)	120.57 (0.24)	121.87 (0.25)	124.45 (0.27)	<0.0001
DBP (mmHg)	70.98 (0.20)	71.24 (0.20)	71.32 (0.22)	71.20 (0.23)	0.003
WC (cm)	94.59 (0.26)	97.16 (0.24)	99.77 (0.25)	101.99 (0.30)	<0.0001
Fasting plasma glucose (mg/dL)	109.49 (1.05)	111.32 (1.15)	116.82 (1.07)	124.53 (1.59)	<0.0001
HbA1c (%)	103.27 (0.56)	104.80 (0.51)	106.80 (0.60)	111.43 (0.86)	<0.0001
2-h glucose (mg/dL)	56.01 (0.28)	53.73 (0.26)	51.98 (0.24)	51.70 (0.25)	<0.0001
HDL-C (mg/dL)	118.74 (2.06)	127.62 (1.83)	133.09 (2.09)	134.91 (2.41)	<0.0001
LDL-C (mg/dL)	115.83 (0.69)	115.33 (0.72)	116.10 (0.77)	110.75 (0.68)	<0.0001
TGs (mg/dL)	5.54 (0.01)	5.53 (0.01)	5.58 (0.01)	5.67 (0.01)	<0.0001
HOMA-IR	3.04 (0.07)	3.33 (0.08)	3.72 (0.09)	4.51 (0.13)	<0.0001

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HbA1c: Glycohemoglobin, SIRI: Systemic Inflammatory Response Index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WC: Waist circumference, TGs: Triglycerides

quartiles of SIRI were accompanied by rising levels of cardiometabolic biomarkers, suggesting the positive relationship between SIRI and CMD risk.

There was no nonlinear relationship between SIRI and CMD or CMM with adjustment of covariates (*P* for nonlinearity >0.05) [Figure 2]. Weighted logistic regression models indicated that higher SIRI level was associated with increased risk of all kinds of CMM status [Table 3]. After adjustment of potential confounding factors in Model 3. Each unit increase in SIRI was associated with 14% increased risk in DM prevalence, 13% increased risk in CAD prevalence, 11% increased risk in stroke prevalence, a 17% increased risk in CMD, and 16% increased risk in CMM prevalence.

We further converted SIRI to quartiles to conduct a sensitivity analysis. Compared to those in the lowest SIRI quartile, participants in the highest SIRI quartile had a significantly higher prevalence of CMD (OR = 1.17; 95% CI: 1.12–1.22) and CMM (OR = 1.16; 95% CI: 1.10–1.23) in fully adjusted Model 3.

ROC curve analysis was used to identify the ability of SIRI to distinguish participants with or without CMD [Figure 3a]. The SIRI had the largest AUC (AUC = 0.564) compared to that of SII (AUC = 0.521), NLR (AUC = 0.549), and MLR (AUC = 0.545). Similarly, according to the ROC curve analysis of CMM [Figure 3b], the indicator with the highest AUC was still SIRI (0.626).

The subgroup analyses indicated that the associations between SIRI and CMD were consistent when stratified by potential confounders [Figure 4a]. With respect to the association between SIRI and CMM, the associations were not statistically significant among participants who were overweight (OR = 1.04; 95% CI: 0.93–1.16)

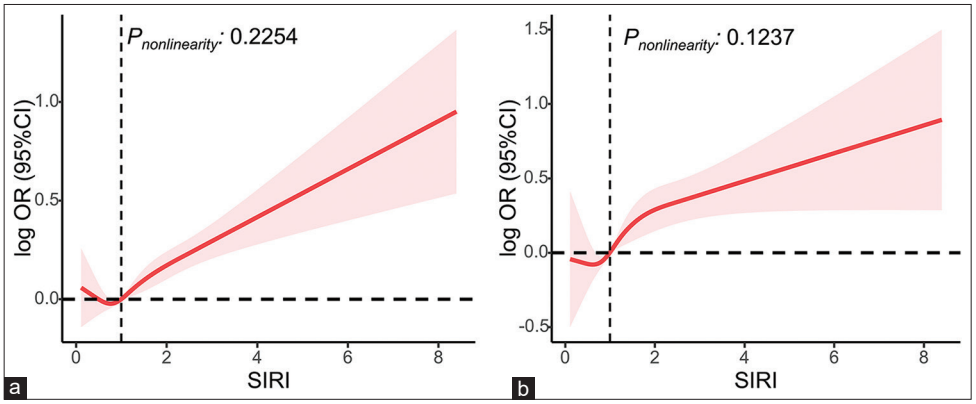

Figure 2: Association between Systemic Inflammatory Response Index (SIRI) with cardiometabolic disease (a) and cardiometabolic multimorbidity (b). Data were fitted using a weighted logistic regression model of RCS with four knots (at the 5th, 35th, 65th, and 95th percentiles). Age, sex, race, educational level, income-to-poverty ratio, body mass index, smoking status, hypertension, and hyperlipidemia were adjusted. The reference point for SIRI was the median (1.00) of the entire population. Red lines indicate adjusted odds ratio, and pink areas indicate the 95% confidence interval

Table 3: Association between Systemic Inflammatory Response Index with cardiometabolic multimorbidity

	DM	Coronary artery disease	Stroke	CMD	CMMs
Model 1					
Continuous	**1.28 (1.23–1.33)**	**1.40 (1.34–1.47)**	**1.29 (1.22–1.36)**	**1.35 (1.30–1.40)**	**1.41 (1.34–1.49)**
Categories					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.00 (0.89–1.12)	**1.24 (1.02–1.51)**	0.96 (0.77–1.19)	1.04 (0.93–1.15)	1.11 (0.90–1.37)
Q3	**1.29 (1.15–1.44)**	**1.79 (1.46–2.19)**	**1.31 (1.01–1.70)**	**1.37 (1.24–1.52)**	**1.70 (1.36–2.12)**
Q4	**1.87 (1.69–2.06)**	**2.93 (2.45–3.49)**	**2.09 (1.70–2.57)**	**2.04 (1.85–2.25)**	**3.26 (2.70–3.94)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Model 2					
Continuous	**1.22 (1.17–1.27)**	**1.21 (1.15–1.27)**	**1.18 (1.11–1.26)**	**1.26 (1.21–1.32)**	**1.26 (1.19–1.33)**
Categories					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.06 (0.95–1.20)	1.08 (0.88–1.34)	0.97 (0.77–1.22)	1.06 (0.94–1.19)	1.07 (0.86–1.33)
Q3	**1.35 (1.19–1.52)**	**1.37 (1.10–1.70)**	**1.25 (0.95–1.65)**	**1.37 (1.22–1.54)**	**1.48 (1.16–1.88)**
Q4	**1.77 (1.59–1.98)**	**1.74 (1.45–2.10)**	**1.66 (1.31–2.10)**	**1.81 (1.63–2.02)**	**2.24 (1.84–2.74)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Model 3					
Continuous	**1.14 (1.09–1.19)**	**1.13 (1.07–1.19)**	**1.11 (1.04–1.19)**	**1.17 (1.12–1.22)**	**1.16 (1.10–1.23)**
Categories					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	0.97 (0.85–1.10)	1.05 (0.83–1.31)	0.90 (0.70–1.15)	0.98 (0.86–1.11)	0.97 (0.76–1.26)
Q3	1.10 (0.95–1.27)	1.19 (0.93–1.52)	1.05 (0.78–1.40)	1.12 (0.98–1.28)	1.20 (0.92–1.56)
Q4	**1.30 (1.14–1.49)**	**1.35 (1.11–1.66)**	**1.29 (1.00–1.68)**	**1.35 (1.19–1.53)**	**1.54 (1.24–1.91)**
P for trend	<0.001	0.003	0.012	<0.001	<0.001

Model 1: Unadjusted, Model 2: Age, sex, race, Model 3: Further adjusted for educational level, income-to-poverty ratio, BMI, smoking status, hypertension, and hyperlipidemia. DM: Diabetes mellitus; CMD: Cardiometabolic disease; CMMs: Cardiometabolic multimorbidities, BMI: Body mass index, Bold values indicate statistically significant

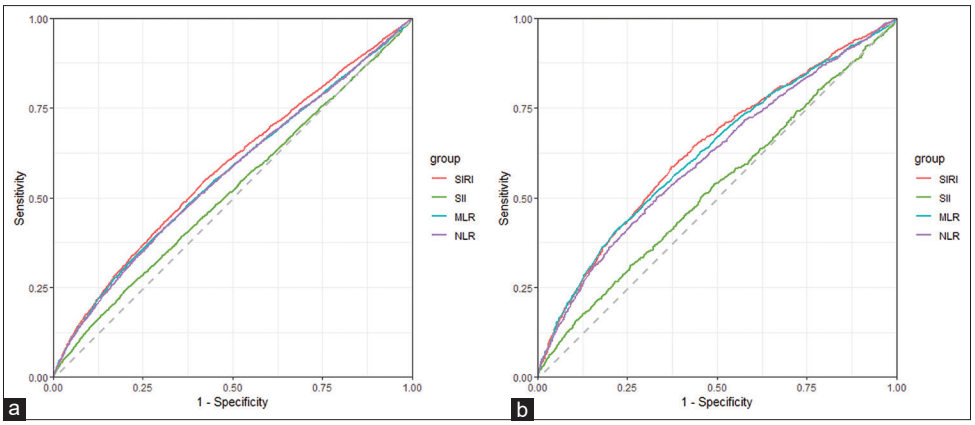

Figure 3: Receiver operating characteristic curve for incidence of cardiometabolic disease (a) and cardiometabolic multimorbidity (b)

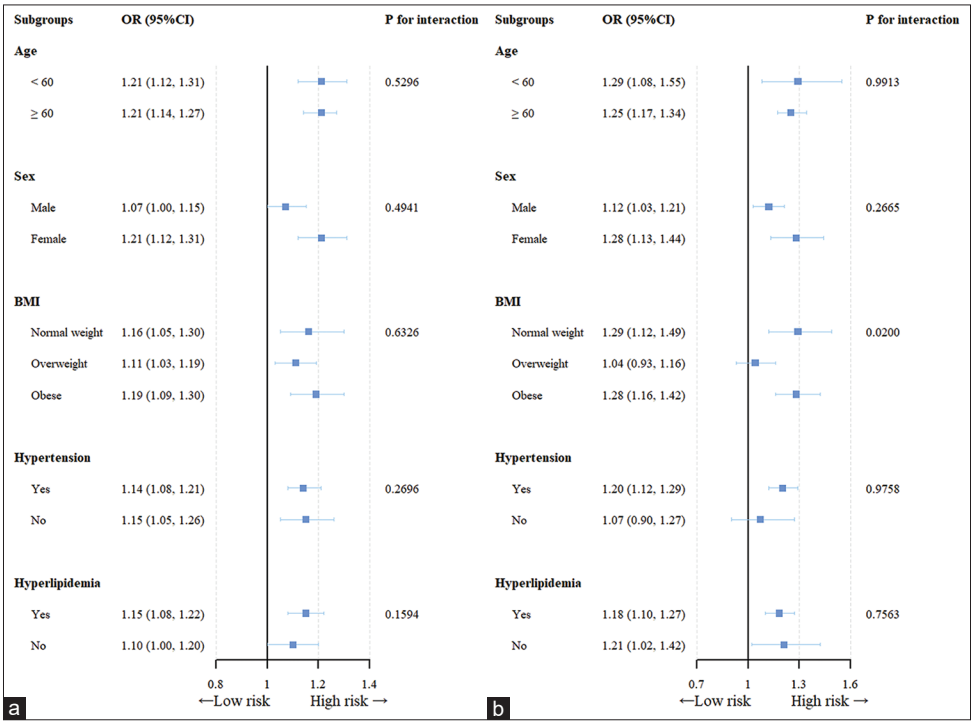

Figure 4: Subgroup analysis for the association between Systemic Inflammatory Response Index and cardiometabolic disease (a) and cardiometabolic multimorbidity (b)

or without hypertension (OR = 1.07; 95% CI: 0.90–1.27) [Figure 4b]. No significant interaction effect between SIRI and these potential risk factors was observed (all *P* for interaction > 0.05). The associations between SIRI, CMD, and CMM were robust in the sensitivity analysis [Supplementary Table 1].

Discussion

This was a large-scale cross-sectional population-based study that enrolled 43,345 individuals. In our study, the SIRI was associated with deteriorating cardiometabolic-related biomarkers. A higher level of SIRI was independently related to increased incidence of CMDs and CMM. This association remained robust after the adjustment of potential confounders. Our results fill a gap in population-level research on inflammation and CMM, suggesting that low-grade chronic inflammatory status may adversely affect different CMM statuses.

Although there is no direct evidence of an association between SIRI and CMM. Several studies have shown that SIRI is related to components of CMD.[10,21,26] A cross-sectional study conducted in rural China reported that the highest tertile of SIRI was related with increased risk of metabolic disorder (OR = 2.092; 95% CI: 1.622–2.699) and cardiovascular disease (OR = 3.397; 95% CI: 1.958–5.849).[10] According to the Kailuan cohort comprising 85,154 individuals, SIRI was related to higher occurrence of stroke and myocardial infarction.[26]

Similarly, a study in Poland that enrolled 699 patients with CAD reported that SIRI was associated with the severity of CAD.[21] In line with these studies, we demonstrated that the increased SIRI was positively associated with the prevalence of DM (OR = 1.14; 95% CI: 1.09–1.19), CAD (OR = 1.13; 95% CI: 1.07–1.19), and stroke (OR = 1.11; 95% CI: 1.04–1.19). Our study together with previous evidence supported a positive dose–response relationship between SIRI and incidence of CMDs.

The presence of CMD multimorbidity status can impact long-term outcomes differently.[3,4] In the Clinical Practice Research Datalink of 2,007,731 UK population, participants who had all three CMDs had a significantly higher all-cause mortality risk than those who had only one or two CMDs.[4] Therefore, finding a diagnostic tool is also of great importance in clinical practice regardless of the fact that CMM only accounts for approximately 5% of the entire population. Consequently, this study evaluated the associations of SIRI with different CMD multimorbidity status, including single CMD component (DM/CAD/stroke), CMD (with more than one CMD), and CMM (with more than two CMDs). SIRI showed positive correlations with all CMD multimorbidity groups. SIRI is a comprehensive blood index employing three critical components on inflammation and immune response (neutrophils, monocytes, and lymphocytes). Due to this, it can be more robust in predicting the prevalence of diseases with complicated mechanisms like CMDs. Numerous studies have reported that SIRI showed a better predictive ability in patients with esophageal squamous cell carcinoma,[27] stroke,[16] and acute coronary syndrome[9,20] compared to NLR, MLR, and platelet–lymphocyte ratio. The results of our study also indicated that SIRI has a better diagnostic value for CMD and CMM than those traditional inflammatory biomarkers. In addition, Wang *et al*. also found that SIRI rather than NLR showed a significant association with the risk of metabolic diseases, suggesting that simple inflammatory biomarker fails to diagnose the CMDs in some situations.[10]

The mechanism underlying the association between SIRI and CMM has not been fully understood, but it may be linked to chronic inflammation and abnormal activation of the immune system. Neutrophils are the most abundant leukocytes with a short life span which has been traditionally viewed as a biomarker of cardiovascular inflammation.[28] High neutrophil counts promote vascular inflammation and are a predictor of future cardiovascular events.[29] In addition, NETosis, a cell death subtype which refers to the process of releasing neutrophil extracellular traps (NETs) by neutrophils, is also related to CMDs.[30] Low level of lymphocytes was associated with worse prognosis in patients with cardiovascular disease.[31] Potential mechanisms include increased lymphocyte apoptosis and downregulated lymphocyte proliferation and differentiation.[32] Monocytes are important circulating leukocytes in both innate and adaptive immunity. Proinflammatory monocytes would be recruited and infiltrated to target tissue in an inflammatory state, whereupon they may differentiate into macrophages and promote inflammation.[33,34] During the development of metabolic syndrome, the recruitment of M1 macrophages dramatically increased due to adipose tissue inflammation. This process can boost the number of macrophages and lead to higher secretion levels of proinflammatory cytokines, such as interleukin (IL)--β and tumor necrosis factor alpha, which in turn promote the progression of CMDs.[35] Moreover, atherosclerosis might have a role in this relationship. We noticed that NLR was highly associated with atherosclerosis, while monocyte is the major immune cell in the formation of atherosclerotic plaque.[36-38] Accumulation of immune cells such as monocytes and neutrophils contributes to the rupture of atherosclerosis plaque,[28] which is known as the main risk factor for cardiovascular disease, stroke, and metabolic disorders.[39] In this case, a higher SIRI level may be associated with increased CMD incidence owing to its tight link with atherosclerosis. Furthermore, it is suggested that the enhanced diagnostic value of SIRI may be attributed to the incorporation of monocyte levels, as opposed to NLR and SII.

There are some clinical implications for our study. First, SIRI is a promising noninvasive biomarker for the identification of people with high risk of CMD and CMM. Integrating SIRI with other cardiometabolic risk profiles may improve early CMM diagnosis and treatment. Second, since inflammation appears to be responsible for long-term complications and poor prognosis in CMD patients, anti-inflammatory treatments like anti-IL-1 β have been introduced in clinical management.[5] Given SIRI's high ORs for CMDs, further research can explore interventions that modulate inflammation to mitigate CMM risk. Lifestyle modification such as having an anti-inflammatory diet also helps reduce the incidence of CMD, based on the evidence from NHANES 2005–2012 with 17,689 participants.[40] Considering the easy accessibility and high diagnostic value of SIRI, monitoring SIRI level enables a comprehensive assessment of patient's overall chronic inflammatory status and aids in determining the effect of long-term treatment. Besides, our findings also provide epidemiological evidence supporting the hypothesis that inflammation is a plausible contributor to the development of CMM.

Our major strength was the large sample size and representative sample selection due to the design of

the NHANES database. Furthermore, we evaluated the association of SIRI with different CMM statuses, which extends the clinical application of SIRI. Nevertheless, there are still some limitations that should be mentioned. First, we cannot infer any causal relationship attributed to the cross-sectional study design. Further large-scale prospective research should be conducted in the future. Second, measuring SIRI from a single blood draw provides only a snapshot of an individual's inflammatory status, potentially leading to misclassification and affecting the observed associations with CMM. Longitudinal studies with dynamic change in SIRI are highly recommended in the future. Third, residual confounding factors are inevitable, although we have adjusted for some potential covariates.

Conclusions

This study provides new evidence on the relationship between the blood inflammatory biomarker SIRI and CMDs. These results support that body inflammatory status may be associated with CMM status. SIRI could be considered a potential noninvasive biomarker for assessing CMD and CMM. Further prospective studies are needed to confirm our findings.

Author contributions

JL: data analysis, software, writing original draft, writing—reviewing and editing. SZ: data analysis, software, writing original draft, writing—reviewing and editing. XZ: data analysis, software, writing original draft, writing—reviewing and editing. SZ: data analysis, software, writing original draft, writing—reviewing and editing. MF: data analysis, software. JW: data analysis, software. RL: data analysis, software. FF: data analysis, software. GL: data analysis, software. SG: conceptualization, funding acquisition, and writing—reviewing and editing. AL: conceptualization, funding acquisition, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

Ethical policy and institutional review board statement

The NHANES survey was approved by the National Center for Health Statistics ethics review board. The study was performed in accordance with the Declaration of Helsinki. Written informed consents were signed by all participants.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Association between SIRI with cardiometabolic multimorbidity after exclusion of participants with abnormal WBC

	DM	Heart disease	Stroke	CMD	CMMs
Model 1 Continuous Categories	**1.35 (1.29, 1.41)**	**1.62 (1.54, 1.71)**	**1.49 (1.40, 1.58)**	**1.48 (1.42, 1.55)**	**1.61 (1.52, 1.70)**
Q1	Reference	Reference	Reference	Reference	Reference
Q2	0.99 (0.90, 1.09)	**1.26 (1.05, 1.50)**	0.89 (0.72, 1.11)	1.03 (0.94, 1.13)	1.08 (0.89, 1.31)
Q3	**1.19 (1.07, 1.32)**	**1.76 (1.48, 2.08)**	**1.27 (1.03, 1.58)**	**1.28 (1.17, 1.41)**	**1.70 (1.40, 2.06)**
Q4	**1.66 (1.51, 1.83)**	**2.91 (2.50, 3.39)**	**2.19 (1.81, 2.65)**	**1.96 (1.80, 2.14)**	**2.93 (2.47, 3.49)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Model 2 Continuous Categories	**1.14 (1.09, 1.20)**	**1.18 (1.12, 1.25)**	**1.22 (1.14, 1.30)**	**1.20 (1.15, 1.25)**	**1.23 (1.16, 1.31)**
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.01 (0.91, 1.12)	1.05 (0.87, 1.27)	0.87 (0.70, 1.09)	1.00 (0.90, 1.11)	1.00 (0.82, 1.21)
Q3	**1.14 (1.02, 1.28)**	**1.24 (1.03, 1.49)**	**1.12 (0.89, 1.41)**	**1.15 (1.03, 1.27)**	**1.36 (1.10, 1.68)**
Q4	**1.31 (1.17, 1.46)**	**1.42 (1.20, 1.67)**	**1.48 (1.19, 1.83)**	**1.39 (1.25, 1.53)**	**1.64 (1.35, 1.99)**
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Model 3 Continuous Categories	**1.09 (1.03, 1.15)**	**1.14 (1.07, 1.21)**	**1.17 (1.10, 1.26)**	**1.14 (1.08, 1.20)**	**1.18 (1.11, 1.26)**
Q1	Reference	Reference	Reference	Reference	Reference
Q2	0.94 (0.85, 1.05)	1.02 (0.85, 1.23)	0.84 (0.67, 1.06)	0.94 (0.85, 1.05)	0.96 (0.78, 1.17)
Q3	0.99 (0.88, 1.12)	1.12 (0.93, 1.35)	1.03 (0.81, 1.29)	1.00 (0.90, 1.12)	1.20 (0.96, 1.49)
Q4	1.10 (0.98, 1.23)	**1.22 (1.04, 1.45)**	**1.28 (1.03, 1.60)**	**1.17 (1.05, 1.30)**	**1.37 (1.12, 1.67)**
P for trend	0.020	0.003	<0.001	<0.001	<0.001

Model 1: unadjusted. Model 2: age, sex, race Model 3: further adjusted for educational level, income to poverty ratio, BMI, smoking status, hypertension, and hyperlipidemia. DM: diabetes mellitus; CMD: cardiometabolic disease; CMM: cardiometabolic multimorbidity. Bold values indicate statistically significant