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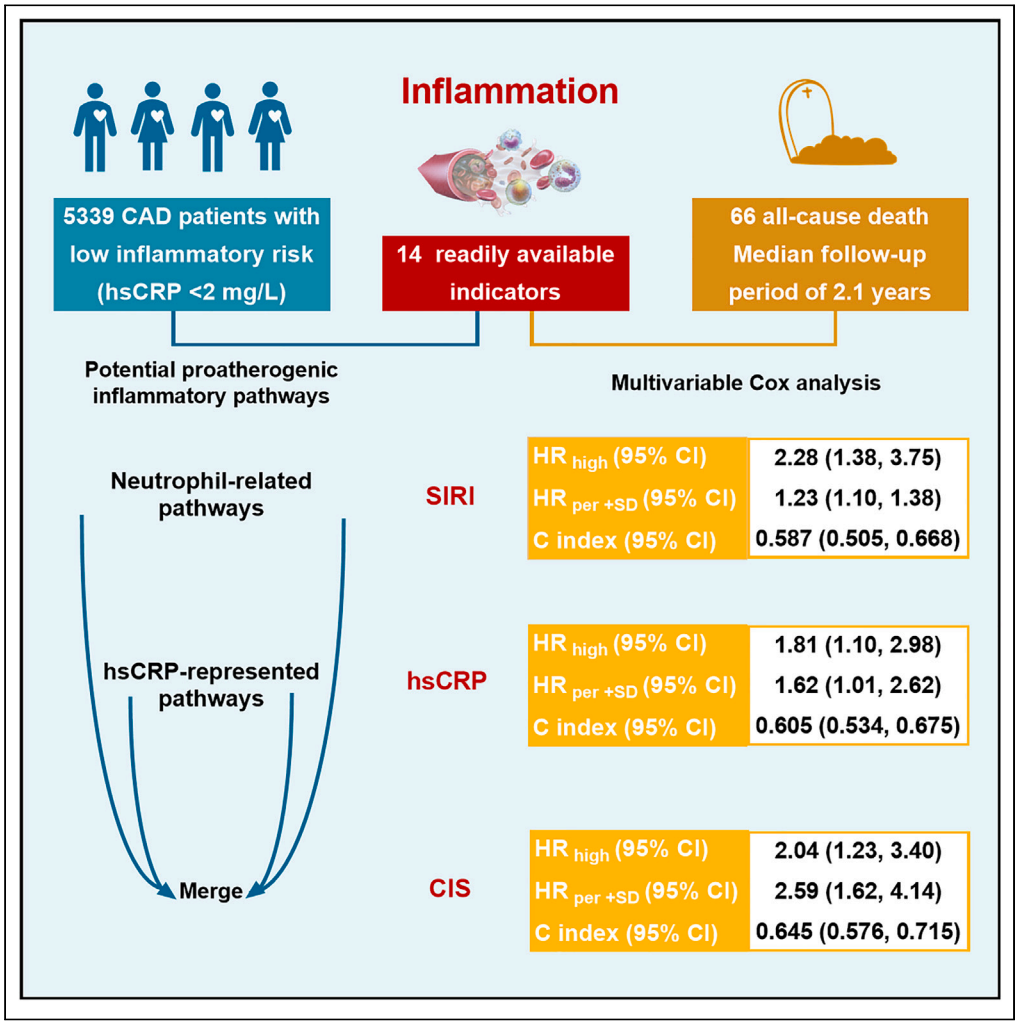


Tianyu Li, Peizhi Wang, Xiaozeng Wang, ..., Pei Zhu, Yaling Han, Jinqing Yuan

dr_jinqingyuan@sina.com

## Highlights

CAD patients with hsCRP levels <2 mg/L still have inflammatory burdens beyond hsCRP

SIRI has the most robust predictive value of all-cause mortality among 14 indicators

The new CIS may offer better inflammation assessment and mortality prediction

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# Prognostic significance of inflammation in patients with coronary artery disease at low residual inflammatory risk

Tianyu Li,[1] Peizhi Wang,[1] Xiaozeng Wang,[2] Zhenyu Liu,[3] Zheng Zhang,[4] Yongzhen Zhang,[5] Zhifang Wang,[6] Yingqing Feng,[7] Qingsheng Wang,[8] Xiaogang Guo,[9] Xiaofang Tang,[10] Jingjing Xu,[10] Ying Song,[10] Yan Chen,[10] Na Xu,[10] Yi Yao,[10] Ru Liu,[10] Pei Zhu,[10] Yaling Han,[3] and Jinqing Yuan[1,10,11,*]

## SUMMARY

**Patients with coronary artery disease (CAD) at low residual inflammatory risk are often overlooked in research and practice. This study examined the associations between fourteen inflammatory indicators and all-cause mortality in 5,339 CAD patients with baseline high-sensitivity C-reactive protein (hsCRP) <2 mg/L who received percutaneous coronary intervention and statin and aspirin therapy. The median follow-up time was 2.1 years. Neutrophil-derived systemic inflammatory response index (SIRI) yielded the strongest and most robust association with all-cause mortality among all indicators. Lower hsCRP remained to be associated with a lower risk of all-cause mortality. A newly developed comprehensive inflammation score (CIS) showed better predictive performance than other indicators, which was validated by an independent external cohort. In conclusion, neutrophil-derived indicators, particularly SIRI, strongly predicted all-cause mortality independent of hsCRP in CAD patients at low residual inflammatory risk. CIS may help identify individuals with inflammation burdens that cannot be explained by hsCRP alone.**

## INTRODUCTION

With the success of canakinumab and colchicine in reducing the incidence of cardiovascular events in secondary prevention of coronary artery disease (CAD),[1–3] controlling residual inflammatory risk has become a consensus in the management of CAD. Although patients on statins with low levels of high-sensitivity C-reactive protein (hsCRP) are considered to be at low residual inflammatory risk and have better event-free survival, 5.37–6.56% of them still experience recurrent myocardial infarction and death.[4–7] Recent evidence indicates a neutrophil-related residual inflammatory risk beyond hsCRP-related risk in patients with hsCRP <2 mg/L.[8] Unfortunately, this population is often excluded from anti-inflammatory clinical trials or treated as a low-risk control group in observational studies. It remains unclear which indicators can reflect low-grade inflammation burden and predict prognosis in these patients.

Inflammatory biomarkers are frequently discussed in the context of CAD research. Blood cell-related indicators have the advantage of being ubiquitously tested through routine blood draws in nearly any clinical scenario. The roles of neutrophils and the neutrophil-to-lymphocyte ratio (NLR) in risk stratification, prognosis prediction, and anti-inflammatory effect monitoring have been widely validated.[9,10] Monocytes consist of diverse heterogeneous subsets, tending toward a proatherogenic phenotype overall.[11] The monocyte-to-lymphocyte ratio (MLR) has been reported to be associated with the severity of carotid plaques[12] and cardiovascular and cerebrovascular events.[13] Platelets release proinflammatory mediators that stimulate thrombus formation. Elevated baseline platelet count and platelet-to-lymphocyte ratio (PLR) can reflect inflammation and atherosclerosis.[14] Recent studies have introduced three novel blood cell-derived indicators—systemic inflammatory response index (SIRI), systemic inflammatory index (SII), and aggregate index of systemic inflammation (AISI)—into the field of cardiovascular disease. SIRI, in particular, is associated with atherosclerotic cardiovascular disease risk,[15] the severity of coronary artery lesions,[16]

[1]National Clinical Research center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
[2]Cardiovascular Research Institute & Department of Cardiology, General Hospital of Northern Theater Command, Shenyang 110016, China
[3]Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
[4]Department of Cardiology, The First Hospital of Lanzhou University, Lanzhou 730000, China
[5]Department of Cardiology, Peking University Third Hospital, Beijing 100191, China
[6]Department of Cardiology, Xinxiang Central Hospital, Xinxiang 453002, China
[7]Department of Cardiology, Guangdong Cardiovascular Institute, Guangzhou 510100, China
[8]Department of Cardiology, The First Hospital of Qinhuangdao, Qinhuangdao 066000, China
[9]Department of Cardiology, The First Affiliated Hospital of Zhejiang University, Hangzhou 314400, China
[10]Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
[11]Lead contact
*Correspondence: dr_jinqingyuan@sina.com
https://doi.org/10.1016/j.isci.2023.108060

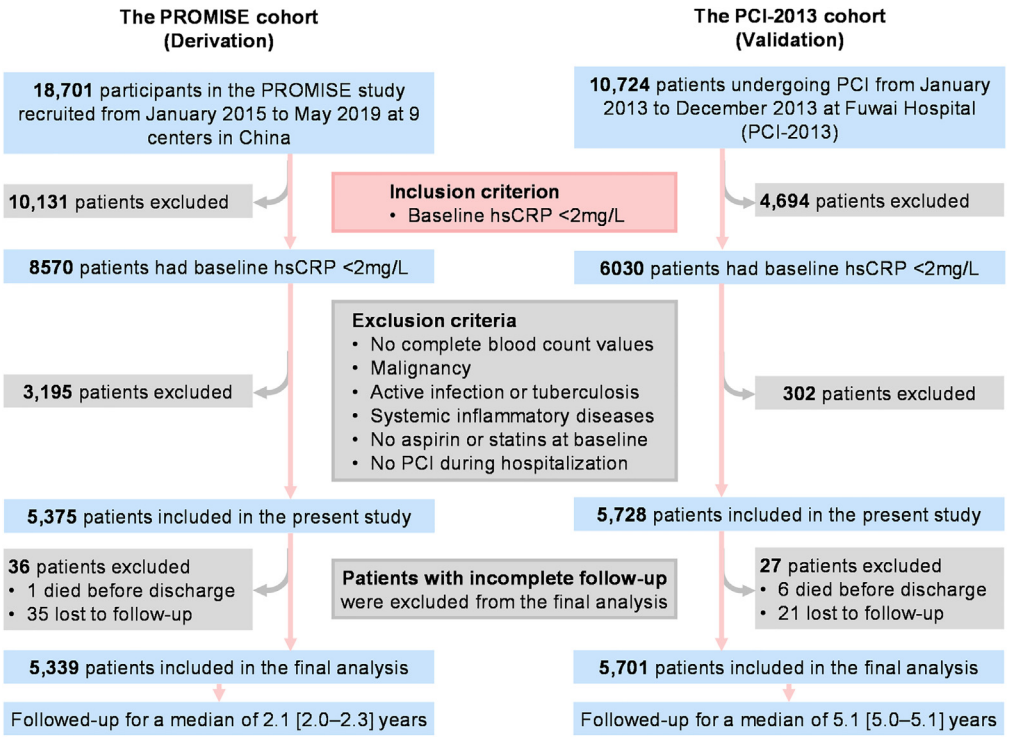


**Figure 1. Study flowchart by cohort**

Abbreviations: hsCRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; PCI-2013, patients undergoing percutaneous coronary intervention in 2013 at Fuwai Hospital; PROMISE, the prospective observational multi-center cohort for ischemic and hemorrhage risk in coronary artery disease patients.

cardiovascular events, and all-cause mortality,[17] and can enhance the predictive value of the Global Registry of Acute Coronary Events (GRACE) risk score.[18] Besides, serum albumin, a commonly measured biomarker, possesses anti-inflammatory, antioxidant, and antithrombotic properties. Low serum albumin levels indicate low-grade inflammation and are associated with increased cardiovascular risk.[19] The prognostic nutritional index (PNI), calculated from serum albumin and lymphocytes,[20] is also of interest as an immunonutritional marker.

This study aims to evaluate the prognostic significance of these easily measurable and widely available biomarkers of the extent of inflammation in a cohort of CAD patients who underwent percutaneous coronary intervention (PCI) and received statin and aspirin therapy with baseline hsCRP <2 mg/L.

## RESULTS

### Study population and baseline characteristics

Figure 1 shows the number of individuals at each stage for the prospective observational multi-center cohort for ischemic and hemorrhage risk in coronary artery disease patients (PROMISE) and an independent prospective cohort of patients undergoing PCI in 2013 at Fuwai Hospital (PCI-2013), which served as an external validation group.

Among the 5,339 PROMISE participants eligible for the final analysis, the median age was 61 years (interquartile range: 53–67 years), 1,274 (23.86%) were female, 1,739 (32.57%) had acute coronary syndrome (ACS), and only 1,560 (29.22%) achieved low-density lipoprotein cholesterol (LDL-c) <1.8 mmol/L. In comparison, patients in the validation cohort were younger and less likely to be female. They had a higher prevalence of ACS but a lower rate of achieving the LDL-c goal. Additionally, the validation cohort presented a lower rate of smoking cessation, lower levels of inflammatory indicators, and a lower frequency of comorbidities (Table 1).

Patients' baseline characteristics were well balanced when stratified by NLR, SIRI, and SII levels but relatively imbalanced by platelets, PLR, serum albumin, PNI, and hsCRP levels. Groups of high white blood cells, neutrophils, monocytes, lymphocytes, and platelets had lower proportions of individuals ≥65 years than their low-level counterparts. Conversely, groups of high levels of other indicators had more individuals ≥65 years than the low-level groups. In most cases, females were fewer or comparable in groups of high inflammatory indicators compared with low-level groups. Patients with high inflammatory indicators were more likely to present with ACS and diabetes, while other comorbidities were generally comparable between groups. The high-hsCRP group had more obese individuals and fewer patients with low residual cholesterol risk than the low-hsCRP group, but this trend was not observed between groups classified by other indicators. Refer to Tables S1–S3 for details on the baseline characteristics of patients stratified by levels of inflammatory indicators.

**Table 1. Patients' baseline characteristics by cohort**

| Variables | PROMISE (n = 5339) | PCI-2013 (n = 5701) | *p* |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, years | 61 [53–67] | 58 [51–65] | <0.001 |
| ≥65 | 1795 (33.62) | 1512 (26.52) | <0.001 |
| Female | 1274 (23.86) | 1243 (21.80) | 0.010 |
| Body mass index, kg/m$^2$ | 25.40 [23.57–27.68] | 25.65 [23.67–27.68] | 0.297 |
| ≥28 | 1148 (21.50) | 1202 (21.08) | 0.592 |
| Smoking history | | | <0.001 |
| Current smoker | 1110 (20.79) | 3166 (55.53) | |
| Former smoker | 1906 (35.70) | 70 (1.23) | |
| Non-Smoker | 2323 (43.51) | 2465 (43.24) | |
| Clinical characteristics | | | |
| Type of CAD | | | <0.001 |
| ACS | 1739 (32.57) | 3085 (54.11) | |
| CCS | 3600 (67.43) | 2616 (45.89) | |
| Diabetes | 2627 (49.20) | 2320 (40.69) | <0.001 |
| Hypertension | 4798 (89.87) | 4685 (82.18) | <0.001 |
| Dyslipidemia | 4983 (93.33) | 4759 (83.48) | <0.001 |
| Peripheral artery disease | 285 (5.34) | 161 (2.82) | <0.001 |
| Chronic kidney disease | 122 (2.29) | 29 (0.51) | <0.001 |
| Prior myocardial infarction | 981 (18.37) | 1196 (20.98) | <0.001 |
| Prior stroke | 757 (14.18) | 559 (9.81) | <0.001 |
| Prior PCI | 1399 (26.20) | 1454 (25.50) | 0.402 |
| Prior CABG | 112 (2.10) | 232 (4.07) | <0.001 |
| Total cholesterol, mmol/L | 3.80 [3.23–4.52] | 3.94 [3.36–4.66] | <0.001 |
| Total triglyceride, mmol/L | 1.37 [1.01–1.90] | 1.49 [1.10–2.02] | <0.001 |
| HDL-c, mmo/L | 1.09 [0.92–1.29] | 1.02 [0.87–1.21] | <0.001 |
| LDL-c, mmol/L | 2.18 [1.72–2.78] | 2.25 [1.79–2.87] | <0.001 |
| ≤1.8 | 1560 (29.22) | 1455 (25.52) | <0.001 |
| LVEF <40% | 73 (1.37) | 51 (0.89) | 0.019 |
| Inflammation indicators | | | |
| White blood cells, ×10$^9$/L | 6.67 [5.54–8.21] | 6.20 [5.27–7.28] | <0.001 |
| Neutrophils, ×10$^9$/L | 4.25 [3.38–5.56] | 3.71 [3.02–4.53] | <0.001 |
| Monocytes, ×10$^9$/L | 0.38 [0.30–0.48] | 0.37 [0.30–0.45] | <0.001 |
| Lymphocytes, ×10$^9$/L | 1.72 [1.36–2.15] | 1.85 [1.49–2.26] | <0.001 |
| Platelets, ×10$^9$/L | 216 [180–254] | 194 [164–229] | <0.001 |
| NLR | 2.42 [1.79–3.46] | 2.00 [1.54–2.61] | <0.001 |
| MLR | 0.22 [0.17–0.28] | 0.20 [0.15–0.25] | <0.001 |
| PLR | 124.88 [97.40–160.09] | 104.67 [83.33–131.97] | <0.001 |
| SIRI | 0.92 [0.62–1.43] | 0.74 [0.51–1.04] | <0.001 |
| SII | 525.94 [372.54–778.97] | 384.89 [285.94–529.65] | <0.001 |
| AISI | 199.46 [127.03–320.56] | 141.32 [94.52–211.78] | <0.001 |
| Serum albumin, g/L | 44.30 [40.70–47.50] | 43.20 [40.40–46.40] | <0.001 |
| PNI | 53.20 [49.35–57.01] | 52.95 [49.35–56.40] | 0.013 |
| hsCRP, mg/L | 0.95 [0.51–1.41] | 0.90 [0.54–1.35] | 0.065 |

(*Continued on next page*)

**Table 1. *Continued***

| Variables | PROMISE (n = 5339) | PCI-2013 (n = 5701) | *p* |
|---|---|---|---|
| Procedural characteristics | | | |
| LM/TVD | 2330 (43.64) | 208 (3.65) | <0.001 |
| SYNTAX score | | | <0.001 |
| ≤22 | 4637 (86.88) | 5140 (90.16) | |
| 23–32 | 575 (10.77) | 469 (8.23) | |
| ≥33 | 125 (2.34) | 92 (1.61) | |
| Unsuccessful PCI | 161 (3.02) | 113 (1.98) | <0.001 |

Values are presented as number (%) or median [interquartile range]. ACS, acute coronary syndrome; AISI, aggregate index of systemic inflammation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; HDL-c, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; LM/TVD, left main stem/three-vessel disease; LVEF, left ventricular ejection fraction; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PCI, percutaneous coronary intervention; PCI-2013, patients undergoing percutaneous coronary intervention in 2013 at Fuwai Hospital; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PROMISE, the prospective observational multi-center cohort for ischemic and hemorrhage risk in coronary artery disease patients; SII, systemic inflammatory index; SIRI, systemic inflammatory response index; SYNTAX, synergy between percutaneous coronary intervention with Taxus and cardiac surgery.

## Correlations between inflammatory indicators

Figure S1 illustrates non-normal distributions of baseline inflammatory indicators in all participants and subgroups. The differences in the distributions of certain indicators between some subgroups reached statistical significance; however, the magnitude of these differences might not be deemed clinically significant.

Spearman's rank correlation analysis showed that neutrophils had a high to strong positive correlation with white blood cells and indexes derived from them; monocytes and platelets had medium correlations with their derived indexes; lymphocytes were negatively correlated with their derived indexes; the indexes NLR, MLR, SIRI, SII, and AISI generally had high to strong correlations with each other; PNI had a weak negative correlation with indexes derived from blood cells; serum albumin and hsCRP showed no correlation with other indicators (Figure 2).

## Associations between inflammatory indicators and clinical outcomes

Sixty-six deaths were recorded during a median follow-up of 2.1 years (interquartile range: 2.0–2.3 years), of which 37 were attributed to cardiac causes. The all-cause death rate was 5.47 per 1,000 person-years. Kaplan-Meier analysis revealed that patients with above-cut-off levels of white blood cells, neutrophils, monocytes, NLR, MLR, PLR, SIRI, AISI, and hsCRP had significantly reduced survival rates. Contrarily, the survival rates did not differ significantly between patients stratified by lymphocytes, platelets, SII, serum albumin, and PNI levels (Figure 3). Figure S2 revealed that patients with above-cut-off levels of neutrophils, SIRI, and hsCRP had significantly reduced cardiac mortality-free survival rates.

On a continuous scale, the unadjusted risk of all-cause mortality declined with elevating serum albumin and PNI and rose with the increase of other inflammatory indicators except for lymphocytes and platelets. The significant association between serum albumin or PNI and the risk of all-cause mortality disappeared after adjustment. The results of inflammatory indicators categorized by receiver operating characteristic (ROC)-determined cut-offs revealed that lymphocytes, platelets, serum albumin, and PNI were still not associated with the risk of all-cause mortality, with or without adjustment. MLR lost its association with the risk of all-cause mortality after adjustment, whereas the opposite was true for SII. The above-cut-off groups of other indicators were significantly associated with an increased risk of all-cause mortality compared with their low-level counterparts, regardless of adjustment (Tables 2 and S4). Table S5 shows that higher levels of neutrophils and SIRI were significantly associated with elevated risk of cardiac mortality, whether analyzed as continuous or categorical variables. White blood cells, SII, and AISI were significantly associated with cardiac mortality in the context of continuous variables, while hsCRP showed significance only when analyzed categorically.

Comparison of univariate Cox models for predicting all-cause mortality showed that hsCRP, both continuous and categorical, had the highest 730-day area under the curve and Harrell's C-index, followed by SIRI category, with relatively small differences between other indicators and hsCRP (Table 3). Inflammatory indicators showed relatively weaker predictive performance for cardiac mortality compared to their performance in predicting all-cause mortality. This disparity could be attributed to the limited number of cardiac mortalities and the fact that the established cut-off points were derived from models for all-cause mortality (Table S6).

## Sensitivity analyses and subgroup analysis

When adjusting for age as the underlying timescale, the differences in survival rates between groups stratified by platelets and SII levels became significant, whereas the significance of the difference between MLR groups was lost (Figure S3). The hazard ratio of a one-standard-deviation increase in hsCRP was borderline significant. Analysis for other indicators generated similar results to the main analysis (Table S7).

When inflammatory indicators were categorized by the medians, the differences in survival rates between groups stratified by serum albumin and PNI levels became significant, whereas the significance of the difference between groups of different levels of monocytes and NLR was lost

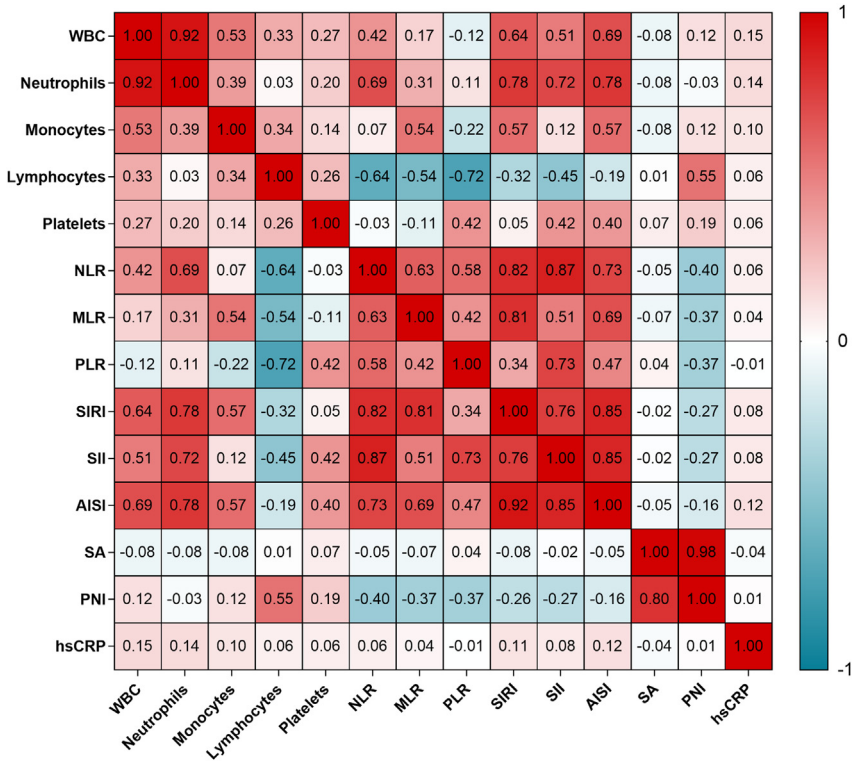


**Figure 2. Spearman correlation between each pair of inflammation indicators**

Abbreviations: AISI, aggregate index of systemic inflammation; hsCRP, high-sensitivity C-reactive protein; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic inflammatory index; SIRI, systemic inflammatory response index; WBC, white blood cells.

(Figure S4). The above-median levels of neutrophils, MLR, SIRI, AISI, serum albumin, PNI, and hsCRP were significantly associated with a higher risk of all-cause mortality than their low-level counterparts without adjustment. However, after adjustment, only the above-median groups of neutrophils, SIRI, AISI, and hsCRP retained a significant association with increased risk of all-cause mortality after adjustment (Table S8).

In conclusion, only neutrophils, SIRI, and AISI consistently predicted the risk of all-cause mortality, both when analyzed continuously or categorically. The results remained robust after adjustment and sensitivity analyses.

SIRI yielded more robust results than other indicators. Specifically, high SIRI had significantly higher hazard ratios for all-cause mortality across all subgroups except for obese and low residual cholesterol risk populations. The effect of high hsCRP on the risk of all-cause mortality appeared to be age dependent, with a significant association observed in the group aged ≥65 years but not in the younger age group. No interaction was observed between other inflammatory indicators categories and subgroup variables (Figure 4).

## Development and validation of a comprehensive inflammation score

Given the robust association between SIRI and clinical outcomes and the strong prognostic significance of hsCRP, we developed a comprehensive inflammation score (CIS) incorporating SIRI and hsCRP. The distributions of CIS were comparable between the two cohorts. Survival rates were significantly lower among patients with high CIS levels. The risk of all-cause mortality increased with the score, with an adjusted hazard ratio of 2.59 (95% confidence interval: 1.62–4.14) and 2.12 (95% confidence interval: 1.30–3.47) per standard deviation in the PROMISE cohort and the validation cohort, respectively. The high-score category had corresponding values of 2.04 (1.23–3.40) and 1.56 (1.15–2.13) in the PROMISE and validation cohorts, respectively. Harrell's C index, area under the curve on day 730, and integrated discrimination improvement showed that CIS produced a better prediction of all-cause mortality than SIRI and hsCRP. Comparison in the validation cohort obtained similar results (Figure 5). In the ACS and chronic coronary syndrome (CCS) subpopulations, the performance of CIS was observed to only slightly surpass those of SIRI and hsCRP numerically, without reaching statistical significance (Figure S5).

## DISCUSSION

This study examined the prognostic significance of fourteen routinely used inflammatory indicators in CAD patients with baseline hsCRP <2 mg/L who underwent PCI and received statin and aspirin therapy. The main findings are as follows: hsCRP remained a significant predictor of all-cause mortality; neutrophils and neutrophil-derived SIRI and AISI were strongly associated with the risk of all-cause mortality, with SIRI

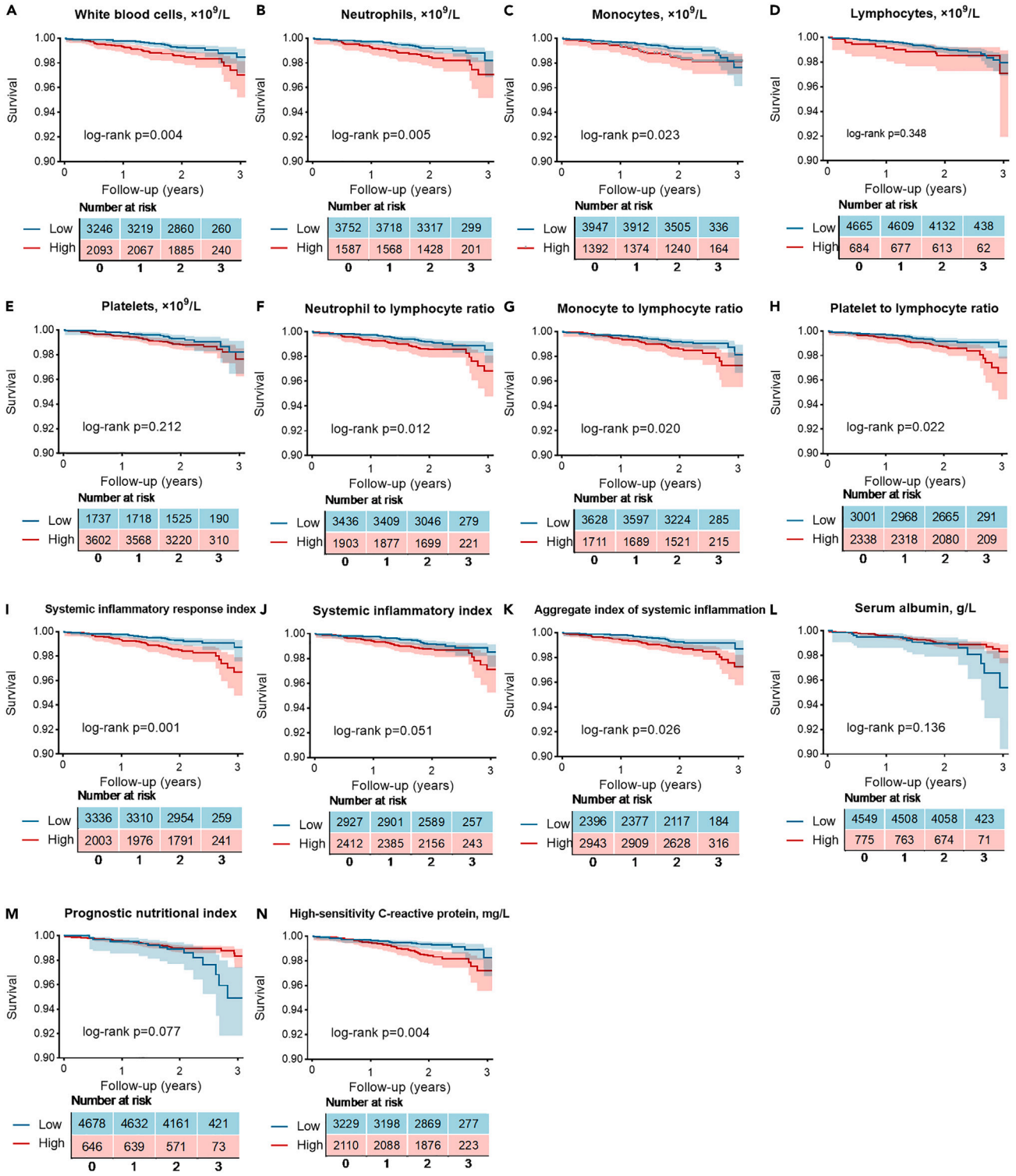


**Figure 3. Survival curves for patients stratified by levels of inflammation indicators**

(A–N) (A) White blood cells; (B) neutrophils; (C) monocytes; (D) lymphocytes; (E) platelets; (F) neutrophil-to-lymphocyte ratio; (G) monocyte-to-lymphocyte ratio; (H) platelet-to-lymphocyte ratio; (I) systemic inflammatory response index; (J) systemic inflammatory index; (K) aggregate index of systemic inflammation; (L) serum albumin; (M) prognostic nutritional index; (N) high-sensitivity C reactive protein. Cut-offs for inflammatory indicators were determined by the receiver operating characteristic analysis.

**Table 2. Multivariable Cox proportional-hazard regression analysis for all-cause mortality**

| Indicators | Event/Total | Event rate per 1000 pys | Adjusted HR (95% CI) | *p* |
|---|---|---|---|---|
| WBC, $\times 10^9$/L (per-SD increase) | | | 1.15 (1.06, 1.24) | 0.001 |
| >7.24 (category) | 38/2093 | 7.90 | 2.12 (1.28, 3.50) | 0.004 |
| ≤7.24 (category) | 28/3246 | 3.85 | Ref. | |
| Neutrophils, $\times 10^9$/L (per-SD increase) | | | 1.15 (1.06, 1.24) | 0.001 |
| >5.21 (category) | 31/1587 | 8.45 | 2.13 (1.29, 3.50) | 0.003 |
| ≤5.21 (category) | 35/3752 | 4.16 | Ref. | |
| Monocytes, $\times 10^9$/L (per-SD increase) | | | 4.15 (1.08, 15.90) | 0.038 |
| >0.47 (category) | 26/1392 | 8.12 | 1.85 (1.11, 3.00) | 0.018 |
| ≤0.47 (category) | 40/3947 | 4.51 | Ref. | |
| Lymphocytes, $\times 10^9$/L (per-SD increase) | | | 0.92 (0.70, 1.21) | 0.540 |
| >2.50 (category) | 11/684 | 7.11 | 1.35 (0.70, 2.62) | 0.374 |
| ≤2.50 (category) | 55/4655 | 5.22 | Ref. | |
| Platelets, $\times 10^9$/L (per-SD increase) | | | 1.00 (1.00, 1.01) | 0.093 |
| >191 (category) | 49/3602 | 6.04 | 1.72 (0.98, 3.04) | 0.061 |
| ≤191 (category) | 17/1737 | 4.30 | Ref. | |
| NLR (per-SD increase) | | | 1.13 (1.06, 1.20) | <0.001 |
| >2.89 (category) | 34/1903 | 7.78 | 1.79 (1.09, 2.91) | 0.020 |
| ≤2.89 (category) | 32/3436 | 4.15 | Ref. | |
| MLR (per-SD increase) | | | 7.45 (1.35, 41.24) | 0.021 |
| >0.26 (category) | 31/1711 | 7.83 | 1.51 (0.92, 2.48) | 0.102 |
| ≤0.26 (category) | 35/3628 | 4.31 | Ref. | |
| PLR (per-SD increase) | | | 1.00 (1.00, 1.01) | 0.027 |
| >132.37 (category) | 38/2338 | 7.20 | 1.68 (1.02, 2.76) | 0.040 |
| ≤132.37 (category) | 28/3001 | 4.12 | Ref. | |
| SIRI (per-SD increase) | | | 1.23 (1.10, 1.38) | <0.001 |
| >1.12 (category) | 39/2003 | 8.43 | 2.28 (1.38, 3.75) | 0.001 |
| ≤1.12 (category) | 27/3336 | 3.62 | Ref. | |
| SII (per-SD increase) | | | 1.00 (1.00, 1.00) | <0.001 |
| >562.24 (category) | 38/2412 | 6.93 | 1.68 (1.02, 2.76) | 0.042 |
| ≤562.24 (category) | 28/2927 | 4.25 | Ref. | |
| AISI (per-SD increase) | | | 1.00 (1.00, 1.00) | <0.001 |
| >182.18 (category) | 46/2943 | 6.84 | 1.80 (1.05, 3.07) | 0.032 |
| ≤182.18 (category) | 20/2396 | 3.74 | Ref. | |
| Serum albumin, g/L (per-SD increase) | | | 0.98 (0.93, 1.03) | 0.372 |
| <39.00 (category) | 14/775 | 7.97 | 0.80 (0.42, 1.50) | 0.480 |
| ≥39.00 (category) | 52/4549 | 5.06 | Ref. | |
| PNI (per-SD increase) | | | 0.98 (0.94, 1.02) | 0.317 |
| <46.55 (category) | 13/646 | 8.75 | 0.94 (0.49, 1.80) | 0.856 |
| ≥46.55 (category) | 53/4678 | 5.02 | Ref. | |
| hsCRP, mg/L (per-SD increase) | | | 1.62 (1.01, 2.62) | 0.046 |
| >1.13 (category) | 38/2110 | 7.91 | 1.81 (1.10, 2.98) | 0.020 |
| ≤1.13 (category) | 28/3229 | 3.85 | Ref. | |

Adjusted for age, sex, body mass index, acute coronary syndrome, prior coronary artery bypass grafting, prior stroke, diabetes, chronic kidney disease, left ventricular ejection fraction <40%, left main stem/three-vessel disease, and unsuccessful percutaneous coronary intervention. AISI, aggregate index of systemic inflammation; CI, confidence interval; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic inflammatory index; SIRI, systemic inflammatory response index; WBC, white blood cells.

**Table 3. Performance of inflammatory indicators in predicting 2-year all-cause mortality**

| Indicators | Harrell's C-index (95% CI) | AUC on day 730 | IDI (95% CI) | *p* | NRI (95% CI) | *p* |
|---|---|---|---|---|---|---|
| WBC | 0.585 (0.505, 0.665) | 0.577 | −0.003 (−0.011, 0.002) | 0.158 | −0.105 (−0.332, 0.184) | 0.396 |
| Category | 0.583 (0.519, 0.647) | 0.582 | −0.001 (−0.009, 0.007) | 0.812 | −0.217 (−0.351, 0.291) | 0.851 |
| Neutrophils | 0.579 (0.498, 0.660) | 0.575 | −0.003 (−0.009, 0.003) | 0.515 | −0.145 (−0.289, 0.220) | 0.653 |
| Category | 0.576 (0.512, 0.640) | 0.574 | 0.000 (−0.009, 0.008) | 0.356 | −0.131 (−0.334, 0.271) | 0.475 |
| Monocytes | 0.562 (0.483, 0.640) | 0.562 | −0.004 (−0.012, 0.001) | 0.119 | −0.226 (−0.328, 0.105) | 0.218 |
| Category | 0.573 (0.510, 0.636) | 0.574 | −0.001 (−0.013, 0.011) | 0.218 | −0.108 (−0.329, 0.299) | 0.495 |
| Lymphocytes | 0.538 (0.456, 0.620) | 0.568 | −0.006 (−0.012, 0.000) | <0.001 | −0.209 (−0.350, −0.015) | 0.020 |
| Category | 0.526 (0.476, 0.576) | 0.528 | −0.007 (−0.015, 0.000) | <0.001 | −0.217 (−0.348, 0.103) | 0.079 |
| Platelets | 0.531 (0.463, 0.600) | 0.522 | −0.006 (−0.013, 0.000) | 0.059 | −0.217 (−0.319, 0.123) | 0.119 |
| Category | 0.547 (0.493, 0.600) | 0.552 | −0.004 (−0.010, 0.000) | 0.020 | −0.217 (−0.320, 0.081) | 0.297 |
| NLR | 0.550 (0.463, 0.636) | 0.510 | −0.003 (−0.012, 0.000) | 0.040 | −0.188 (−0.306, 0.141) | 0.277 |
| Category | 0.567 (0.503, 0.631) | 0.572 | −0.001 (−0.009, 0.007) | 0.634 | −0.217 (−0.341, 0.267) | 0.713 |
| MLR | 0.574 (0.496, 0.652) | 0.533 | −0.004 (−0.012, 0.001) | 0.099 | −0.192 (−0.328, 0.108) | 0.238 |
| Category | 0.562 (0.498, 0.626) | 0.562 | −0.001 (−0.009, 0.006) | 0.317 | −0.217 (−0.363, 0.237) | 0.574 |
| PLR | 0.548 (0.472, 0.625) | 0.532 | −0.005 (−0.009, 0.000) | 0.020 | −0.244 (−0.346, 0.047) | 0.099 |
| Category | 0.556 (0.492, 0.620) | 0.550 | −0.001 (−0.009, 0.005) | 0.416 | −0.217 (−0.319, 0.189) | 0.535 |
| SIRI | 0.587 (0.505, 0.668) | 0.548 | −0.004 (−0.012, 0.000) | 0.059 | −0.165 (−0.299, 0.111) | 0.297 |
| Category | 0.592 (0.528, 0.656) | 0.591 | 0.001 (−0.007, 0.008) | 0.693 | 0.178 (−0.361, 0.310) | 0.733 |
| SII | 0.560 (0.478, 0.641) | 0.501 | −0.005 (−0.011, 0.001) | 0.119 | −0.190 (−0.294, 0.104) | 0.337 |
| Category | 0.552 (0.488, 0.616) | 0.551 | −0.003 (−0.009, 0.006) | 0.455 | −0.217 (−0.314, 0.232) | 0.614 |
| AISI | 0.590 (0.513, 0.668) | 0.550 | −0.005 (−0.013, 0.001) | 0.079 | −0.184 (−0.320, 0.145) | 0.238 |
| Category | 0.560 (0.499, 0.620) | 0.557 | −0.002 (−0.010, 0.000) | <0.001 | 0.002 (−0.335, 0.198) | 0.891 |
| Serum albumin | 0.563 (0.490, 0.637) | 0.542 | −0.001 (−0.006, 0.002) | 0.673 | −0.091 (−0.253, 0.194) | 0.733 |
| Category | 0.507 (0.461, 0.553) | 0.501 | −0.002 (−0.013, −0.001) | <0.001 | −0.148 (−0.297, −0.002) | 0.040 |
| PNI | 0.562 (0.489, 0.636) | 0.547 | −0.001 (−0.010, 0.002) | 0.178 | −0.146 (−0.324, 0.136) | 0.297 |
| Category | 0.514 (0.470, 0.558) | 0.504 | −0.007 (−0.014, −0.001) | <0.001 | −0.177 (−0.322, −0.023) | 0.020 |
| hsCRP | 0.605 (0.534, 0.675) | 0.604 | −0.001 (−0.003, 0.001) | 0.356 | −0.097 (−0.256, 0.124) | 0.455 |
| Category | 0.605 (0.542, 0.668) | 0.609 | Ref. | – | Ref. | – |

Cut-offs for inflammatory indicators were determined by the receiver operating characteristic analysis. AISI, aggregate index of systemic inflammation; AUC, area under the curve; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NRI, net reclassification improvement; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic inflammatory index; SIRI, systemic inflammatory response index; WBC, white blood cells.

yielding the greatest robustness across subgroups; and the newly developed score, CIS, that incorporates SIRI and hsCRP outperformed either indicator alone in predicting all-cause mortality. These findings highlight the continued importance of monitoring low-grade inflammation burden in patients generally considered to be at low residual inflammatory risk.

HsCRP is widely recognized as an indicator of residual inflammatory risk and adverse prognosis, as it is a biomarker of the NLRP3 (NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]-, and PYD [pyrin domain]-containing protein 3)/interleukin (IL)-1β/IL-6 pathway—a classic proatherogenic inflammatory pathway. The present study indicated that even when hsCRP was controlled at <2 mg/L, a relatively high level of hsCRP was still significantly associated with an increased risk of all-cause mortality. A previous study found that ACS patients with hsCRP between 0.9 and 1.9 mg/L had a 1.5 times higher risk of recurrent coronary events than those with hsCRP <0.9 mg/L.[4] A secondary analysis from the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) suggested that lower is better for inflammation reduction with canakinumab.[21] These observations suggest that even mildly elevated hsCRP levels are associated with a poorer prognosis, and further lowering of hsCRP may cf. survival benefits.

The present study observed neutrophils and neutrophil-derived SIRI and AISI strongly predicted all-cause mortality in CAD patients with hsCRP <2 mg/L. These indicators were not correlated with hsCRP, suggesting that neutrophils and hsCRP represent different atherogenic inflammatory pathways that independently contribute to low-grade inflammation burden. Neutrophils contribute to atherosclerosis through neutrophil extracellular trap formation in addition to their involvement in the NLRP3 pathway.[10] A recent proteomic analysis found a predominance of neutrophil-signaling-related proteins associated with recurrent atherosclerotic cardiovascular risk in patients with hsCRP <2 mg/L,

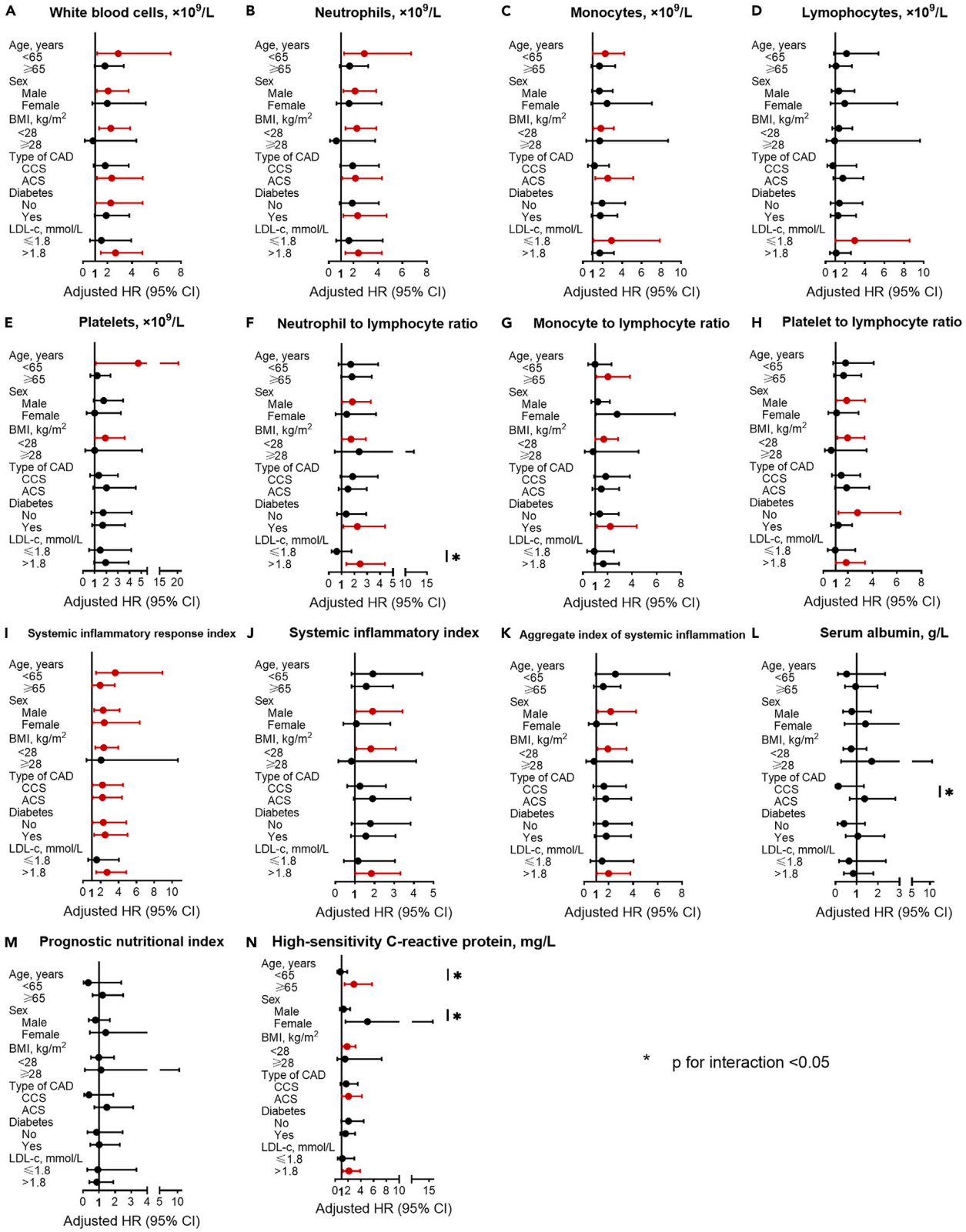
A White blood cells, ×10⁹/L
B Neutrophils, ×10⁹/L
C Monocytes, ×10⁹/L
D Lymphocytes, ×10⁹/L
E Platelets, ×10⁹/L
F Neutrophil to lymphocyte ratio
G Monocyte to lymphocyte ratio
H Platelet to lymphocyte ratio
I Systemic inflammatory response index
J Systemic inflammatory index
K Aggregate index of systemic inflammation
L Serum albumin, g/L
M Prognostic nutritional index
N High-sensitivity C-reactive protein, mg/L
Age, years
<65
≥65
Sex
Male
Female
BMI, kg/m²
<28
≥28
Type of CAD
CCS
ACS
Diabetes
No
Yes
LDL-c, mmol/L
≤1.8
>1.8
Adjusted HR (95% CI)
*
* p for interaction <0.05

**Figure 4. Subgroup analysis of inflammatory indicators (compared with their lower counterparts)**

(A–N) (A) White blood cells; (B) neutrophils; (C) monocytes; (D) lymphocytes; (E) platelets; (F) neutrophil-to-lymphocyte ratio; (G) monocyte-to-lymphocyte ratio; (H) platelet-to-lymphocyte ratio; (I) systemic inflammatory response index; (J) systemic inflammatory index; (K) aggregate index of systemic inflammation; (L) serum albumin; (M) prognostic nutritional index; (N) high-sensitivity C reactive protein. Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CCS, chronic coronary syndrome; CI, confidence interval; HR, hazard ratio; LDL-c, low-density lipoprotein cholesterol. Adjusted for age, sex, body mass index, acute coronary syndrome, prior coronary artery bypass grafting, prior stroke, diabetes, chronic kidney disease, left ventricular ejection fraction <40%, left main stem/three-vessel disease, and unsuccessful percutaneous coronary intervention. * p for interaction <0.05.

in contrast to a clear IL-6 signal in high hsCRP patients.[8] A substudy of the Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease 2 (LoDoCo2) trial found that administering colchicine significantly attenuated 37 proteins, of which only six were related to hsCRP. The strongest attenuation was seen in proteins related to neutrophil degranulation.[22] Ziltivekimab, an IL-6 inhibitor, was found to reduce both neutrophil counts and hsCRP levels; however, the populations affected did not overlap.[23] Moreover, colchicine and the IL-1 inhibitor canakinumab can lower neutrophil counts, resulting in a decrease in cardiovascular events.[9] This evidence suggests that neutrophils, as well as SIRI and AISI, are modifiable and that lowering the levels of these indicators can be beneficial for CAD patients with low residual inflammatory risk.

In line with previous research, the present study supports the superiority of SIRI and AISI over other indicators in predicting all-cause mortality.[15–17] In light of the inclusion of monocytes in the formulas of SIRI and AISI, attention has been directed toward whether monocytes constitute a source of residual inflammatory risk when hsCRP <2 mg/L. Monocytes comprise multiple heterogeneous subsets, including the classical, intermediate, and nonclassical subsets, with an overall skewing to a proatherogenic profile.[11] Further investigation is required to determine whether and how the proportions and functions of monocyte subsets are altered in low hsCRP conditions. Recently, anti-inflammatory drugs targeting the monocyte-related proatherogenic inflammatory pathway, CCL2 (C-C motif chemokine ligand 2)/CCR2 (CC receptor 2) axis, have been undergoing clinical trials for atheroprotection.[24] These trials typically apply hsCRP as a marker of therapeutic efficacy, but it would also be worthwhile to monitor on-treatment monocyte counts, SIRI, or AISI and investigate whether their changes are associated with better clinical outcomes.

Taking into account the contribution of hsCRP-, neutrophil-, and monocyte-related pathways to atherosclerosis, we developed CIS by incorporating SIRI and hsCRP. The score outperformed hsCRP or SIRI alone in predicting all-cause mortality. It might help identify individuals who may benefit from further control of low-grade inflammation burden, even if they are already at low residual inflammatory risk. However, it should be noted that in the validation cohort, the predictive performance of CIS for all-cause mortality was modest, and the advantage of CIS over hsCRP or SIRI alone diminished. Thus, it is prudent to regard CIS as an exploratory score.

In the subgroup of LDL-c <1.8 mmol/L, almost all indicators failed to predict all-cause mortality, contrary to our pre-specified hypothesis according to previous evidence.[6,25] We attempted to explain the unexpected finding. A secondary analysis of the further cardiovascular outcomes research with PCSK9 inhibition subjects with elevated risk (FOURIER) trial[25] showed that the difference in cardiovascular event rates between the high (1–3 mg/L) and low (<1 mg/L) hsCRP groups dropped from 2.7% to 1.8% as LDL-c decreased. Another study found that the difference in recurrent stroke rates between high (≥2 mg/L) and low (<2 mg/L) hsCRP groups decreased from 3.6% to 0.7% as LDL-c decreased. The association between hsCRP levels and the risk of recurrent stroke disappeared when LDL-C was <1.42 mmol/L (55 mg/dL).[26] Therefore, we hypothesized that the association between inflammatory indicators and clinical events might be attenuated at very low LDL-c levels. For patients with both LDL-c levels below 1.8 mmol/L and hsCRP levels below 2.0 mg/L, the difference in cardiovascular event risk attributed to slight changes in the levels of inflammatory indicators may be further diminished. Nevertheless, this finding should be considered hypothetical due to the limited statistical power resulting from the small sample size of patients who achieved both low residual inflammatory and residual cholesterol risks. Larger-scale studies are required to substantiate the impact of low-grade inflammation burden on the prognosis of this low-risk population.

The present study focused on CAD patients with hsCRP <2 mg/L, a population often neglected in inflammation burden assessment. Our findings have several clinical implications for the management of these patients. First, integrating neutrophil-derived indicators, particularly SIRI, into the management of CAD patients with low hsCRP levels may assist in identifying individuals at residual inflammatory risk that cannot be explained by hsCRP alone. Moreover, SIRI and CIS have the potential to serve as markers of anti-inflammatory drug efficacy and tools for screening individuals who may benefit from intensive anti-inflammatory therapy. This proposal is supported by the strong correlation between SIRI and NLR; the latter is a reliable marker for anti-inflammatory therapy response and is unaffected by lipid-lowering agents.[9] Finally, given the strong association between SIRI and all-cause mortality, exploring its underlying mechanisms may offer valuable insights into novel targets for anti-inflammatory drugs. However, it should be noted that blood cells are non-specific indicators of inflammation. The failure of methotrexate demonstrates the infeasibility of non-specific inhibition of blood cells.[27] Anti-inflammatory targets should be sought in blood cell-related proatherogenic pathways.

## Limitations of the study

The limitations of the study should be acknowledged. Firstly, the data were sourced from real-world settings, which, although more clinically relevant, may introduce unknown or unmeasured confounders due to the observational nature of the study. Secondly, the cohort was primarily composed of Chinese populations, which restricts the generalizability of the results to other ethnicities since inflammation levels in East Asian populations tend to be lower than those in Western populations.[28] Moreover, inflammatory indicators were only measured at baseline, and potential confounding due to possible changes in inflammation levels during follow-up cannot be ruled out. Lastly, this study did not include other inflammatory biomarkers, such as IL-1β, IL-6, myeloperoxidase, etc., which limits the exploration of the underlying mechanisms. However, there is still a long way to go before these indicators can be integrated into routine clinical practice. Inexpensive and readily available inflammatory indicators are likely to remain the mainstream assessment tools.

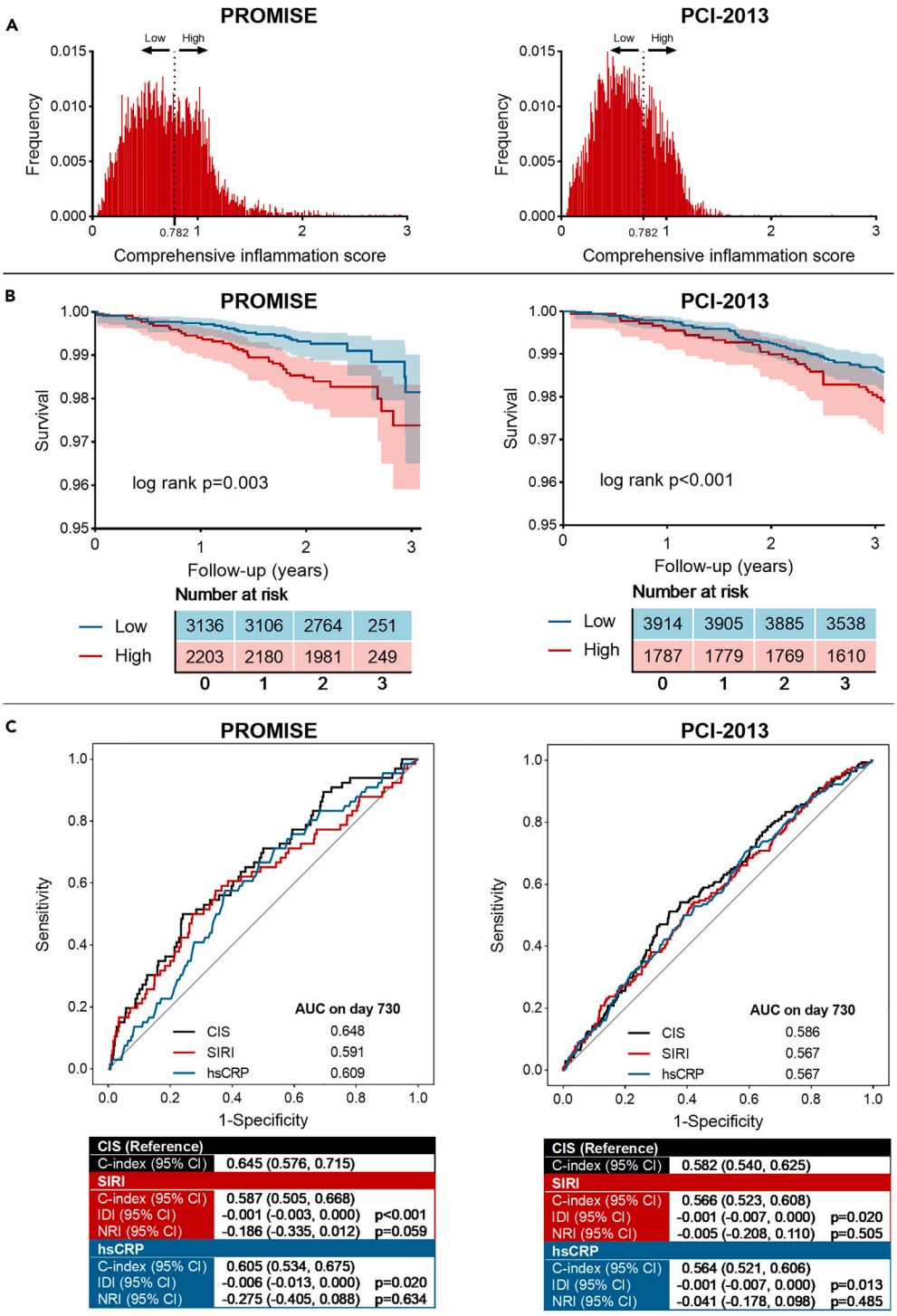


**Figure 5. Comparison of CIS in the PROMISE study and PCI-2013 cohort**

(A) Distributions of CIS in the PROMISE study (left panel) and PCI-2013 cohort (right panel).

(B) Survival curves for patients stratified by levels of CIS in the PROMISE study (left panel) and PCI-2013 cohort (right panel).

(C) Performance of SIRI, hsCRP, and CIS in predicting 2-year all-cause mortality in the PROMISE study (left panel) and PCI-2013 cohort (right panel). CIS was calculated as 0.209 × SIRI +0.485 × hsCRP. Abbreviations: AUC, area under the curve; CI, confidence interval; CIS, comprehensive inflammation score; hsCRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; NRI, net reclassification Improvement; PCI-2013, patients undergoing percutaneous coronary intervention in 2013 at Fuwai Hospital; PROMISE, the prospective observational multi-center cohort for ischemic and hemorrhage risk in coronary artery disease patients; SIRI, systemic inflammatory response index.

### Conclusions

For CAD patients at low residual inflammatory risk already, lower hsCRP was still associated with better survival. Neutrophil-derived indicators, particularly SIRI, independently predicted all-cause death. Integrating SIRI monitoring into the management of CAD may help identify individuals with low-grade inflammation burden that cannot be explained by hsCRP alone. The value of SIRI and the comprehensive inflammatory score as indicators of anti-inflammatory therapy efficacy warrants further study. Exploring the underlying mechanisms of low-grade inflammation burden in patients with low hsCRP levels may offer valuable insights into novel targets for anti-inflammatory drugs.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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## SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.108060.

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## AUTHOR CONTRIBUTIONS

Conceptualization, J.Y. and Y.H.; Methodology; X.W., Z.L., Z.Z., Y.Z., Z.W., Y.F., Q.W., and X.G.; Formal analysis, T.L. and P.W.; Validation, X.T.; Resources, J.Y. and Y.H.; data curation, X.T., J.X., Y.S., Y.C., N.X., Y.Y., R.L, and P.Z.; Writing – original draft preparation, T.L.; Writing – review and editing, J.Y.; Visualization, T.L. and P.W.; Supervision, J.Y. and Y.H.; Project administration, X.W., Z.L., Z.Z., Y.Z., Z.W., Y.F., Q.W., and X.G.; Funding acquisition, J.Y. and X.W.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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## STAR★METHODS

### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| Deposited data | | |
| Summary statistic data | This study | https://github.com/TianyuLI0707/Inflammatory-indicators.git |
| Software and algorithms | | |
| R (v4.2.0) | R CRAN | https://cran.r-project.org/ |
| survival (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=survival |
| survMisc (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=survMisc |
| rms (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=rms |
| survivalROC (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=survivalROC |
| survIDINRI (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=survIDINRI |
| survC1 (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=survC1 |
| Hmisc (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=Hmisc |
| gdata (v4.2.0) | R CRAN | https://CRAN.R-project.org/package=gdata |
| GraphPad Prism (version 9.0.0) | GraphPad Software | https://graphpad.com/ |

### RESOURCE AVAILABILITY

#### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Jinqing Yuan (dr_jinqingyuan@sina.com).

#### Materials availability

This study did not generate new unique reagents.

#### Data and code availability

- The complete original data reported in this study cannot be deposited in a public repository because these data are confidential medical records. To request access, contact Dr. Jinqing Yuan (dr_jinqingyuan@sina.com). In addition, the dataset for survival analysis has been deposited on GitHub (https://github.com/TianyuLI0707/Inflammatory-indicators.git) and is publicly available.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from Dr. Jinqing Yuan (dr_jinqingyuan@sina.com) upon request.

### EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The PROMISE is a prospective, multi-center cohort study that consecutively recruited 18,701 hospitalized CAD patients from nine centers in China from January 2015 to May 2019. Its goal is to develop innovative scores for quantifying ischemic and bleeding risk in CAD patients in China. It consisted entirely of Chinese participants, with 4715 (25.21%) females. Their ages ranged from 24 to 94, with a median age of 61 (interquartile range: 54–68 years). The PROMISE study complied with the Declaration of Helsinki. The Ethics Committee of Fuwai Hospital approved the study protocol. All participants gave written informed consent.

The external validation of the newly developed score was conducted in the PCI-2013 cohort, an independent prospective, single-center cohort of 10,724 consecutive CAD patients undergoing PCI at Fuwai Hospital from January to December 2013. All participants were Chinese, among which 22.86% were female (n=2452). The age distribution spanned from 18 to 91, with a median age of 59 (interquartile range: 51–66 years). The PCI-2013 study complied with the Declaration of Helsinki. The Ethics Committee of Fuwai Hospital approved the study protocol. All participants provided written informed consent.

This secondary analysis aims to determine readily available clinical indicators of low-grade inflammation burden in CAD patients with low residual inflammatory risk and to examine the associations between these indicators and all-cause mortality. The present study pertains to participants who had an hsCRP level <2 mg/L on admission and received PCI and statin and aspirin therapy. Individuals without baseline complete blood count values, those with malignancy, active infection or tuberculosis, systemic inflammatory diseases, those not having aspirin or statins at baseline, and those not undergoing PCI during hospitalization were excluded from this study. Patients who died before discharge

and those who lost to follow-up were excluded from the final analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

## METHOD DETAILS

### Blood sampling and laboratory testing

Venous blood samples were obtained as part of routine clinical practice. Specifically, for patients with ACS, blood samples were procured and tested immediately upon admission. Regarding patients with CCS, their blood samples were collected and analyzed within the first 24 hours subsequent to their admission. HsCRP was measured with immunoassay analyzers (Beckman Assay, Brea, CA, USA). Complete blood counts were measured with automated hematology analyzers (XN2000, Sysmex, Kobe, Japan). Serum albumin was measured with automated chemistry analyzers (AU5400, Olympus, Tokyo, Japan). Lipid profiles were measured with automatic biochemistry analyzers (Hitachi 7150, Tokyo, Japan), and LDL-c was calculated using the Friedewald Equation.

### Medications

All patients were prescribed with secondary prevention medications for CAD, encompassing statins, aspirin, β-blockers, and angiotensin converting enzyme inhibitors/ angiotensin receptor blockers during hospitalization and at discharge, unless contraindicated. Among patients who underwent PCI and had no contraindications, dual antiplatelet therapy comprising aspirin and an additional P2Y12 inhibitor was administered.

### Inflammatory indicators

Fourteen inflammatory indicators were applied to assess low-grade inflammation burden. The indicators were analyzed both as continuous and categorical variables. Lower serum albumin and PNI levels and higher levels of other indicators were assumed to reflect a higher burden of low-grade inflammation. The cut-offs of these indicators were determined as the points on the ROC curves that achieved the largest sum of sensitivity and specificity. Units or formulas for all indicators and corresponding cut-offs are described in Table S9.

The CIS was developed by incorporating SIRI, hsCRP, and their β coefficients derived from their respective multivariable Cox models. The score was calculated as 0.209 × SIRI + 0.485 × hsCRP. The cut-off of CIS was 0.782, calculated by substituting the cut-offs of SIRI and hsCRP into the above formula. The score's distribution, survival curves, and time-dependent ROC were analyzed in all participants and subpopulations with ACS or CCS.

### Definition of covariables

Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L, glycated hemoglobin ≥48 mmol/mol, oral antidiabetic medication or insulin use, or self-reported diabetes. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 ml/min/1.73m2 or self-reported CKD. Three-vessel disease was defined as angiographically significant stenosis (≥50%) of all three main coronary arteries. Endpoints and Follow-up.

The primary endpoint was all-cause mortality, and the secondary endpoint was cardiac mortality. In-hospital events were obtained through a review of electronic medical records. Outcomes and medications were followed up through clinic visits, telephone calls, text messages, and letters by an independent group of clinical research coordinators one and two years after discharge for the PROMISE cohort and at one, six, 12, 24 months, and five years after discharge for the PCI-2013 cohort.

## QUANTIFICATION AND STATISTICAL ANALYSIS

The distributions of inflammatory indicators were displayed using violin plots. The correlation between each pair of indicators was assessed using Spearman's rank correlation analysis. The strength of a correlation is classified as follows: no correlation ($r \leq 0.2$), weak correlation ($0.2 < r \leq 0.4$), medium correlation ($0.4 < r \leq 0.6$), high correlation ($0.6 < r \leq 0.8$), and strong correlation ($r > 0.8$). Categorical variables were expressed as numbers (percentages) and compared using $\chi 2$ test. Continuous variables were expressed as median (interquartile range) and compared using Student's t-test or Mann–Whitney U test as appropriate.

The survival rate was analyzed using Kaplan–Meier curves and the log-rank test. The associations between indicators and clinical outcomes were examined using Cox regression by estimating hazard ratios and 95% confidence intervals. Covariables for adjustment included age, sex, body mass index, ACS, prior coronary artery bypass grafting, prior stroke, diabetes, CKD, left ventricular ejection fraction <40%, left main stem/ three-vessel disease, and unsuccessful PCI. To further adjust for age, survival analysis was repeated using age as the underlying timescale as a sensitivity analysis. To examine the robustness of the main results, all indicators were categorized by median as another sensitivity analysis.

A pre-specified subgroup analysis was performed based on six variables: age (≥65 years versus <65 years, according to the definition of elderly for the Chinese population), sex, body mass index (≥28 kg/$m^2$ versus <28 kg/$m^2$, according to the definition of obesity for the Chinese population), type of CAD (ACS versus CCS), diabetes, and LDL-c levels (>1.8 mmol/L versus ≤1.8 mmol/L, according to the classification of residual cholesterol risk).

The performances of inflammatory indicators in predicting clinical outcomes were evaluated using time-dependent ROC analysis and Harrell's C-index and were compared using integrated discrimination improvement and net reclassification improvement.

Statistical analyses were done with R version 4.2.0 (R Core Team 2022, Vienna, Austria). Two-tailed *p* values <0.05 were considered statistically significant. Figures were prepared with GraphPad Prism version 9.0.0 (GraphPad Software, San Diego, CA, USA).