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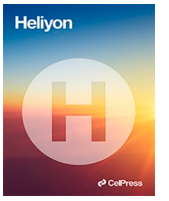

Baseline high-sensitivity C-reactive protein and glycosylated hemoglobinA1c predict adverse outcomes in patients with chronic coronary syndromes undergoing percutaneous coronary intervention

Xiao-Fang Tang, De-Shan Yuan, Pei Zhu, Na Xu, Yi Yao, Pei-Zhi Wang, Yan Chen, Li-Jian Gao, Lei Song, Yue-Jin Yang, Run-Lin Gao, Xue-Yan Zhao, Jin-Qing Yuan *

Department of Cardiology, Centre for Coronary Heart Disease, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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ABSTRACT

Introduction: This study explored the ability of high-sensitivity C-reactive protein (hs-CRP) and glycosylated hemoglobin A1c (HbA1c) to predict adverse cardiac and cerebrovascular outcomes in patients with chronic coronary syndromes (CCS) undergoing percutaneous coronary intervention (PCI).

Methods: In total, 4083 consecutive patients with CCS undergoing PCI were investigated throughout 2013 at a single center. The primary endpoint was all-cause death at the 5-year follow-up. Hs-CRP and HbA1c data were collected on admission.

Results: The highest quartile of hs-CRP had a significantly increased the risk of all-cause death, with an adjusted HR of 1.747 (95 % CI 1.066–2.863), while, there was no difference in all-cause death among the groups of HbA1c after adjustment, with an adjusted HR of 1.383 (95 % CI 0.716–2.674). The highest quartiles for hs-CRP and HbA1c in the study population had a significantly increased risk of major adverse cardiac and cerebrovascular events (MACCE), with an adjusted hazard ratios (HR) of 1.263 (95 % confidence intervals [CI] 1.032–1.545) for hs-CRP and an adjusted HR of 1.417 (95 % CI 1.091–1.840) for HbA1c. Remarkably, the incidence of all-cause death and that of MACCE were significantly increased when both hs-CRP and HbA1c were elevated (HR 1.971, 95 % CI 1.079–3.601, $P = 0.027$ and HR 1.560, 95 % CI 1.191–2.042), $P = 0.001$, respectively). Addition of hs-CRP and HbA1c to conventional risk factors significantly improved prediction of the risk of all cause death (net reclassification index 0.492, $P < 0.001$; integrated discrimination improvement 0.007, $P = 0.011$) and MACCE (net reclassification index 0.160, $P < 0.001$; integrated discrimination improvement 0.006, $P < 0.001$).

Conclusions: Hs-CRP and HbA1c can serve as independent predictors of MACCE in patients with CCS undergoing PCI. Furthermore, a combination of hs-CRP and HbA1c could predict all cause death and MACCE better than each component individually.

* Corresponding author. postal code: 100037; from Beilishi Road 167, Xicheng District, Beijing, China.
E-mail address: dr_jinqingyuan@126.com (J.-Q. Yuan).

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1. Introduction

Chronic inflammation has long been recognized as having a critical role in the pathogenesis and progression of atherosclerotic disease [1–3]. C-reactive protein (CRP) is a biomarker of inflammation. With advances in technology, a method for measurement of high-sensitivity (hs)-CRP has been developed, which can measure CRP with high accuracy even at low concentrations, and thus detect mild elevation of CRP caused by chronic inflammation. Accumulating data suggest that hs-CRP has an important role in different stages of formation and development of atherosclerosis [4–7]. Elevated hs-CRP has been shown to be an independent predictor of cardiovascular events in healthy individuals [8,9] and an independent predictor of the short-term and long-term outcomes in patients with acute myocardial infarction (MI) [10–14] and patients undergoing percutaneous coronary intervention (PCI) [15–17]. Several studies have investigated the prognostic significance of hs-CRP in patients with chronic coronary syndromes (CCS), and most of the participants in those studies received pharmacological treatment [18–20]. However, information on the prognostic value of hs-CRP in patients with CCS undergoing PCI is limited.

It is well known that impaired glucose metabolism is involved in the development of atherosclerotic disease. Previous studies have shown that poor glycemic control can promote genesis of oxidative stress and inflammation-related injury, which is directly responsible for progression of atherosclerosis [21]. Glycated hemoglobin A1c (HbA1c) is a pivotal biomarker that reflects glycemic control over the previous 8–12 weeks. It has several advantages over fasting blood glucose and oral glucose tolerance tests, including greater convenience, greater pre-analytical stability, and fewer day-to-day perturbations during periods of stress and illness [22]. Several studies have demonstrated an association between elevated HbA1c and poor clinical outcomes in the general population [23], in patients with acute coronary syndrome with or without diabetes mellitus [24–28], and in patients with CCS [29,30].

Previous studies have demonstrated a relationship between elevated levels of HbA1c and an increase in inflammatory markers, such as hs-CRP [31–35]. Therefore, a combination of multiple biomarkers may have more significant predictive value than individual biomarkers. However, few studies have investigated the ability of a combination of hs-CRP and HbA1c to predict adverse cardiac and cerebrovascular outcomes in patients with CCS.

The 2019 China Cardiovascular Health and Disease Report published in 2020 estimated that there were 11 million patients with coronary artery disease (CAD) in China. The prevalence and mortality rate of CAD have become the most important causes of disability and death among both urban and rural Chinese residents. The incidence rate of CCS is increasing with age [36]. In this study, we investigated the relationship between serum hs-CRP, HbA1c, and adverse clinical outcomes in a: (1) determining the ability of hs-CRP alone and HbA_{1c} alone to predict adverse clinical outcomes in patients with CCS undergoing PCI; (2) assessing their ability to predict adverse clinical outcomes when combined.

2. Patients and methods

2.1. Study population

The study had a single-center prospective observational design. In total, 4293 patients with CCS undergoing PCI were consecutively recruited at Fuwai Hospital in Beijing, China, between January 1, 2013 and December 31, 2013. The definition of CCS based on 2019 ESC Guidelines for the diagnosis and management of CCS [37].

Serum hs-CRP levels were measured by particle-enhanced immune turbidimetry method (Beckman Coulter, Brea, CA, USA) using an RIA analyzer. This assay has a minimal detectable concentration of 0.03 mg/L and a total imprecision of 5.1 % and 2.5 % at concentrations of 0.2 and 1.9 mg/L, respectively [38]. HbA1c was assessed using a turbidimetric inhibition immunoassay (Roche Tina-quant Gen.2 HbA1c on Integra 800) with inter-assay and intra-assay coefficients of variation of 1.3 % and 0.8 % at a mean level of 5.3 % (34 mmol/mol) and 1.0 % and 0.9 % at a mean level of 10.2 % (88 mmol/mol), respectively, and a lower limit of detection of 2.9 %. The exclusion criteria were as follows: no documented hs-CRP or HbA1c testing on admission; progressive renal insufficiency (the increase in blood creatinine exceeds 50 % within one week), hepatic dysfunction (Child-Pugh grading B or C), or active malignancy; acute or chronic infection, surgery, or trauma within the previous 3 months; autoimmune diseases; inability to manage own affairs or sign informed consent; breast feeding; and pregnancy. Finally, 4083 patients with CCS and documented hs-CRP and HbA1c test results who underwent PCI were enrolled in the study (Supplementary Fig. 1). The study protocol was approved by our institutional review board. All patients provided written informed consent at enrollment. Independent clinical research coordinators collected the clinical and procedural data and entered them in the database.

2.2. Procedural details and medications

The PCI strategy was at the discretion of the treating physician. Patients received 300 mg of aspirin and clopidogrel (loading dose 300 mg) or ticagrelor (loading dose 180 mg) orally at least 24 h before surgery if not already on long-term aspirin or a P2Y12 inhibitors. After PCI, aspirin 75–100 mg/day was prescribed indefinitely and clopidogrel 75 mg daily or ticagrelor 90 mg twice daily were prescribed for at least 1 year after the procedure.

2.3. Endpoints and definitions

All patients were assessed in the clinic or by telephone at 1, 3, 6, and 12 months after PCI and annually thereafter until 5 years. The primary endpoint was all-cause death. The secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE), which

is a composite of all-cause death, MI, stroke, or unplanned revascularization. Cardiac death was considered cardiac unless an unequivocal noncardiac cause could be established. MI was defined by the fourth universal definition of MI [39]. Unplanned revascularization was defined as repeated revascularization for ischemic symptoms and events driven by PCI or surgery to any vessel. All endpoints were adjudicated in a blinded fashion by an independent review committee using medical records.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and were compared among groups by analysis of variance. Categorical variables were shown as the number and percentage and were compared among groups using the chi-squared test or Fisher's exact test as appropriate. Event-free survival rates were calculated using the Kaplan–Meier method and were compared using the log-rank test. Associations between different groups and each outcome of interest were examined in univariable and multivariable Cox proportional regression models. Multivariable Cox regression analysis was used to identify associations between two groups and each outcome of interest after adjusting for potential confounding factors, namely, sex, age, body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease (CKD), hyperuricemia, current smoking, family history of CAD, left ventricular ejection fraction, SYNTAX (Synergy between percutaneous coronary intervention with Taxus and cardiac surgery) score, old MI, previous PCI. The area under the receiver-operating characteristic curve (AUC), net reclassification index (NRI), and integrated discrimination improvement (IDI) were used to evaluate the ability of hs-CRP and HbA1c to predict all cause death and MACCE during 5 years of follow-up over and above that of conventional factors [40]. All statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA), with the exception of those for AUC, NRI, and IDI, which was performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). All P-values were two-sided, and $P < 0.05$ was considered statistically significant.

Table 1
Clinical baseline characteristic and medication data of participants by quartiles of hs-CRP.

Variable	Quartile of hs-CRP in CCS patients					
	Total	1st quartile CRP <0.7	2nd quartile 0.7≤CRP<1.34	3rd quartile 1.34≤CRP <2.72	4th quartile CRP ≥2.72	
	(n = 4083)	(n = 1009)	(n = 1030)	(n = 1028)	(n = 1016)	p value
Age (years)	58.3 ± 10.1	58.1 ± 9.8	57.6 ± 10.1	58.5 ± 10.2	59.2 ± 10.4	0.002
Sex (male, %)	3172 (77.7)	809 (80.2)	800 (77.7)	799 (77.7)	764 (75.2)	0.064
Body mass index (kg/m^2)	26.0 ± 3.2	25.3 ± 3.1	25.9 ± 2.9	26.3 ± 3.2	26.5 ± 3.3	<0.001
Left ventricular ejection fraction (%)	63.5 ± 7.1	63.7 ± 6.8	63.8 ± 6.8	63.4 ± 7.1	63.0 ± 7.7	0.102
Chronic kidney disease (n, %)	130 (3.2)	17 (1.7)	25 (2.4)	26 (2.5)	62 (6.1)	<0.001
Hypertension (n, %)	2685 (65.8)	586 (58.1)	685 (66.5)	694 (67.5)	720 (70.9)	<0.001
Hyperlipidemia (n, %)	2839 (69.5)	680 (67.4)	730 (70.9)	726 (70.6)	703 (69.2)	0.297
Diabetes mellitus (n, %)	1316 (32.2)	284 (28.1)	334 (32.4)	323 (31.4)	375 (36.9)	<0.001
Hyperuricemia (n, %)	778 (19.1)	124 (12.3)	187 (18.2)	223 (21.7)	244 (24.0)	<0.001
Current smoker (n, %)	2251 (55.1)	523 (51.8)	549 (53.3)	591 (57.5)	588 (57.9)	0.011
Family history of coronary artery disease (n, %)	1006 (24.6)	251 (24.9)	246 (23.9)	263 (25.6)	246 (24.2)	0.816
Stroke history (n, %)	433 (10.6)	99 (9.8)	96 (9.3)	116 (11.3)	122 (12.0)	0.167
Peripheral artery disease (n, %)	138 (3.4)	35 (3.5)	32 (3.1)	30 (2.9)	41 (4.0)	0.519
Old myocardial infarction (n, %)	1151 (28.2)	298 (29.5)	295 (28.6)	284 (27.6)	274 (27.0)	0.590
Previous PCI (n, %)	1181 (28.9)	327 (32.4)	324 (31.5)	268 (26.1)	262 (25.8)	<0.001
Previous CABG (n, %)	187 (4.6)	47 (4.7)	40 (3.9)	46 (4.5)	54 (5.3)	0.486
Medication (cases, %)						
Aspirin	4037 (98.9)	993 (98.4)	1018 (98.8)	1022 (99.4)	1004 (98.9)	0.198
Clopidogrel	4032 (98.8)	994 (98.5)	1015 (98.5)	1019 (99.1)	1004 (98.8)	0.568
DAPT	3988 (97.7)	979 (97.0)	1003 (97.4)	1014 (98.6)	992 (97.6)	0.091
Statin	3922 (96.1)	975 (96.6)	979 (95.0)	993 (96.6)	975 (96.0)	0.217
B-blocker	3764 (92.2)	914 (90.6)	959 (93.1)	950 (92.4)	941 (92.6)	0.162
Lesions involving LM	110 (2.7)	23 (2.3)	18 (1.7)	32 (3.1)	37 (3.6)	0.039
Lesions involving LAD	3676 (90.0)	922 (91.4)	924 (89.7)	937 (91.1)	893 (87.9)	0.033
Lesions involving LCX	702 (17.2)	150 (14.9)	166 (16.1)	174 (16.9)	212 (20.9)	0.002
Lesions involving RCA	917 (22.5)	248 (24.6)	234 (22.7)	225 (21.9)	210 (20.7)	0.195
SYNTAX score						
≤22	3587 (87.9)	896 (88.8)	918 (89.1)	900 (87.5)	873 (85.9)	0.110
23-32	421 (10.3)	102 (10.1)	92 (8.9)	104 (10.1)	123 (12.1)	0.125
≥33	75 (1.8)	11 (1.1)	20 (1.9)	24 (2.3)	20 (2.0)	0.196
HbA1c (%)	6.6 ± 1.2	6.4 ± 1.0	6.6 ± 1.2	6.7 ± 1.2	6.9 ± 1.4	<0.001
hs-CRP (mg/L)	2.44 ± 3.02	0.39 ± 0.20	0.98 ± 0.18	1.88 ± 0.38	6.51 ± 3.64	<0.001

CCS, chronic coronary syndromes; PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet treatment; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; SYNTAX, the synergy between percutaneous coronary intervention with Taxus and cardiac surgery; HbA1c, hemoglobin, type A1C; hs-CRP, high –C reaction protein.

3. Results

3.1. Baseline characteristics of the study population

First, the study population was divided into four groups according to the quartiles of hs-CRP levels. The baseline characteristics of the study population are shown according to hs-CRP quartile in Table 1. Patients with higher hs-CRP concentrations were older, had higher BMI and higher HbA1c values, and had higher rates of diabetes mellitus, and lesions of left circumflex (LCX) than those with lower hs-CRP levels ($P < 0.05$). The prevalence of hypertension, CKD, hyperuricemia, and current smoking increased with rising hs-CRP quartile ($P < 0.05$).

The study population was then divided into four groups according to HbA1c quartile. The baseline characteristics of the study population are shown according to $HbA1_c$ quartile in Table 2. Patients with higher HbA1c value had a higher BMI and a higher hs-CRP level and were less likely to be male than were patients with lower HbA1c levels ($P < 0.05$). The prevalence of CKD, hypertension, hyperlipidemia, the previous history of DM, peripheral artery disease, and previous PCI all increased significantly with rising quartile of HbA1c ($P < 0.05$).

3.2. Association of hs-CRP or HbA1c with clinical outcomes

In total, 377 patients (9.2 %) were lost to follow-up. Cumulative survival rate curves for the primary and secondary endpoints during 5 years of follow-up were shown according to hs-CRP quartile in Fig. 1(a–f) by Kaplan-Meier analysis. The incidence of all-cause death, cardiac death and MACCE increased with the hs-CRP level in a dose-response manner ($P < 0.05$, Fig. 1(a, b and f), and Supplementary Table 1). The rates of nonfatal MI, unplanned revascularization, and stroke did not differ significantly according to hs-CRP quartile ($P > 0.05$, Fig. 1(c–e), and Supplementary Table 1). All-cause death was significantly higher in patients with CCS undergoing PCI who were in the highest hs-CRP quartile than in those who were in the lowest hs-CRP quartile (*hazard ratio* [HR] 2.231, 95 %

Table 2
Clinical baseline characteristic and medication data of participants by quartiles of HbA1c.

Variable	Quartile of HbA1c in CCS patients					
	Total	1st quartile HbA1C < 5.9	2nd quartile 5.9≤HbA1C < 6.3	3rd quartile 6.3≤ HbA1C < 7.0	4th quartile HbA1C ≥ 7.0	
	(n = 4083)	(n = 943)	(n = 1068)	(n = 1013)	(n = 1059)	p value
Age (years)	58 ± 10	55 ± 10	59 ± 10	61 ± 10	59 ± 10	<0.001
Sex (male, %)	3172 (77.7)	787 (83.5)	839 (78.6)	770 (76.0)	776 (73.3)	<0.001
Body mass index (kg/m^2)	26.0 ± 3.2	25.8 ± 3.1	25.6 ± 3.1	26.1 ± 3.3	26.5 ± 3.1	<0.001
Left ventricular ejection fraction (%)	63.5 ± 7.1	63.8 ± 6.9	63.9 ± 7.3	63.2 ± 6.9	62.9 ± 7.3	0.004
Chronic kidney disease	130 (3.2)	14 (1.5)	22 (2.1)	43 (4.2)	51 (4.8)	<0.001
Hypertension (n, %)	2685 (65.8)	580 (61.5)	687 (64.3)	681 (67.2)	737 (69.6)	0.001
Hyperlipidemia (n, %)	2839 (69.5)	621 (65.9)	728 (68.2)	713 (70.4)	777 (73.4)	0.002
History of diabetes mellitus (n, %)	1316 (32.2)	36 (3.8)	88 (8.2)	312 (30.8)	880 (83.1)	0.001
Hyperuricemia (n, %)	778 (19.1)	190 (20.1)	216 (20.2)	221 (21.8)	151 (14.3)	<0.001
Current smoker (n, %)	2251 (55.1)	525 (55.7)	612 (57.3)	542 (53.5)	572 (54.0)	0.288
Family history of coronary artery disease (n, %)	1006 (24.6)	264 (28.0)	245 (22.9)	266 (26.3)	231 (21.8)	0.004
Stroke history (n, %)	433 (10.6)	78 (8.3)	96 (9.0)	131 (12.9)	128 (12.1)	0.001
Peripheral artery disease (n, %)	138 (3.4)	12 (1.3)	29 (2.7)	37 (3.7)	60 (5.7)	<0.001
Old myocardial infarction (n, %)	1151 (28.2)	247 (26.2)	294 (27.5)	298 (29.4)	312 (29.5)	0.297
Previous PCI (n, %)	1181 (28.9)	224 (23.8)	295 (27.6)	323 (31.9)	339 (32.0)	<0.001
Previous CABG (n, %)	194 (4.6)	33 (3.5)	35 (3.3)	53 (5.2)	66 (6.2)	0.003
Medication (cases, %)						
Aspirin	4037 (98.9)	929 (98.5)	1055 (98.8)	1001 (98.8)	1052 (99.3)	0.354
Clopidogrel	4032 (98.8)	931 (98.7)	1052 (98.5)	1004 (99.1)	1045 (98.7)	0.647
DAPT	3988 (97.7)	917 (97.2)	1039 (97.3)	994 (98.1)	1038 (98.0)	0.402
Statin	3922 (96.1)	910 (96.5)	1038 (97.2)	963 (95.1)	1011 (95.5)	0.052
B-blocker	3764 (92.2)	853 (90.5)	988 (92.5)	931 (91.9)	992 (93.7)	0.059
Lesions involving LM	110 (2.7)	18 (1.9)	37 (3.5)	26 (2.6)	29 (2.7)	0.195
Lesions involving LAD	3676 (90.0)	867 (91.9)	973 (91.1)	908 (89.6)	928 (87.6)	0.007
Lesions involving LCX	702 (17.2)	146 (15.5)	177 (16.6)	173 (17.1)	206 (19.5)	0.110
Lesions involving RCA	917 (22.5)	171 (18.1)	231 (21.6)	239 (23.6)	276 (26.1)	<0.001
SYNTAX score						
≤22	3587 (87.9)	842 (89.3)	945 (88.5)	896 (88.5)	904 (85.4)	0.033
23-32	421 (10.3)	81 (8.6)	109 (10.2)	97 (9.6)	134 (12.7)	0.019
≥33	75 (1.8)	20 (2.1)	14 (1.3)	20 (2.0)	21 (2.0)	0.514
HbA1c (%)	6.6 ± 1.2	5.6 ± 0.2	6.0 ± 0.1	6.5 ± 0.2	8.3 ± 1.2	<0.001
hs-CRP (mg/L)	2.44 ± 3.02	2.10 ± 2.76	2.36 ± 3.09	2.43 ± 2.92	2.83 ± 3.23	<0.001

CCS, chronic coronary syndromes; PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet treatment; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; SYNTAX, the synergy between percutaneous coronary intervention with Taxus and cardiac surgery; HbA1c, hemoglobin, type A1C; hs-CRP, high –C reaction protein.

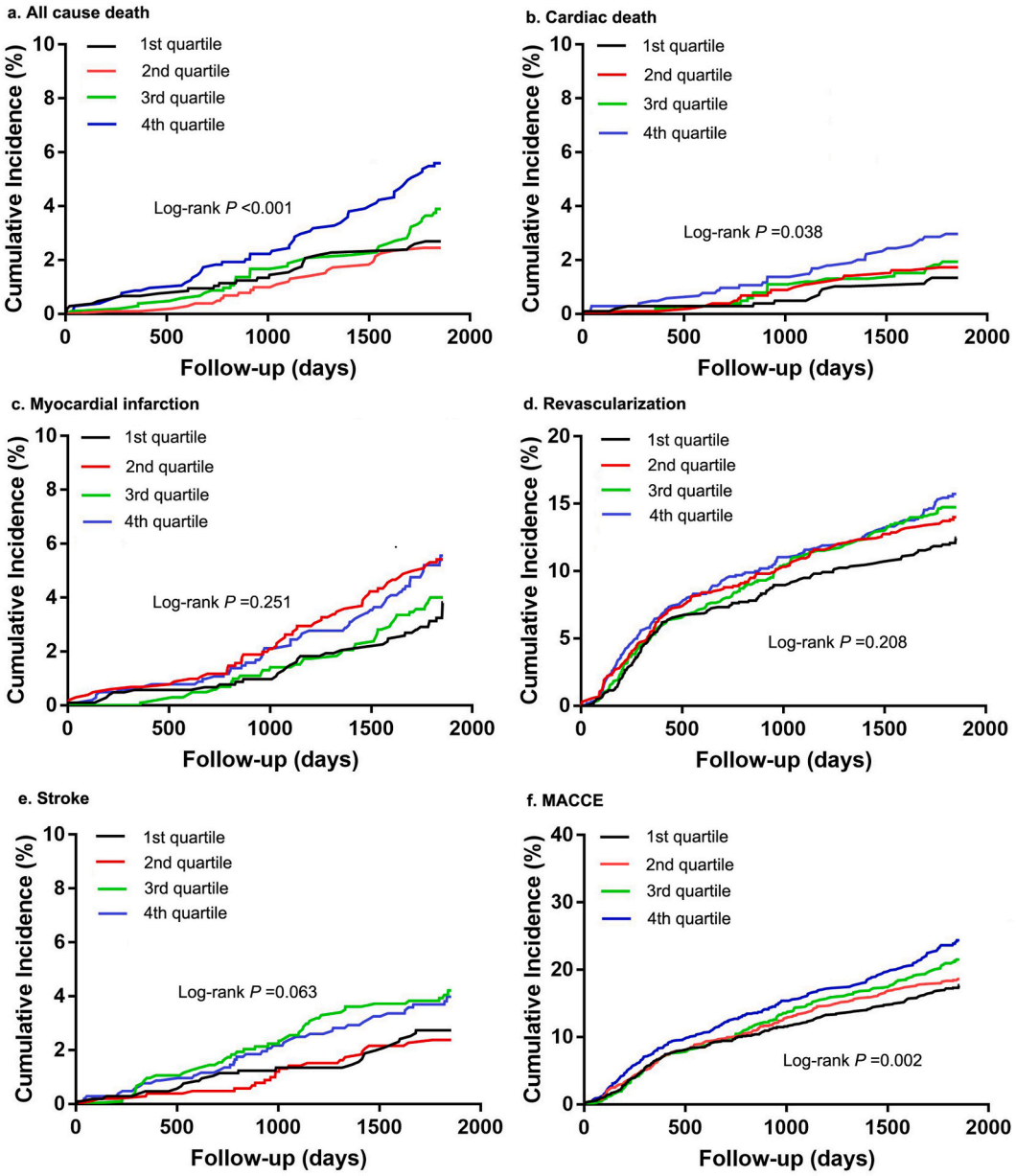

Fig. 1. Kaplan-Meier survival curves for hs-CRP alone. (a) All cause death; (b) cardiac death, (c) myocardial infarction, (d) revascularization, (e) stroke, and (f) MACCE. hs-CRP, high-sensitivity C-reactive protein; MACCE, major adverse cardiac and cerebrovascular events.

confidence interval [CI]): 1.393–3.575, P = 0.001; Table 3). After adjusting for multiple covariates, all-cause death was significantly higher in the highest hs-CRP quartile than in the lowest hs-CRP quartile (HR 1.747, 95 % CI: 1.066–2.863), P = 0.027; Table 3). Meanwhile, the incidence of MACCE was significantly higher in patients with CCS undergoing PCI in both the third and fourth hs-CRP quartiles than in the lowest hs-CRP quartile (fourth vs. lowest: HR 1.393, 95 % CI 1.151–1.685, P = 0.001; third vs. lowest: HR 1.253, 95 % CI 1.032–1.522, P = 0.022; Table 4). However, after adjusting for multiple covariates, the incidence of MACCE was significantly increased only in the highest hs-CRP quartile in comparison with the lowest quartile (HR 1.263, (95 % CI 1.032–1.545, P = 0.023; Table 4).

Cumulative survival rate curves for the primary and secondary endpoints during 5 years of follow-up were shown according to HbA1c quartile in Fig. 2(a–f) by Kaplan-Meier analysis. The incidences of all cause death, unplanned revascularization and MACCE were higher in the fourth HbA1c quartile than in the other quartiles (P < 0.05, Fig. 2 (a, d and f), and Supplementary Table 2). There was no significant difference in the incidence of cardiac death, non-fatal MI, or stroke among the HbA1c quartiles (P > 0.05, Fig. 2 (b, c and e), and Supplementary Table 2). The risk of all-cause death was significantly higher in the second and fourth HbA1c quartiles than in the lowest HbA1c quartile (second vs. lowest, HR 1.802, 95 % CI 1.041–3.118, P = 0.035; fourth vs. lowest, HR 2.432 95 % CI

Table 3
The independent and combined effect of hs-CRP and HbA1c on the prediction of all cause death.

	No. (%) of clinical outcomes		Unadjusted		Adjusted[a]	
		P value	HR (95%CI)	P value	HR (95%CI)	P value
hs-CRP						
Quartile 1	25 (2.4)	0.001	1		1	
Quartile 2	24 (2.3)		0.936 (0.535–1.640)	0.818	0.817 (0.466–1.432)	0.480
Quartile 3	39 (3.8)		1.557 (0.945–2.567)	0.082	1.229 (0.738–2.048)	0.428
Quartile 4	54 (5.3)		2.231 (1.393–3.575)	0.001	1.747 (1.066–2.863)	0.027
HbA1C						
Quartile 1	19 (2.0)	0.005	1			
Quartile 2	39 (3.7)		1.802 (1.041–3.118)	0.035	1.399 (0.800–2.448)	0.239
Quartile 3	32 (3.2)		1.565 (0.887–2.760)	0.122	0.953 (0.522–1.739)	0.874
Quartile 4	52 (4.9)		2.432 (1.438–4.113)	0.001	1.383 (0.716–2.674)	0.335
hs-CRP and HbA1c						
Hs-CRP< 2.72 and HbA1C < 7.0	57 (2.4)	<0.001	1			
HSCRP1<2.72and HbA1C ≥ 7.0	31 (4.3)		1.748 (1.129–2.707)	0.012	1.429 (0.837–2.439)	0.191
HSCRP1≥2.72 and HbA1C < 7.0	33 (4.8)		2.006 (1.306–3.079)	0.001	1.764 (1.129–2.756)	0.013
HSCRP1≥2.72 and HbA1C ≥ 7.0	21 (6.4)		2.634 (1.597–4.345)	<0.001	1.971 (1.079–3.601)	0.027

Hs-CRP, high –C reaction protein; HbA1c, hemoglobin, type A1C; HR, hazard ratio; CI, confidence interval.
[a] Adjusted for gender, age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, hyperuricemia, current smoker, the family history of coronary artery disease, left ventricular ejection fraction, the synergy between percutaneous coronary intervention with Taxus and cardiac surgery score, old myocardial infarction, previous percutaneous coronary intervention.

Table 4
The independent and combined effect of hs-CRP and HbA1c on the prediction of MACCE.

	No. (%) of clinical outcomes		Unadjusted		Adjusted[a]	
		P value	HR (95%CI)	P value	HR (95%CI)	P value
hs-CRP						
Quartile 1	182 (18.0)	0.005	1		1	
Quartile 2	195 (18.9)		1.050 (0.858–1.285)	0.634	1.035 (0.843–1.270)	0.744
Quartile 3	225 (21.9)		1.253 (1.032–1.522)	0.022	1.203 (0.985–1.469)	0.071
Quartile 4	241 (23.7)		1.393 (1.151–1.685)	0.001	1.263 (1.032–1.545)	0.023
HbA1C						
Quartile 1	155 (16.4)	<0.001	1			
Quartile 2	223 (20.9)		1.273 (1.037–1.562)	0.021	1.193 (0.968–1.470)	0.098
Quartile 3	204 (20.1)		1.237 (1.004–1.524)	0.046	1.134 (0.908–1.417)	0.266
Quartile 4	261 (24.6)		1.543 (1.265–1.882)	<0.001	1.417 (1.091–1.840)	0.009
HSCRP1 and HbA1C						
Hs-CRP< 2.72 and HbA1C < 7.0	433 (18.5)	<0.001	1			
HSCRP1<2.72and HbA1C ≥ 7.0	169 (23.2)		1.281 (1.073–1.531)	0.006	1.218 (0.973–1.523)	0.085
HSCRP1≥2.72 and HbA1C < 7.0	149 (21.7)		1.194 (0.991–1.438)	0.062	1.122 (0.927–1.359)	0.237
HSCRP1≥2.72 and HbA1C ≥ 7.0	92 (27.9)		1.569 (1.253–1.964)	<0.001	1.560 (1.191–2.042)	0.001

Hs-CRP, high –C reaction protein; HbA1c, hemoglobin, type A1C; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events.
[a] Adjusted for gender, age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, hyperuricemia, current smoker, the family history of coronary artery disease, left ventricular ejection fraction, the synergy between percutaneous coronary intervention with Taxus and cardiac surgery score, old myocardial infarction, previous percutaneous coronary intervention.

1.438–4.113, P = 0.035; Table 3). However, after adjusting for multiple covariates, there was no significantly difference in all-cause death among the HbA1c quartiles (P > 0.05; Table 3). Meanwhile, the second, third, and fourth HbA1c quartiles were associated with significantly higher rates of MACCE than the lowest quartile during the 5-year follow-up period (second vs. lowest, HR 1.273, 95 % CI 1.037–1.562, P = 0.021; third vs. lowest, HR 1.237, 95 % CI 1.004–1.524, P = 0.046; fourth vs. lowest, HR 1.543, 95 % CI 1.265–1.882, P < 0.001; Table 4). However, after adjusting for multiple covariates, the incidence of MACCE remained significantly higher only in the highest HbA1c quartiles (HR 1.417, 95 % CI 1.091–1.840, P = 0.009, Table 4).

3.3. Ability of hs-CRP and HbA1c in combination to predict clinical outcomes

To investigate the ability of elevated hs-CRP and increased HbA1c to predict clinical outcomes when used in combination, the study participants were divided into four groups based on hs-CRP and HbA1c values: group 1 (hs-CRP <2.72 and HbA1c < 7.0, n = 2338); group 2 (hs-CRP <2.72and HbA1c ≥ 7.0, n = 729), group 3 (hs-CRP ≥2.72 and HbA1c < 7.0, n = 686), and group 4 (hs-CRP ≥2.72 and HbA1c ≥ 7.0, n = 330). Cumulative survival rate curves for the primary and secondary endpoints during 5 years of follow-up according to the hs-CRP and HbA1c levels in combination were shown in Fig. 3(a–f) by Kaplan-Meier analysis. All-cause death was significantly

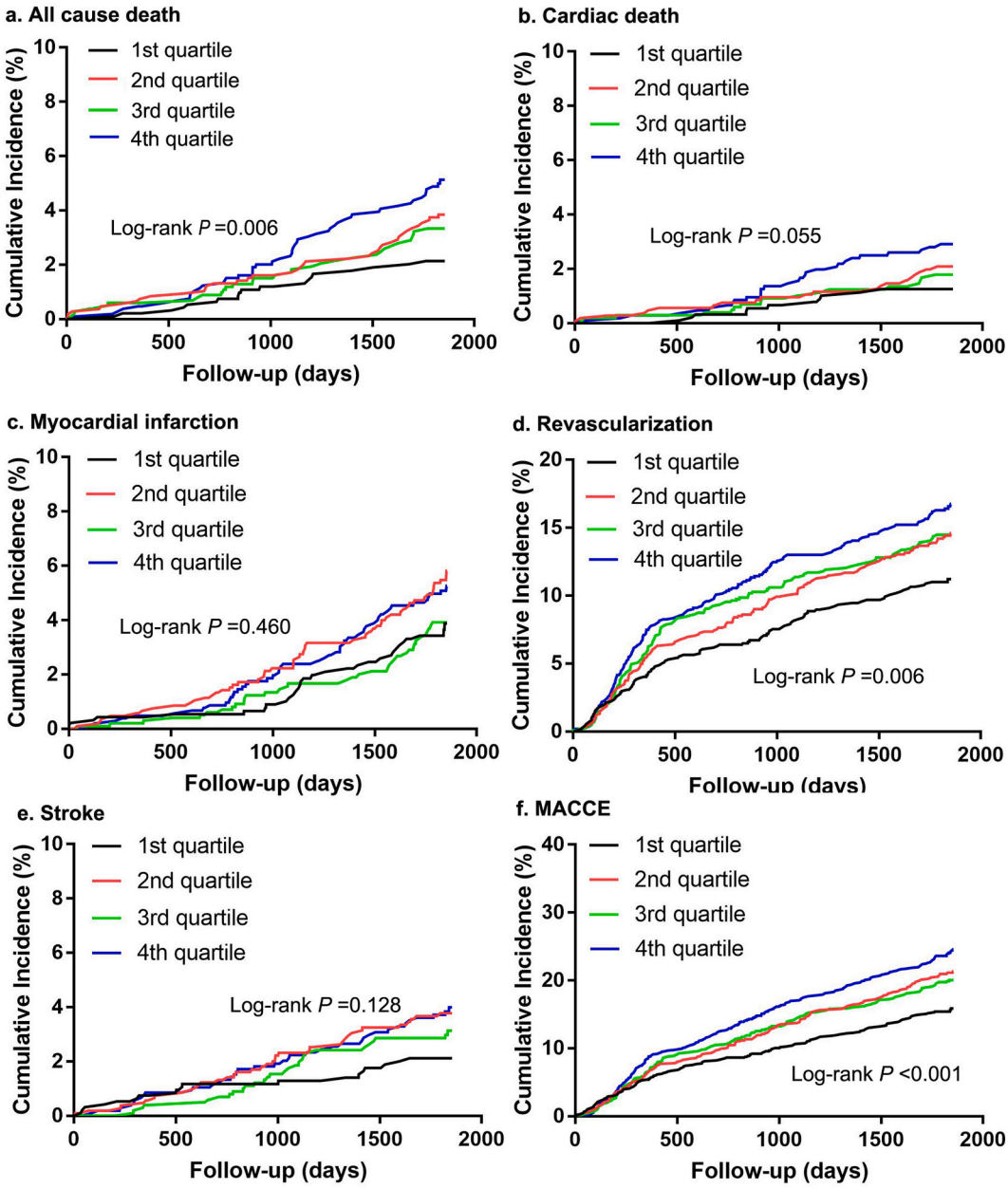

Fig. 2. Kaplan-Meier survival curves for HbA1c **alone. (a) All cause death; (b) cardiac death, (c) myocardial infarction, (d) revascularization, (e) stroke, and (f) MACCE. HbA1c, glycated hemoglobin; MACCE, major adverse cardiac and cerebrovascular events.**

higher in groups 2, 3, and 4 than in group 1 (group 2 vs. group 1, HR 1.748, 95 % CI 1.129–2.707, P = 0.012; group 3 vs. group 1, HR 2.006,95 % CI 1.306–3.079, P = 0.001; group 4 vs. group 1, HR 2.634,95 % CI 1.597–4.345, P < 0.001; Table 3). Notably, group 4 had the highest risk of all-cause death. After adjusting for multiple covariates, all-cause death was still significantly higher in groups 3 and 4 than in group 1 (group 3 vs. group 1, HR 1.764, 95 % CI 1.129–2.756, P = 0.013; group 4 vs. group 1, HR 1.971,95 % CI 1.079–3.601, P = 0.027; Table 3). Meanwhile, the incidence of MACCE was significantly higher in groups 2 and 4 than in group 1 (group 2 vs. group 1, HR 1.281, 95 % CI 1.073–1.531, P = 0.006; group 4 vs. group 1, HR 1.569, 95 % CI 1.253–1.964, P < 0.001; Table 4). However, after adjusting for multiple covariates, the incidence of MACCE was significantly higher only in group 4 (HR 1.560, 95 % CI 1.191–2.042, P = 0.001, Table 4).

3.4. Incremental predictive value of hs-CRP and/or HbA1c

Addition of hs-CRP and/or HbA1c to conventional factors for prediction of 5-year all cause death and MACCE was evaluated

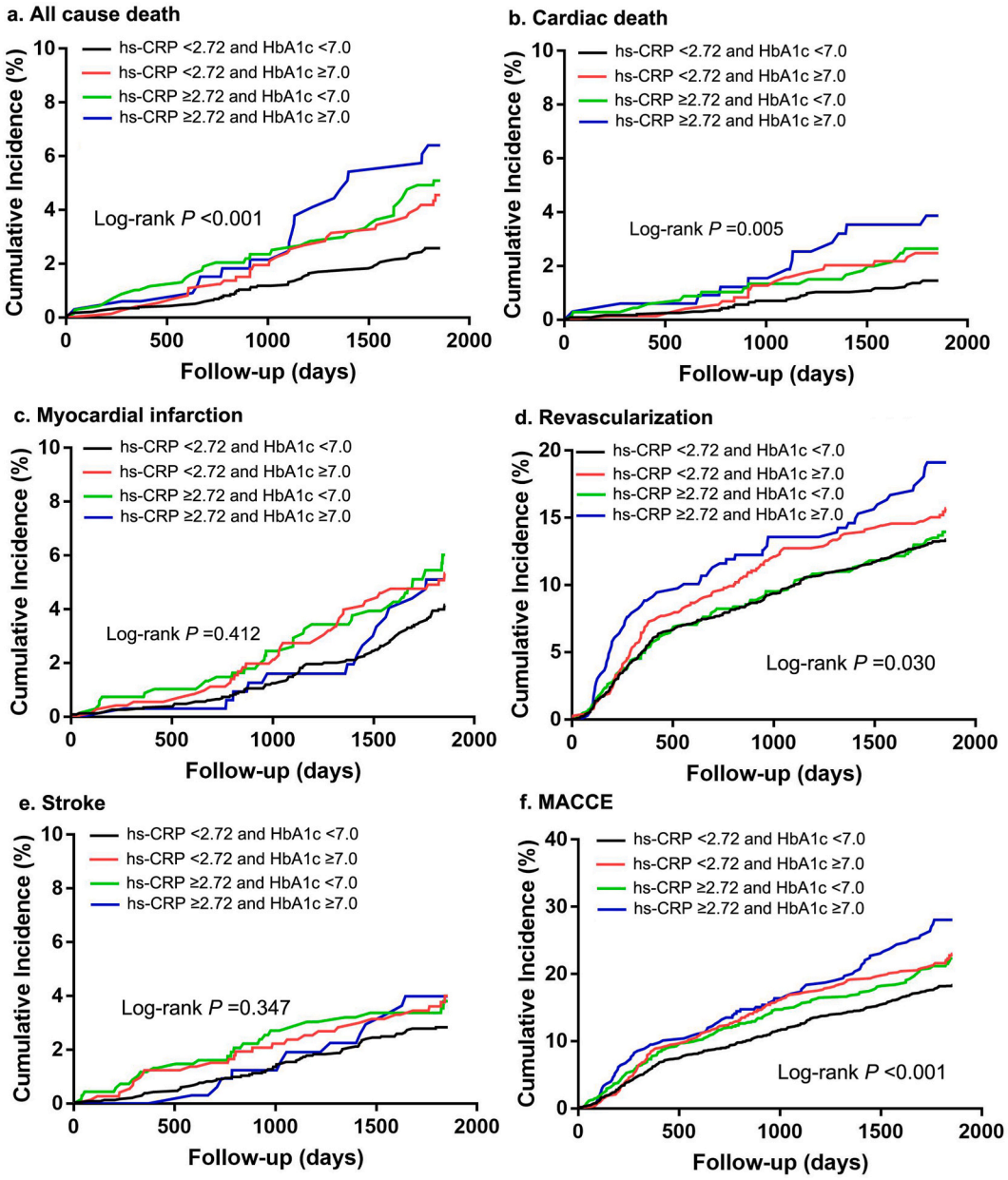

Fig. 3. Kaplan-Meier survival curves for hs-CRP and HbA1c in combination. (a) All cause death; (b) cardiac death, (c) myocardial infarction, (d) revascularization, (e) stroke, and (f) MACCE, major adverse cardiac and cerebrovascular events. Hs-CRP, high-sensitivity C-reactive protein; HbA1c, glycated hemoglobin; MACCE, major adverse cardiac and cerebrovascular events.

further. Compared with the conventional model, addition of hs-CRP or HbA1c significantly improved the discriminatory power and reclassification of risk in patients with CCS undergoing PCI (Table 5). The AUC, NRI, and IRI values for all cause death were 0.823 (P = 0.476), 0.014 (P = 0.867), and 0.006 (P = 0.009) for hs-CRP, and 0.827 (P = 0.195), −0.045 (P = 0.590), and 0.002 (P = 0.335) for HbA1c, respectively. As expected, adding the combination of hs-CRP and HbA1c to the conventional model resulted in greater improvement of the ability to predict all cause death, with AUC, NRI, and IRI values of 0.829 (P = 0.009), 0.492 (P < 0.001), and 0.007 (P = 0.011), respectively.

4. Discussion

According to our results showed that a higher hs-CRP level but not a higher HbA1c level, was independently associated with an increased risk of all-cause death in patients with CCS undergoing PCI after adjustment for multiple covariates. We also found that

Table 5
Reclassification and discrimination statistics for 5-year all-cause death and MACCE by hs-CRP and/or HbA1c.

Model	AUC		NRI		IDI	
	Estimate (95%CI)	P value	Estimate (95%CI)	P value	Estimate (95%CI)	P value
All cause death						
Conventional model[a]	0.820 (0.788–0.853)	–	Reference	–	Reference	–
Conventional model + hs-CRP	0.823 (0.790–0.855)	0.476	0.014(-0.148–0.175)	0.867	0.006(0.002–0.011)	0.009
Conventional model + HbA1c	0.827 (0.796–0.859)	0.195	−0.045(-0.210–0.119)	0.590	0.002(-0.002–0.005)	0.335
Conventional model + hs-CRP + HbA1c	0.829 (0.798–0.860)	0.009	0.492(0.325–0.658)	<0.001	0.007(0.002–0.012)	0.011
MACCE						
Conventional model[a]	0.667 (0.647–0.687)	–	Reference	–	Reference	–
Conventional model + hs-CRP	0.671 (0.651–0.691)	0.1365	0.064(-0.006–0.134)	0.072	0.003(0.001–0.004)	<0.001
Conventional model + HbA1c	0.672 (0.652–0.692)	0.1069	0.117(0.043–0.192)	0.002	0.004(0.002–0.006)	<0.001
Conventional model + hs-CRP + HbA1c	0.675 (0.655–0.695)	0.0233	0.160(0.086–0.234)	<0.001	0.006(0.003–0.008)	<0.001

AUC, area under the curve; NRI, net reclassification index; IDI, integrated discrimination improvement; CI, confidence interval; Hs-CRP, high –C reaction protein; HbA1c, hemoglobin, type A1C; MACCE, major adverse cardiac and cerebrovascular events.

[a] The conventional model included gender, age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, hyperuricemia, current smoker, the family history of coronary artery disease, left ventricular ejection fraction, the synergy between percutaneous coronary intervention with Taxus and cardiac surgery score, old myocardial infarction, previous percutaneous coronary intervention.

patients with both elevated hs-CRP and elevated HbA1c had the higher risks of all-cause death and MACCE than patients with an elevated hs-CRP alone or an elevated HbA1calone.

Previous studies had found that inflammation promotes formation of atherosclerotic lesions and instability of atherosclerotic plaques, indicating that inflammation plays a key role in CAD [4,6,41]. As one of the well-known inflammatory markers, hs-CRP has been shown to be associated with CAD events, and adding CRP to risk prediction models among initially intermediate-risk individuals improves risk stratification [42]. Previous studies found that hs-CRP to be a significant predictor of adverse cardiovascular events in patients with CCS, most of whom received medical therapy alone [18,19], while other studies had shown that patients undergoing PCI for CCS or unstable angina who have elevated hs-CRP also have an increased incidence of adverse cardiovascular events [15–17]. In our study, we demonstrated the clinical significance of hs-CRP in predicting poor outcomes in patients with CCS undergoing PCI during long-term follow-up. We found that higher hs-CRP levels were associated with an increased risk of 5-year all-cause death and MACCE in patients with CCS undergoing PCI either before or after adjusting for multiple covariates.

The prognostic value of HbA1c in CAD remains controversial. A previous study demonstrated that an elevated HbA1c value could be used as a biomarker for predicting CAD [43]. Another study found that an elevated HbA1c value was an independent risk factor for mortality in non-diabetic patients with CAD [44]; however, a further study found that HbA1c was not an independent predictor of the severity of CAD in non-diabetic patients [45]. Yet another study found that the baseline HbA1c appeared to be an independent predictor of a poor prognosis in patients with CCS before and after adjustment for multiple covariates [30]. Our present findings indicate that an elevated HbA1c level is independently associated with an increased risk of MACCE in patients with CCS undergoing PCI during long term follow-up before and after adjustment for multiple covariates. However, after adjusting for multiple covariates, HbA1c was not associated with an increased risk of all-cause death in these patients.

The ability of the combination of hs-CRP and HbA1c to predict a poor clinical outcome in patients with CCS treated by PCI was carefully evaluated and validated in this study. The ability of elevated hs-CRP and elevated HbA1c in combination to predict all-cause death was higher than their respective predictive abilities alone. Moreover, the combination of hs-CRP and HbA1c had a significant incremental predictive value when compared with conventional factors. A combination of multiple biomarkers has been demonstrated to improve prediction of the mortality risk [46–48]. To the best of our knowledge, this study is the first to systematically assess the combined ability of hs-CRP and HbA1c to predict the risk of a poor prognosis in patients with CCS undergoing PCI. Our findings could be of considerable significance in clinical practice, leading to simultaneous monitoring of hs-CRP and HbA1c when screening for high-risk populations in the future. More intensive surveillance and provision of higher-quality health care for high-risk individuals may reduce the risks of adverse clinical outcomes during long-term follow-up.

The mechanism underlying the association between hs-CRP/HbA1c and a poor prognosis in patients with CCS has not been fully elucidated. Several explanations may provide some hints. It is well known that inflammation has an important role in the development and progression of atherosclerosis. As a sensitive marker of inflammation, hs-CRP can reflect underlying inflammatory activity or disease, including the ability of CRP to activate complement and colocalization of CRP and complement in ruptured atherosclerotic plaques [49], to bind to leukocytes and endothelial cells, to cause both upregulation of adhesion molecules and decreased production of nitric oxide, and to induce atherosclerosis [50]. An elevated HbA1c level may be the result of long-term insulin resistance or a metabolic disorder associated with insulin resistance, including hyperglycemia, dyslipidemia, and a hypercoagulable state [51], and is associated with progression of atherosclerotic plaques [52]. The above reasons may be the main pathological mechanisms for the adverse effects of elevated HbA1c on CAD. Nevertheless, the pathophysiological basis of the association of hs-CRP and HbA1c with a poor prognosis in patients with CAD needs to be investigated further.

This study has several limitations. First, it had a real-world observational design. Although multivariate analysis was employed, unmeasured confounding factors that may have influenced the findings cannot be ruled out. Therefore, selection or confounding bias that cannot be excluded and our findings should be interpreted with caution. Second, this study was performed at a single-center,

which may limit the generalizability of our results. Third, the baseline hs-CRP and HbA1c values measured at admission do not reflect the overall disease course during long-term follow-up in patients with CCS undergoing PCI. In future studies, we intend to monitor the hs-CRP and HbA1c levels in such patients more closely during follow-up, explore the mechanism of the inflammatory response combined with impaired glucose metabolism, and perform risk stratification in these patients to further guide the clinical treatment strategy.

5. Conclusions

An elevated plasma hs-CRP or HbA1c level could serve as an independent predictor of the 5-year risk of MACCE in patients with CCS undergoing PCI. Furthermore, the combination of hs-CRP and HbA1c could predict 5-year all cause death and MACCE better than either of these variables alone. In future research, dynamic monitoring of plasma hs-CRP and HbA1c levels and more sensitive biomarkers, will be used to better identify populations at high-risk.

6. Data availability statement

Data will be made available on request.

7. Ethics statement

The study was approved by the ethics committee of Fuwai Hospital (approval number 2021-1501), and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Xiao-Fang Tang: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **De-Shan Yuan:** Formal analysis, Data curation. **Pei Zhu:** Formal analysis, Data curation. **Na Xu:** Project administration, Formal analysis. **Yi Yao:** Methodology, Data curation. **Pei-Zhi Wang:** Project administration, Formal analysis. **Yan Chen:** Methodology, Investigation. **Li-Jian Gao:** Supervision, Conceptualization. **Lei Song:** Supervision, Project administration. **Yue-Jin Yang:** Project administration, Investigation. **Run-Lin Gao:** Supervision, Conceptualization. **Xue-Yan Zhao:** Supervision, Conceptualization. **Jin-Qing Yuan:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23900.

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