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ORIGINAL RESEARCH

Prognostic Value of the Systemic Inflammatory Response Index in Patients with Acute Coronary Syndrome and Obstructive Sleep Apnea

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Purpose: This study aimed to investigate the effects of the systemic inflammatory response index (SIRI) on the long-term prognosis of patients with acute coronary syndrome (ACS) and obstructive sleep apnea (OSA).

Patients and Methods: This prospective cohort study enrolled patients with ACS and OSA at the Beijing Anzhen Hospital between June 2015 and January 2020. The SIRI was calculated at admission for all patients. Patients with SIRI $\geq 1.16 \times 10^9$/L were classified into the high SIRI group based on the optimal cutoff value for predicting major adverse cardiovascular and cerebrovascular events (MACCE) determined by the receiver operating characteristic (ROC) curve of our cohort study. The other patients were categorized into the low SIRI group. The primary endpoint was a composite of MACCE, including cardiovascular death, recurrent myocardial infarction (MI), stroke, and ischemia-driven revascularization.

Results: A total of 1011 patients with ACS and OSA were enrolled, 435 of whom (43%) were in the high SIRI group. Over a median follow-up of 2.8 (1.4–3.6) years, 179 patients experienced MACCE. Kaplan–Meier survival analysis showed a higher cumulative incidence of MACCE in the high-SIRI group (log-rank $P < 0.001$). A restricted cubic spline analysis also showed a monotonic increase with a greater SIRI value for MACCE ($P = 0.011$). After adjusting for clinically relevant confounders, a high SIRI was independently associated with elevated MACCE risk (adjusted HR = 1.44, 95% CI 1.02–2.05, $P = 0.039$).

Conclusion: A high SIRI was associated with poorer clinical outcomes during long-term follow-up in patients with ACS and OSA.

Keywords: systemic inflammatory response index, acute coronary syndrome, obstructive sleep apnea, prognosis

Introduction

Obstructive sleep apnea (OSA) is a widespread sleep disorder that affects nearly 1 billion adults worldwide.[1] OSA is characterized by recurrent episodes of complete or partial upper airway collapse (apneas or hypopneas), resulting in the exposure of the cardiovascular system to cycles of hypoxia, excessive negative intrathoracic pressure, or sleep arousal.[2,3] In patients with acute coronary syndrome (ACS), the prevalence of OSA is as high as 36–68%.[4–6] Growing evidence, including our previous study, indicates that OSA worsens the prognosis in patients with ACS.[6–8]

OSA can induce or exacerbate cardiovascular comorbidities, including ACS, through mechanisms such as intermittent hypoxia, oxidative stress, and systemic inflammation, with systemic inflammation being particularly significant. Increasing evidence suggests that intermittent hypoxia plays a role in the pathophysiology of cardiovascular complications in OSA by activating proinflammatory pathways.[9] However, while the cause of coronary vessel disease (CVD) in OSA via the inflammatory pathway seems plausible and convincing in terms of basic science research, clinical trials are

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not as convincing.[10] Therefore, there is a need to explore the impact of inflammation in patients with OSA combined with ACS in large prospective cohort studies.

Peripheral blood inflammatory cell counts and their derived indicators, such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), can reflect the systemic inflammatory response status within the body and are now widely used in clinical practice. These indicators have been demonstrated to effectively predict the prognosis of CVD.[11–13] The systemic inflammatory response index (SIRI) is a novel composite indicator first developed in 2016 to predict survival in patients with pancreatic adenocarcinoma after chemotherapy.[14] Since its introduction, SIRI has been established as a prognostic marker in patients with malignancies.[15,16] In recent years, the diagnostic performance of the SIRI has been investigated in many diseases. For example, SIRI was found to be associated with CVD occurrence[17] and identified as an independent predictor of OSA severity.[18] Furthermore, SIRI has been widely considered for disease diagnosis and prognostic evaluation in recent years.[19–21] Although the pathophysiological processes of the inflammatory response have been demonstrated in both ACS and OSA, it remains unclear whether SIRI is an independent risk factor for poor prognosis in patients with both conditions. Therefore, in this prospective cohort study, we investigated the long-term prognostic value of SIRI in patients with ACS and OSA.

Methods

Study Design and Participants

This study was a substudy of the OSA-ACS project (NCT 03362385), the specific research methods of which have been previously reported.[6,7,22,23] From June 2015 to January 2020, consecutive patients with ACS were recruited from Beijing Anzhen Hospital. Inclusion criteria were as follows: adults aged 18–85 with a confirmed ACS diagnosis, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA),[24] as well as a diagnosis of OSA.[25] Eligible patients were required to provide informed consent. Exclusion criteria included cardiac arrest or cardiogenic shock, a history of malignancy, failed sleep monitoring, central sleep apnea, prior or ongoing continuous positive airway pressure (CPAP) treatment, or discharge from the hospital with CPAP therapy. Patients without comprehensive SIRI data were also excluded.

This study followed the Helsinki Declaration's recommendations and gained approval from Beijing Anzhen Hospital's Ethics Committee (No. 2013025), and written informed consent was obtained from participants.

Sleep Study and Management

Once clinically stable during their hospital stay, participants underwent an overnight sleep study using a portable cardiorespiratory polygraphy device (ApneaLink Air; ResMed). Trained research staff, blinded to clinical details, conducted these studies adhering to the American Academy of Sleep Medicine.[26] Monitored signals encompassed nasal airflow, chest and abdominal movements, snoring episodes, heart rate, and oxygen saturation (SaO_2). Apnea was classified by an airflow cessation $\geq$ 10 seconds (distinguished as obstructive or central based on chest and abdominal movements). Hypopnea was identified by a $\geq$ 10-second airflow decrease of $\geq$ 30% coupled with a >4% SaO_2 drop. The AHI was calculated by dividing the total number of apneas and hypopneas by sleep hours.[25,27]

Laboratory Measurements

Blood samples for complete blood count analysis were obtained from venous blood draws within 24 hours of hospital admission as part of routine clinical care. The timing of blood collection followed standard clinical protocols for ACS management at our institution, typically occurring before revascularization procedures, to minimize confounding effects of acute interventions on inflammatory biomarkers, and were measured in the Clinical Laboratory of Beijing Anzhen Hospital, using an Automated Hemocytometer (LH 570, Beckman Coulter), which we obtained from medical records.

Siri

SIRI was defined as neutrophils × monocytes/lymphocytes.[14] Optimal SIRI thresholds for major adverse cardiovascular and cerebrovascular events (MACCE) were calculated using receiver operating characteristic (ROC) analysis. The Youden index, which combines sensitivity and specificity, aided in selecting a SIRI threshold. Our cohort's ROC analysis identified an optimal SIRI cutoff of 1.16×10^9/L, dividing patients into low and high SIRI groups. (Supplementary Figure 1).

Endpoints and Follow-Up

Patients were closely monitored after discharge through regular follow-up appointments at specified intervals. Any clinical adverse events were documented by an impartial committee unaware of the patients' medical history and sleep study findings through outpatient visits or telephone follow-ups.

The main focus of the study was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), which include cardiovascular death, myocardial infarction (MI), stroke, and ischemia-driven revascularization. Secondary endpoints included individual components of MACCE. Criteria for these endpoints were established according to standardized definitions outlined by the Cardiovascular Trials Standardized Data Collection Initiative.[28]

Statistical Analysis

Quantitative data were expressed as mean ± standard deviation (SD) or median (first and third quartiles) and were examined using Student's *t*-test or Mann–Whitney *U*-test. Qualitative data were displayed as percentages (%) and were analyzed using χ^2 statistics or Fisher's exact test. A ROC curve analysis was conducted to establish the cutoff value for SIRI in predicting MACCE, with the area under the ROC curve being calculated. SIRI was then assessed as a categorical variable. The cumulative incidence rates for primary and secondary endpoints were illustrated through Kaplan–Meier curves, with differences between curves evaluated using the Log rank test. Furthermore, Cox proportional hazard analyses were performed using four models to identify independent risk factors by determining hazard ratios (HR) and 95% confidence intervals (CI). Subgroup analyses were carried out based on age, sex, hypertension, diabetes, dyslipidemia, and ACS type. Additionally, a restricted cubic spline (RCS) curve with four knots was employed to demonstrate the potential nonlinear relationship between SIRI as a continuous variable and the risk of clinical outcomes. We also assessed the correlation between SIRI and High sensitivity C-reactive protein (Hs-CRP) using Spearman's rank correlation coefficient. The prognostic performance of SIRI and Hs-CRP was compared through receiver operating characteristic (ROC) curve analysis with DeLong's test for statistical significance.

All statistical analyses were conducted using IBM SPSS 27 and R version 4.3.3. Significance was determined at $P < 0.05$ for two-sided tests.

Results

Demographic and Clinical Characteristics

A total of 1011 patients were included in the final analysis, with 435 (43%) classified into the high SIRI group (Figure 1). Compared to those with low SIRI, patients with high SIRI were more often male and had higher rates of hyperlipidemia, current smoking, MI, and percutaneous intervention (PCI). They also exhibited higher systolic blood pressure (BP), neutrophil and monocyte counts, Hs-CRP levels, and lower LVEF and lymphocyte counts. The poorer health status in the high SIRI group may explain their worse prognosis. As for medications on discharge, these patients were more frequently prescribed $P2Y_{12}$ inhibitors, β-blockers, and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs). Other characteristics were generally well-matched in both the low and high SIRI groups (Table 1).

No significant differences were observed between the two groups in terms of OSA parameters, including AHI, minimum and mean SaO_2, T 90, and the Epworth Sleep Scale (ESS) scores (all $P > 0.05$) (Table 2).

Outcome Analyses Between Low and High SIRI Groups

During a median follow-up of 2.8 years (1.5, 3.6), 179 patients experienced MACCE, with the incidence of MACCE being higher in the high SIRI group (23.2% vs 13.5%). In unadjusted analyses, the high-SIRI group demonstrated significantly

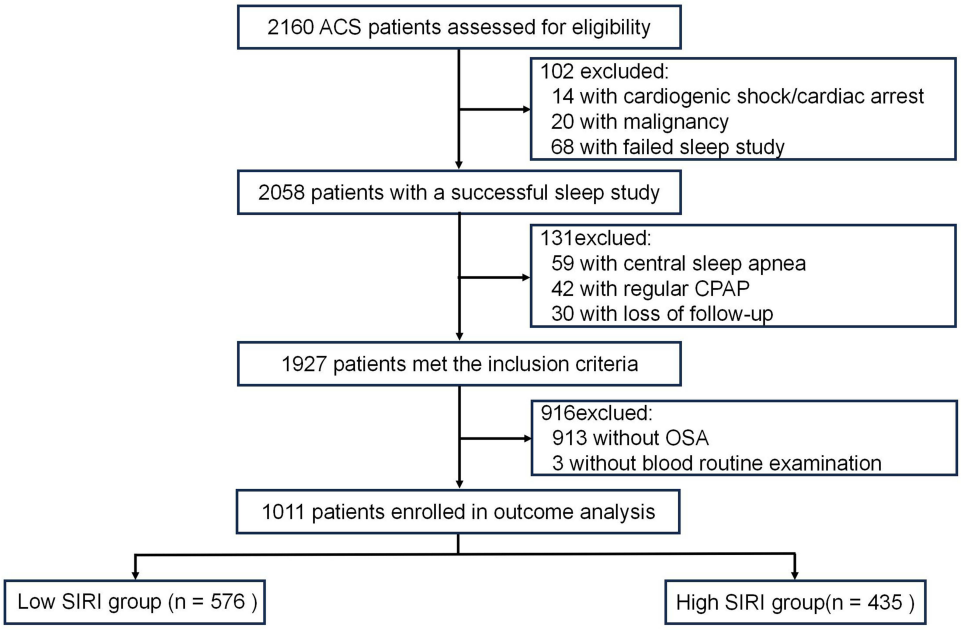

Figure 1 Study flowchart.

elevated risks of recurrent MI (HR=1.72, 95% CI 1.09–2.71; P=0.02) and ischemia-driven revascularization (HR=2.07, 95% CI 1.31–3.27; P=0.002). While trends toward increased cardiovascular death (HR=1.56, 95% CI 0.86–2.83; P=0.14) and stroke (HR=1.32, 95% CI 0.67–2.62; P=0.42) were observed, these associations did not reach statistical significance. Kaplan–Meier survival analysis showed a higher cumulative incidence of MACCE in the high-SIRI group (log-rank P < 0.001) (Table 3 and Figure 2A). Considering the components of MACCE, patients with a higher SIRI had a higher cumulative incidence of recurrent MI (log-rank P = 0.02) (Table 3 and Figure 2B) and ischemia-driven revascularization (log-rank P = 0.002) (Table 3

Table 1 Demographic and Clinical Characteristics by SIRI Categories

Variables	Low SIRI Group (SIRI<1.16) (n=576)	High SIRI Group (SIRI≥1.16) (n=435)	*P* Value
Subjects			
Age, years	56.5±9.9	56.6±11.4	0.914
Male	489(84.9)	394(90.6)	0.007
BMI, kg/m^2	28.2±3.5	27.8±3.6	0.06
Waist-to-hip ratio	0.99(0.96–1.02)	0.99(0.96–1.03)	0.57
Neck circumference, cm	41(39–44)	41.5(39–43.6)	0.655
Systolic BP, mmHg	128(120–139)	125(113–138)	0.006
Diastolic BP, mmHg	79(70–86)	75(70–85)	0.058
Medical history			
Diabetes	191(33.2)	127(29.2)	0.179
Hypertension	393(68.2)	297(68.3)	0.987
Hyperlipidemia	216(37.5)	125(28.7)	0.004
Prior stroke	63(10.9)	58(13.3)	0.245
Prior MI	109(18.9)	67(15.4)	0.144
Prior PCI	141(24.5)	92(21.1)	0.213
Prior CABG	13(2.3)	5(1.1)	0.187
Current Smoking	259(45)	235(54)	0.017

(*Continued*)

Table 1 (Continued).

Variables	Low SIRI Group (SIRI<1.16) (n=576)	High SIRI Group (SIRI≥1.16) (n=435)	*P* Value
Baseline tests			
eGFR, mL min^{-1} 1.73 m^{-2}	103.2(89.6–118.9)	102.9(86.4–119)	0.680
HbA1c, %	6.1(5.7–7.1)	6.1(5.6–7.1)	0.421
Hs-CRP, mg/L	1.66(0.76–4.24)	5.41(2–16.98)	<0.001
LVEF, %	62(58–66)	59(53–65)	<0.001
TC, mmol/L	4.15(3.48–4.86)	4.17(3.53–4.9)	0.590
TG, mmol/L	1.62(1.14–2.34)	1.51(1.11–2.11)	0.062
LDL-C, mmol/L	2.42(1.92–3.05)	2.51(1.97–3.15)	0.161
HDL-C, mmol/L	0.99(0.86–1.15)	0.96(0.85–1.12)	0.188
Neutrophil count, $\times10^9$/L	4.06(3.3–4.86)	6.73(5.39–8.39)	<0.001
Monocyte count, $\times10^9$/L	0.36(0.3–0.43)	0.53(0.41–0.64)	<0.001
Lymphocyte count, $\times10^9$/L	2.03(1.67–2.5)	1.63(1.23–2.13)	<0.001
SIRI, $\times10^9$/L	0.72(0.54–0.93)	1.88(1.41–3.22)	<0.001
Diagnosis			<0.001
STEMI	73(12.7)	177(40.7)	
NSTEMI	89(15.5)	101(23.2)	
Unstable angina	414(71.9)	157(36.1)	
Procedures			
PCI	342(59.4)	324(74.5)	<0.001
CABG	39(6.8)	21(4.8)	0.195
Medications on discharge			
Aspirin	559(97)	425(97.7)	0.524
$P2Y_{12}$ inhibitors	524(91)	411(94.5)	0.036
β-Blockers	439(76.2)	357(82.1)	0.024
ACEIs/ARBs	359(62.3)	305(70.1)	0.010
Statins	563(97.7)	431(99.1)	0.102

Notes: The data is presented as mean ± SD, median (first quartile to third quartile), or n (%).
Abbreviations: ACEI, angiotensin-converting enzymes inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; Hs-CRP, High sensitivity C-reactive protein; total cholesterol(TC); triglyceride(TG); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; SIRI, Systemic inflammatory response index; NSTEMI, Non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; UA, unstable angina; SIRI, systemic inflammatory response index.

Table 2 Overnight Sleep Monitoring Results Stratified by SIRI

Variables	Low SIRI Group	High SIRI Group	*P* Value
Sleep study			
AHI, events H^{-1}	28.5(20.2–41.9)	29.5(21.7–42.8)	0.192
Minimum SaO_2, %	82(77–86)	83(78–86)	0.317
Mean SaO_2, %	93(92–94)	93(02–94)	0.980
T90, %	6.4(2–17)	6(2–15)	0.548
Epworth Sleepiness Scale	8(5–12)	8(4–12)	0.570

Notes: The data is presented as median (first quartile to third quartile).
Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation; T90=percentage of Time with SaO_2 <90%.

and Figure 2C), However, there was no statistically significant difference between the two groups in terms of cardiovascular death (log-rank P = 0.116) (Table 3 and Figure 2D) and stroke (log-rank P = 0.889) (Table 3 and Figure 2E) events. Univariate Cox regression analysis further verified these associations. After adjusting for clinically relevant confounders such as age, sex, BMI, smoking status, hypertension, diabetes, dyslipidemia, prior MI and PCI, ACS type, hs-CRP, low-density lipoprotein

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Table 3 Kaplan-Meier Analysis for Clinical Outcomes According to SIRI Categories

Clinical Outcomes	Low SIRI Group (n, %)	High SIRI Group (n, %)	*P* Value
MACE	78(13.5)	101(23.2)	<0.001
Recurrent MI	11(1.9)	21(4.8)	0.02
Cardiovascular death	7(1.2)	12(2.8)	0.116
Stroke	14(2.4)	11(2.5)	0.889
Ischemia-driven revascularization	55(9.5)	73(16.8)	0.002

Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG), a high SIRI still independently predicted the occurrence of MACCE (adjusted HR = 1.44, 95% CI: 1.02–2.05, P = 0.039) and ischemia-driven revascularization (adjusted HR = 1.55, 95% CI: 1.03–2.33, P = 0.034) (Table 4). Based on univariate analysis, the RCS with four knots revealed that SIRI as a continuous variable was positively associated with MACCE (Figure 3).

Sensitivity Analyses

In patients with an ODI ≥ 15, the high SIRI group had a significantly higher risk of MACCE (HR = 1.64, 95% CI: 1.2–2.25, P = 0.002). Similar associations were observed for nocturnal hypoxemia indicators, such as minimum SaO_2 < the median (HR = 2.12, 95% CI: 1.34–3.34, P = 0.001) and mean SaO_2 < the median (HR = 2.28, 95% CI: 1.34–3.87, P = 0.002). No such associations were found in patients with ODI < 15, minimum SaO_2 > the median, and mean SaO_2 > the median (Figure 4).

Subgroup Analyses

Subgroup analyses according to sex, age, hypertension, diabetes, dyslipidemia, and ACS type revealed no significant association between SIRI and MACCE in female patients or patients presenting with diabetes, STEMI, and NSTEACS, or those without hypertension and dyslipidemia (Figure 5).

Biomarker Performance Between SIRI and Hs-CRP

Spearman's test revealed a moderate positive correlation between SIRI and Hs-CRP (r=0.42, P<0.001), indicating partial overlap yet distinct biological information (Supplementary Table 1 and Supplementary Figure 2). While SIRI and Hs-CRP showed comparable discriminative capacity for MACCE (AUC 0.59 vs 0.56, respectively) (Supplementary Table 2 and Supplementary Figure 3). SIRI's unique composition reflects distinct pathophysiological processes: neutrophil-monocyte axis activation from OSA-related hypoxia coupled with lymphocyte depletion from ACS-induced stress responses. This integrative profile enables SIRI to bridge OSA-driven inflammation with ACS prognosis more effectively than acute-phase reactants.

Discussion

This study explored the effects of SIRI on clinical outcomes in patients with ACS and OSA. In these patients, a high SIRI was found to be independently associated with an increased risk of MACCE, even though OSA severity was similar across the patient groups.

Cumulative epidemiological evidence suggests that the prevalence of OSA increases the risk of cardiovascular mortality or morbidity.[18,29] More and more evidence indicates that OSA is associated with the pathogenesis and prognosis of ACS.[30,31] OSA may result in oxidative stress and systemic inflammation, which contribute to coronary atherosclerosis.[3] Despite a great deal of effort up front, the pathophysiologic mechanisms between OSA and ACS remain unclear. Previous findings emphasize that systemic inflammatory cascade might play an important role in the cardiovascular effects of OSA,[32] but clinical trials remain controversial. Therefore, evaluating the inflammatory response status of OSA combined with ACS patients in a large cohort study may help explain the relationship between systemic inflammation and patients with OSA combined with ACS.

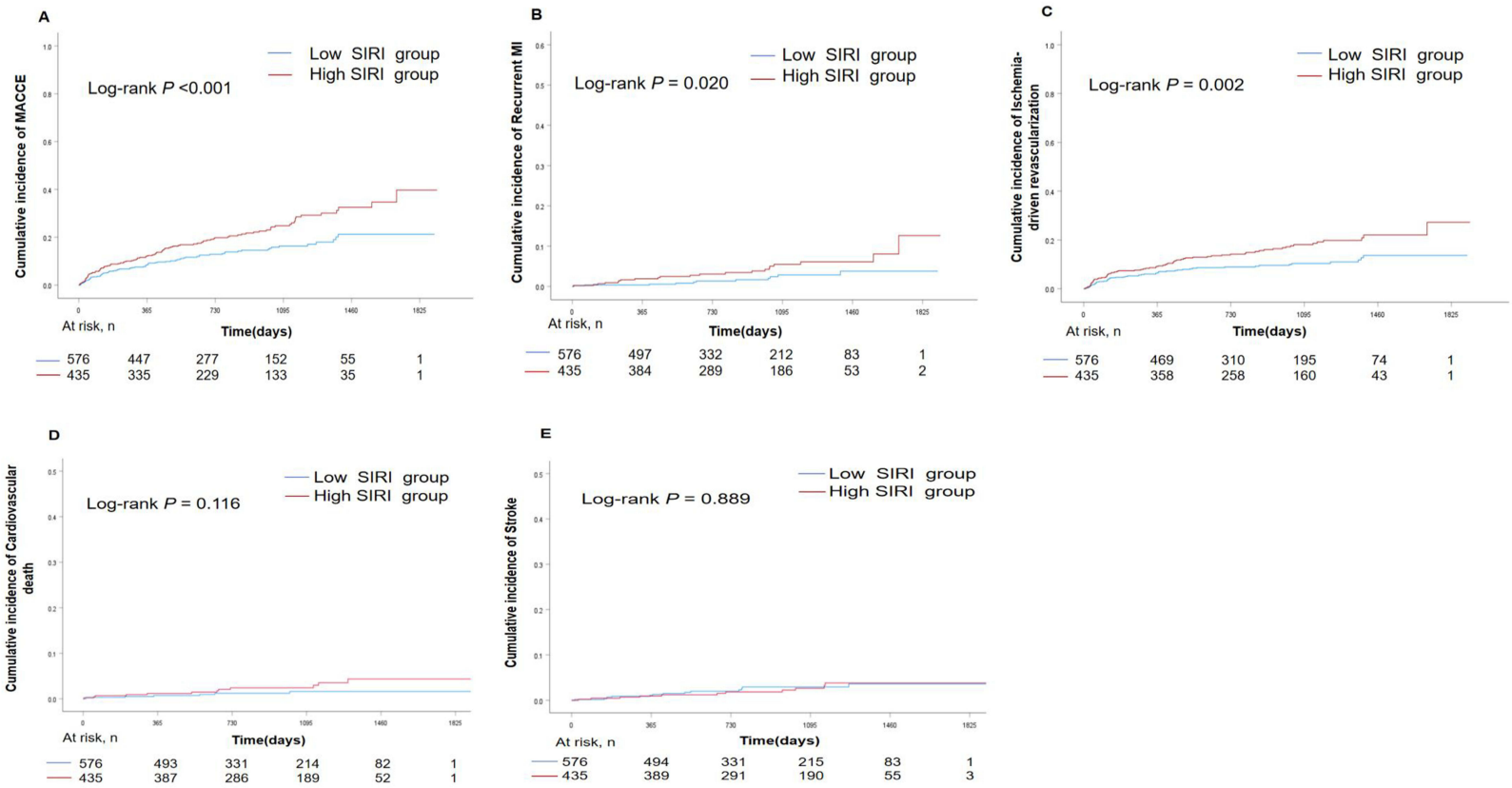

Figure 2 Kaplan-Meier curves in SIRI categories for (**A**) MACCE, and (**B**) Ischemia-driven revascularization, and (**C**) Recurrent MI, and (**D**) Cardiovascular death, and (**E**) Stroke.
Abbreviations: SIRI, systemic inflammatory response index; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

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Table 4 Cox Regression Analysis for Clinical Outcomes According to SIRI Categories During Follow-up

Variables	HR	95% CI	*P* Value
MACCE			
Model 1	1.647	1.226–2.214	<0.001
Model 2	1.734	1.281–2.347	<0.001
Model 3	1.504	1.09–2.077	0.013
Model 4	1.444	1.019–2.047	0.039
Recurrent MI			
Model 1	2.317	1.117–4.808	0.024
Model 2	2.166	1.018–4.609	0.045
Model 3	1.952	0.868–4.389	0.106
Model 4	1.701	0.691–4.185	0.248
Cardiovascular death			
Model 1	2.079	0.818–5.285	0.124
Model 2	2.484	0.926–6.661	0.071
Model 3	3.268	1.093–9.767	0.034
Model 4	2.653	0.824–8.543	0.102
Stroke			
Model 1	0.945	0.429–2.083	0.889
Model 2	1.058	0.472–2.372	0.891
Model 3	1.082	0.455–2.574	0.858
Model 4	0.760	0.287–2.016	0.582
Ischemia-driven revascularization			
Model 1	1.718	1.211–2.438	0.002
Model 2	1.797	1.261–2.561	0.001
Model 3	1.478	1.013–2.155	0.043
Model 4	1.551	1.034–2.327	0.034

Notes: Model 1: unadjusted; Model 2: adjusted for age (continuous), sex (male or female), BMI (<28, ≥28); Model 3: Model 2 + smoking (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), prior MI (yes or no), prior PCI (yes or no), clinical presentation (MI, UA); Model 4: Model 3 + hs-CRP (continuous), LDL-C (continuous), HDL-C (continuous), TC (continuous), TG (continuous).

Abbreviations: HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

Various inflammatory markers, such as hs-CRP, neutrophil count, and monocyte count, are associated with the prognosis of coronary heart disease. However, a single inflammatory marker is insufficient to predict the severity of inflammation. Although the NLR effectively identifies patients at higher risk for poor outcomes,[33–35] as the fundamental component of non-specific immunity, the roles of monocytes and macrophages must also be considered. SIRI, which incorporates neutrophils, monocytes, and lymphocytes as the three inflammatory biomarkers, represents an integrated indicator that reflects the status of systemic inflammation and immune response and stands out as a comprehensive, easily obtainable, and cost-effective marker of chronic low-grade inflammation. Li et al[36] evaluated the prognostic values of five lymphocyte-based inflammatory indices—PLR, NLR, MLR, systemic immune inflammation index (SII), and SIRI—in patients with ACS and found that lymphocyte-based inflammatory indices were significantly and independently associated with MACCE in patients with ACS who underwent PCI. SIRI outperformed the other four indices in predicting MACCE. Zhao et al[20] investigated the value of preoperative inflammatory biomarkers in predicting aorta-related adverse events (AAEs) after thoracic endovascular aortic repair (TEVAR) for type B aortic dissection and found that increased preoperative SIRI was an independent risk factor for AAEs after TEVAR. Intermittent hypoxia in OSA triggers systemic inflammation through the activation of pro-inflammatory cytokines and oxidative stress, which contribute to endothelial dysfunction and atherosclerotic plaque instability.[9,32] These mechanisms may explain the increased cardiovascular risk in OSA patients. Notably, our study provides novel evidence supporting this inflammatory paradigm. Despite similar OSA severity (AHI, SaO_2)

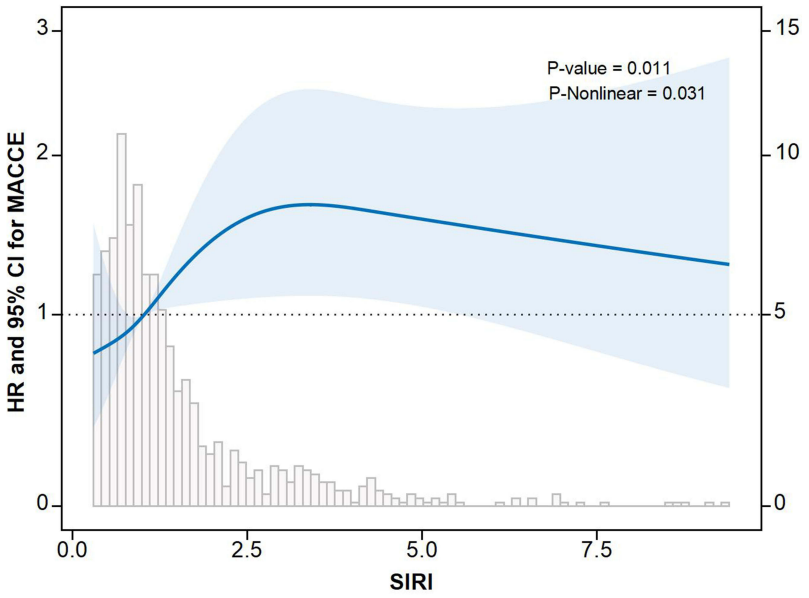

Figure 3 The association between SIRI and MACCE by unadjusted restricted cubic splines.
Abbreviations: SIRI, systemic inflammatory response index; MACCE, major adverse cardiovascular and cerebrovascular event.

Grouping	Low SIRI group (MACCE n,%)	High SIRI group (MACCE n, %)	HR (CI 95%)	*P* value
ODI < 15	8(17.4)	4(20)	1.19(0.36-3.96)	0.775
ODI ≥ 15	66(13.1)	92(22.7)	1.64(1.2-2.25)	0.002
MinimumSaO_2 < median	30(10.4)	48(23)	2.12(1.34-3.34)	0.001
MinimumSaO_2 ≥ median	46(16.5)	52(23.3)	1.35(0.91-2.01)	0.14
MeanSaO_2 < median	21(11.9)	39(28.1)	2.28(1.34-3.87)	0.002
MeanSaO_2 ≥ median	55(14)	61(20.8)	1.42(0.98-2.04)	0.061

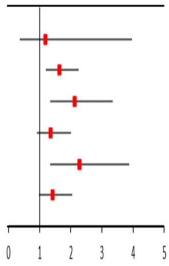

Figure 4 Forest plot for MACCE in Low SIRI group versus High SIRI group stratified by other OSA-related characteristics.
Abbreviations: SIRI, systemic inflammatory response index; MACCE, major adverse cardiovascular and cerebrovascular event; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation.

between high- and low-SIRI groups, elevated SIRI (≥1.16×10^9/L) independently predicted MACCE (adjusted HR=1.44, P=0.039), with heightened risk in patients experiencing significant nocturnal hypoxemia (ODI≥15: HR=1.64, P=0.002). This dissociation suggests that SIRI—a composite marker integrating neutrophils, monocytes, and lymphocytes—may more sensitively capture OSA-driven systemic inflammation than conventional metrics like AHI, thereby serving as a prognostic bridge between OSA and adverse cardiovascular outcomes.

In ACS patients without OSA, reported SIRI thresholds range widely (1.5–2.848×10^9/L). For example, Han et al found that SIRI ≥1.7×10^9/L predicted increased MACCE risk in ACS patients undergoing PCI. A similar result was reported in another cohort, and the SIRI threshold was 2.848×10^9/L.[37] Our observed lower threshold (1.16×10^9/L) in ACS-OSA patients suggests that OSA-induced chronic low-grade inflammation and immune dysregulation further modify prognostic thresholds. This may arise from OSA-driven intermittent hypoxia, which promotes neutrophil activation and monocyte polarization, exacerbating coronary plaque instability even at lower SIRI values.

The role of SIRI in diagnosing malignant diseases has been extensively studied, and its diagnostic performance has also been studied in many diseases characterized by inflammation. SIRI has been positively associated with the risk and poor prognosis of ischemic stroke.[19,38] SIRI can identify patients with ACS at high risk of MACCE[21] and is an independent predictor of 30-day and 90-day mortality in patients with acute myocardial infarction (AMI).[39] In this

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Subgroup	Low SIRI group (MACCE n,%)	High SIRI group (MACCE n, %)	HR (95% CI)	*P* value
Sex				
Male	65(13.3)	87(22.1)	1.6(1.16-2.2)	0.004
Female	13(14.9)	14(34.1)	2.12(1-4.52)	0.051
Age ≥ 65				
Yes	20(15.6)	32(27.4)	1.78(1.02-3.11)	0.044
No	58(12.9)	69(21.7)	1.58(1.11-2.24)	0.01
Hypertension				
Yes	54(13.7)	76(25.6)	1.77(1.25-2.52)	0.001
No	24(13.1)	25(18.1)	1.33(0.76-2.33)	0.321
Diabetes				
Yes	30(15.7)	31(24.4)	1.53(0.93-2.53)	0.096
No	48(12.5)	70(22.7)	1.73(1.2-2.5)	0.003
Dyslipidemia				
Yes	24(11.1)	33(26.4)	2.41(1.42-4.08)	0.001
No	54(15)	68(21.9)	1.4(0.98-2.01)	0.064
ACS type				
STEMI	16(21.9)	53(29.9)	1.38(0.79-2.41)	0.26
NSTEACS	62(12.3)	48(18.6)	1.46(1-2.12)	0.051

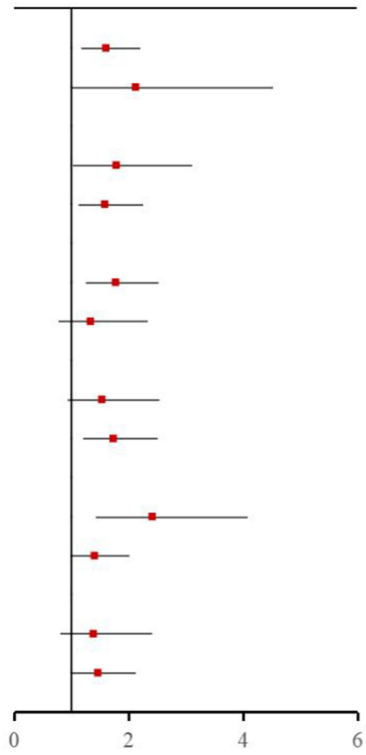

Figure 5 Subgroup analyses for MACCE in the Low SIRI group versus the High SIRI group.
Abbreviation: SIRI, systemic inflammatory response index.

study, we found that a higher SIRI was associated with poor clinical presentation, including higher rates of hyperlipidemia, current smoking, MI, and PCI. Patients with a high SIRI also had higher neutrophil and monocyte counts and Hs-CRP levels but lower LVEF and lymphocyte counts, indicating more severe low-grade inflammation.

In this study, we compared the biomarker performance between SIRI and the classic inflammatory index Hs-CRP, While the discriminative capacity of SIRI for MACCE did not statistically surpass Hs-CRP in either the overall cohort (AUC 0.59 vs 0.55, P=0.15) or severe OSA subgroup (AUC 0.61 vs 0.58, P=0.21), its novel composite formula (neutrophil × monocyte/lymphocyte) provides unique pathophysiological insights into OSA-ACS comorbidity. Unlike Hs-CRP – a downstream marker of IL-6-mediated hepatic responses[40] – SIRI directly quantifies three cellular processes amplified by chronic intermittent hypoxia (CIH): (1) neutrophil activation via HIF-1α-driven NETosis that destabilizes plaques through histone release,[41] (2) monocyte polarization toward pro-inflammatory CD14++CD16+ subsets secreting MMP-9,[42] and (3) lymphocyte depletion via Fas/FasL-mediated apoptosis, reducing plaque-stabilizing Tregs.[43] This triad captures hypoxia-adapted immune dysregulation more precisely than acute-phase reactants. Clinically, SIRI's rapid component turnover (neutrophils: 6–8 hr[44] vs Hs-CRP half-life 19 hr[45]) may better track nocturnal hypoxemia-induced inflammatory bursts. Importantly, SIRI's cellular targets align with emerging therapies – DNase I for NET degradation,[46] CCR2 inhibitors for monocyte recruitment blockade,[47] and IL-7 for lymphocyte reconstitution[48] – offering a mechanistically grounded stratification tool beyond pure prognostic prediction. Thus, even in the absence of superior discriminative performance, SIRI advances our understanding of OSA-driven vascular inflammation through its cell-specific resolution.

While SIRI can predict the severity of OSA and ACS, this study found no significant differences in AHI, T90, minimum SaO_2, mean SaO_2, or ESS (all $P > 0.05$) between the low- and high-SIRI groups. Although the severity of OSA could not be distinguished in patients with ACS having low and high SIRI, after adjusting for traditional CVD risk factors and inflammatory factors, a high SIRI remained independently associated with the occurrence of MACCE. Further research is needed to clarify the value of SIRI in these patients and explore its impact on the prognosis of patients with OSA and ACS.

Limitation

This study has certain limitations. First, it was a single-center cohort study, and potential confounders may not have been fully accounted for. Second, the diagnosis of OSA relied on portable polygraphy, which could underestimate the AHI by overestimating actual sleep time. Third, the dataset lacked information regarding formal follow-up visits at sleep centers and OSA treatment adherence after hospital discharge, preventing evaluation of the impact of OSA treatment on MACCE. Fourth, We recruited patients over a wide range of periods, and we cannot rule out the influence of seasonal fluctuations on the results of blood draws. Fifth, our study did not exclude patients with infections or recent glucocorticosteroid therapies since the original medical records lacked corresponding diagnoses and medical histories. While these patients likely constitute a minority of the population, this unavoidable selection bias should be acknowledged.Finally, this study was conducted using a prospective cohort design, which may have resulted in an overestimation of the extent of the association between exposure and outcome compared to the results of randomized controlled trials.

Conclusion

In this prospective cohort study, elevated SIRI independently predicted major adverse cardiovascular events in ACS and OSA. As a composite biomarker integrating neutrophil activation, monocyte-driven inflammation, and lymphocyte exhaustion, SIRI uniquely bridges OSA-induced systemic inflammation with coronary plaque vulnerability, outperforming traditional OSA severity metrics like apnea-hypopnea index. Future studies should explore whether SIRI-guided interventions improve cardiovascular outcomes in this high-risk population.

Data Sharing Statement

All individual patient data collected during the study will be shared. All available data can be obtained by contacting the corresponding author (Shaoping Nie, spnie@ccmu.edu.cn). A detailed protocol for the proposed study must be provided and approved by an ethics committee before a signed data access agreement is supplied, and discussion with the original authors is initiated for re-analysis.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698. doi:10.1016/S2213-2600(19)30198-5
2. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*. 2009;373(9657):82–93. doi:10.1016/S0140-6736(08)61622-0
3. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive Sleep Apnea and Cardiovascular Disease: a Scientific Statement From the American Heart Association. *Circulation*. 2021;144(3). doi:10.1161/CIR.0000000000000988
4. Lee CH, Khoo SM, Tai BC, et al. Obstructive Sleep Apnea in Patients Admitted for Acute Myocardial Infarction. *Chest*. 2009;135(6):1488–1495. doi:10.1378/chest.08-2336
5. Koo CY, De La Torre AS, Loo G, et al. Effects of Ethnicity on the Prevalence of Obstructive Sleep Apnoea in Patients with Acute Coronary Syndrome: a Pooled Analysis of the ISAACC Trial and Sleep and Stent Study. *Heart Lung Circ*. 2017;26(5):486–494. doi:10.1016/j.hlc.2016.09.010
6. Fan J, Wang X, Ma X, Somers VK, Nie S, Wei Y. Association of Obstructive Sleep Apnea With Cardiovascular Outcomes in Patients With Acute Coronary Syndrome. *J Am Heart Assoc*. 2019;8(2):e010826. doi:10.1161/JAHA.118.010826

7. Wang X, Fan J, Guo R, et al. Association of obstructive sleep apnoea with cardiovascular events in women and men with acute coronary syndrome. *Eur Respir J*. 2023;61(1):2201110. doi:10.1183/13993003.01110-2022
8. Randerath W, Bonsignore MR, Herkenrath S. Obstructive sleep apnoea in acute coronary syndrome. *Eur Respir Rev*. 2019;28(153):180114. doi:10.1183/16000617.0114-2018
9. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. *Eur Respir J*. 2009;33(5):1195–1205. doi:10.1183/09031936.00111208
10. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord*. 2015;16(1):25–34. doi:10.1007/s11154-014-9304-x
11. Dentali F, Nigro O, Squizzato A, et al. Impact of neutrophils to lymphocytes ratio on major clinical outcomes in patients with acute coronary syndromes: a systematic review and meta-analysis of the literature. *Int J Cardiol*. 2018;266:31–37. doi:10.1016/j.ijcard.2018.02.116
12. Balta S, Ozturk C. The platelet-lymphocyte ratio: a simple, inexpensive and rapid prognostic marker for cardiovascular events. *Platelets*. 2015;26(7):680–681. doi:10.3109/09537104.2014.979340
13. Xu N, Tang X, Yao Y, et al. Predictive value of neutrophil to lymphocyte ratio in long-term outcomes of left main and/or three-vessel disease in patients with acute myocardial infarction. *Catheter Cardiovasc Interv*. 2018;91(S1):551–557. doi:10.1002/ccd.27495
14. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer*. 2016;122(14):2158–2167. doi:10.1002/cncr.30057
15. Zhou Q, Su S, You W, Wang T, Ren T, Zhu L. Systemic Inflammation Response Index as a Prognostic Marker in Cancer Patients: a Systematic Review and Meta-Analysis of 38 Cohorts. *Dose-Response*. 2021;19(4):155932582110647. doi:10.1177/15593258211064744
16. Wei L, Xie H, Yan P. Prognostic value of the systemic inflammation response index in human malignancy: a meta-analysis. *Medicine*. 2020;99(50):e23486. doi:10.1097/MD.0000000000023486
17. Jin Z, Wu Q, Chen S, et al. The Associations of Two Novel Inflammation Indexes, SII and SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: a Ten-Year Follow-Up Study in 85,154 Individuals. *J Inflamm Res*. 2021;14:131–140. doi:10.2147/JIR.S283835
18. Elfeky SEF, Ali A, Moazen EM, et al. Systemic inflammatory response index as an independent predictor of severity in patients with obstructive sleep apnea. *Egypt J Bronchol*. 2024;18(1):1. doi:10.1186/s43168-023-00253-y
19. Zhang Y, Xing Z, Zhou K, Jiang S. The Predictive Role of Systemic Inflammation Response Index (SIRI) in the Prognosis of Stroke Patients. *Clin Interv Aging*. 2021;16:1997–2007. doi:10.2147/CIA.S339221
20. Zhao Y, Hong X, Xie X, et al. Preoperative systemic inflammatory response index predicts long-term outcomes in type B aortic dissection after endovascular repair. *Front Immunol*. 2022;13:992463. doi:10.3389/fimmu.2022.992463
21. Han K, Shi D, Yang L, et al. Prognostic value of systemic inflammatory response index in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Ann Med*. 2022;54(1):1667–1677. doi:10.1080/07853890.2022.2083671
22. Hao W, Wang X, Fan J, et al. Prognostic Implications of OSA in Acute Coronary Syndrome by Obesity Status. *CHEST*. 2023;164(1):219–230. doi:10.1016/j.chest.2023.02.001
23. Zhen L, Chen X, Fan J, et al. Prognostic Value of Neutrophil-to-lymphocyte Ratio for Patients with Acute Coronary Syndrome with Obstructive Sleep Apnea. *Cardiovascular Innovations and Applications*. 2024;9(1). doi:10.15212/CVIA.2024.0016.
24. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267–315. doi:10.1093/eurheartj/ehv320
25. Sateia MJ. International Classification of Sleep Disorders-Third Edition. *Chest*. 2014;146(5):1387–1394. doi:10.1378/chest.14-0970
26. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for Scoring Respiratory Events in Sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events: deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;08(05):597–619. doi:10.5664/jcsm.2172
27. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. *J Clin Sleep Med*. 2009;05(03):263–276. doi:10.5664/jcsm.27497.
28. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. *J Am Coll Cardiol*. 2015;66(4):403–469. doi:10.1016/j.jacc.2014.12.018
29. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep Apnea and Cardiovascular Disease: lessons From Recent Trials and Need for Team Science. *Circulation*. 2017;136(19):1840–1850. doi:10.1161/CIRCULATIONAHA.117.029400
30. Correia LCL, Souza AC, Garcia G, et al. Obstructive Sleep Apnea Affects Hospital Outcomes of Patients with non-ST-Elevation Acute Coronary Syndromes. *Sleep*. 2012;35(9):1241–1245. doi:10.5665/sleep.2078
31. Nakashima H. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. *Eur Heart J*. 2006;27(19):2317–2322. doi:10.1093/eurheartj/ehl219
32. Vitulano N. Obstructive sleep apnea and heart disease the biomarkers point of view. *Front Biosci*. 2013;S5(2):588–599. doi:10.2741/S392
33. Wang RH, Wen WX, Jiang ZP, et al. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. *Front Immunol*. 2023;14:1115031. doi:10.3389/fimmu.2023.1115031
34. Lee H, Kim I, Kang BH, Um SJ. Prognostic value of serial neutrophil-to-lymphocyte ratio measurements in hospitalized community-acquired pneumonia. *PLoS One*. 2021;16(4):e0250067. doi:10.1371/journal.pone.0250067
35. Dong CH, Wang ZM, Chen SY. Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: a systematic review and meta-analysis. *Clin Biochem*. 2018;52:131–136. doi:10.1016/j.clinbiochem.2017.11.008
36. Li Q, Ma X, Shao Q, et al. Prognostic Impact of Multiple Lymphocyte-Based Inflammatory Indices in Acute Coronary Syndrome Patients. *Front Cardiovasc Med*. 2022;9:811790. doi:10.3389/fcvm.2022.811790
37. Song G, Wang X, Wei C, et al. The Complex Inflammatory and Nutritional Indices to Predict Prognostic Risk for Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *Immunity, Inflammation and Disease*. 2025;13(3). doi:10.1002/iid3.70180.
38. Zhou Y, Zhang Y, Cui M, Zhang Y, Shang X. Prognostic value of the systemic inflammation response index in patients with acute ischemic stroke. *Brain Behav*. 2022;12(6):e2619. doi:10.1002/brb3.2619

39. Wang Y, Chen H. A nonlinear relationship between systemic inflammation response index and short-term mortality in patients with acute myocardial infarction: a retrospective study from MIMIC-IV. *Front Cardiovasc Med*. 2023;10:1208171. doi:10.3389/fcvm.2023.1208171
40. Ngwa DN, Pathak A, Agrawal A. IL-6 regulates induction of C-reactive protein gene expression by activating STAT3 isoforms. *Mol Immunol*. 2023;146:50–56.
41. Thomas C, Leleu D, Masson D. Cholesterol and HIF-1a: dangerous Liaisons in Atherosclerosis. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.868958
42. Watanabe R, Maeda T, Zhang H, et al. Matrix Metalloprotease-9 (MMP-9)-Producing Monocytes Enable T Cells to Invade the Vessel Wall and Cause Vasculitis. *Circ Res*. 2019;123(6):700–715.
43. Veltkamp C, Anstaett M, Wahl K, et al. Apoptosis of regulatory T lymphocytes is increased in chronic inflammatory bowel disease and reversed by anti-TNFa treatment. *Inflammatory Bowel Dis*.
44. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. *Trends in Immunology*. 2010;31(8):318–324. doi:10.1016/j.it.2010.05.006
45. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805–1812. doi:10.1172/JCI200318921
46. Park HH, Park W, Lee YY, et al. Bioinspired DNase-I-Coated Melanin-Like Nanospheres for Modulation of Infection-Associated NETosis Dysregulation.
47. Fujimura N. CCR2 inhibition sequesters multiple subsets of leukocytes in the bone marrow. *Sci Rep*. 2015;5:11664.
48. Mackall CL, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application. *Nat Rev Immunol*. 2020;11:330–352.