Independent Prognostic Value of High-sensitivity C-reactive Protein in Patients with Coronary Artery Ectasia

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Abstract

Background: Despite its severity, coronary artery ectasia (CAE) is still poorly understood. High-sensitivity C-reactive protein (hs-CRP) has been recognized as a prognostic factor in some cardiovascular diseases but not assessed in CAE. The aim of this observational study was to investigate the prognostic value of hs-CRP in CAE.

Methods: Our analysis evaluated the effect of the baseline hs-CRP on cardiovascular events (CVs) (cardiac death and nonfetal myocardial infarction) in consecutively enrolled stable CAE patients. We used the Cox proportional hazards regression models to examine the association between baseline hs-CRP level and follow-up CVs in CAE. The net reclassification improvement and integrated discrimination improvement (IDI) of hs-CRP were also assessed.

Results: We obtained the follow-up results of 540 patients over a median follow-up period of 36 (37.41 ± 15.88) months. The multivariable Cox analysis showed that the hs-CRP was a significant predictor of adverse outcomes in CAE (hazard ratio [*HR*]: 2.99, 95% confidence interval [*CI*]: 1.31–6.81, $P = 0.0091$). In Kaplan–Meier analysis, the group with hs-CRP >3 mg/L had a lower cumulative 66-month event-free survival rate (log-rank test for trend, $P = 0.0235$) and a higher risk of CVs (*HR* = 2.66, 95% *CI*: 1.22–5.77, $P = 0.0140$) than the group with hs-CRP ≤3 mg/L. Hs-CRP added predictive information beyond that given by the baseline model comprising the classical risk factors (*P* value for IDI = 0.0330).

Conclusions: A higher level of hs-CRP was independently associated with cardiac death and nonfatal myocardial infarction in CAE patients. The hs-CRP level may therefore provide prognostic information for the risk stratification of CAE patients.

Key words: C-reactive Protein; Coronary Artery Ectasia; Coronary Heart Disease; Prognosis

Introduction

With the rapid increase in the applications of coronary angiography, a growing number of coronary artery ectasia (CAE) cases have been detected. CAE is an independent predictor of mortality, and aneurysmal patients with nonobstructive diseases have mortality rates similar to those of patients with 3-vessel diseases.[1,2]

The largest cohort study of CAE to date found that aneurysmal patients had a 5-year mortality rate of 26% mortality in 1983.[1] Two decades later, the 5-year mortality rate of patients with coronary aneurysms remained as high as 29% despite the progressive advances and improvements in medical therapy for coronary artery diseases, and there was no statistically significant difference between the survival rate of aneurysmal patients with and without obstructive coronary artery disease (O-CAD).[2]

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Previous studies suggested that inflammation might be involved in CAE.[3] Several inflammatory biomarkers have been found to be associated with CAE. In particular, the high-sensitivity C-reactive protein (hs-CRP) has attracted researchers' attention.[4] The hs-CRP was found to be significantly higher in patients with CAE than in those with O-CAD or with normal coronary angiography.[4] Inflammation contributes to the initiation and progression

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of atherosclerosis, but its role in the progression of CAE remains unclear.[5]

The prognostic value of hs-CRP in cardiovascular diseases has been well evaluated, such as in stable coronary artery disease[6] and acute coronary syndrome.[7] In addition, the hs-CRP could improve risk prediction accuracy for adverse cardiovascular events (CVs).[8] However, the prognostic value of hs-CRP in established CAE has not been assessed so far. Since death and myocardial infarction are the prominent features of CAE,[9] the present investigation was designed to evaluate whether the baseline hs-CRP could predict the composite CVs (cardiac death and nonfetal myocardial infarction) associated with CAE. If so, it might be used to guide the risk stratification and clinical decisions of CAE patients.

Methods

Study design and enrollment

The study population consisted of consecutively enrolled CAE patients who had been admitted to our hospital and had undergone a coronary angiography during January 2009 and July 2013. The indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia. CAE was defined as a localized or diffused luminal dilation exceeding 1.5-fold of the normal adjacent arterial segment.[1] The CAE patients were included consecutively, regardless of whether they had an O-CAD or not. Those who presented the following characteristics were excluded from the study: acute coronary syndrome, acute or chronic infection, renal failure, hepatic dysfunction, malignant disease, hematological disorder, pregnancy, severe valvular disease, cardiomyopathy, congenital heart disease, and drugs or alcohol abuse. The patients' medical history and physician-administered physical examination information were obtained from the hospital's medical records.

All patients provided their informed consent, and the study was approved by local Ethics Committee.

Laboratory examinations

The baseline hs-CRP values and other blood biomarkers were also collected from our medical records system, and all these biomarkers were measured from the samples collected in the morning after an overnight fast. The hs-CRP was determined with an AUS5400 (Olympus, Japan) molecular analyzer at our clinical laboratory department.

Follow-up

The follow-up was performed through telephone interviews and consultation of the hospital's medical records in July 2014. The researchers who conducted the follow-up were blind to the baseline status of the CAE patients. The observational outcome was the composite of two CVs: cardiac death and nonfatal myocardial infarction. Cardiac deaths were defined as death diagnosed by medical practitioners as definitely cardiogenic or unexplained sudden death. Where a patient had reached more than one end point, only the first event was taken into count.

Statistical analysis

All the data were analyzed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA), and a two-tailed $P < 0.05$ was considered statistically significant.

The continuous variables were expressed as mean ± standard deviation while the categorical data were given as counts and percentages. The Student's *t*-test or Wilcoxon's rank-sum test (as appropriate) were used to compare the continuous variables, and we used the Chi-square test to analyze the categorical variables.

To determine the independent prognostic value of baseline hs-CRP for predicting CVs, we employed multivariable Cox proportional hazards regression models. Three parts of variables were adjusted: (1) the prognostic factors of CAE identified in a previous study (such as age, diabetes mellitus, and hyperlipidemia),[2] (2) the baseline demographics and routine laboratory examination results having statistical significance ($P < 0.05$) in comparison between groups with CVs and without CVs, and (3) the baseline characteristics variables with $P < 0.05$ according to the Centers for Disease Control (CDC) and the American Heart Association (AHA) recommended cutoff point of hs-CRP (3 mg/L) for high-risk category.[10]

Next, the event-free survival rate of categorized hs-CRP (>3 mg/L vs. ≤3 mg/L) was illustrated with a Kaplan-Meier curve, and the values were compared with a log-rank test. The adjusted Kaplan–Meier curve and hazard ratios (*HR*s) were also obtained.

Subsequently, we examined the net reclassification improvement (NRI) and of the risk categories (>3 mg/L, ≤3 mg/L) for the prediction of the 3-year event-free survival and the integrated discrimination improvement (IDI) by adapting recent approaches to convert the numbers into suitable survival data. The NRI measures the correctness of reclassification of patients based on their predicted probabilities of events using the new model with the option of imposing meaningful risk categories (>3 mg/L, ≤3 mg/L). The IDI measures the new model's improvement in average sensitivity without sacrificing average specificity.[11] The multivariate logistic regression model was used for this analysis. A combination of the classical cardiovascular risk factors (age, sex, body mass index (BMI), low-density lipoprotein (LDL)/high-density lipoprotein ratio, smoking, diabetes, hypertension, and number of diseased vessels) was included in the basic model to derive the basic categories. Moreover, the hs-CRP (>3 mg/L, ≤3 mg/L) was added into the new model based on the basic model.[12]

Results

Based on the inclusion and exclusion criteria, 577 CAE patients were included in our study cohort, and we eventually obtained follow-up results for 540 (93.6%) of them. The

median follow-up period was 36 (37.41 ± 15.88) months. The longest follow-up duration was about 66 months, while the shortest was 12 months. During this follow-up period, 30 CVs–12 cardiac deaths and 18 nonfatal myocardial infarctions–were verified.

Comparisons of the baseline characteristics between the groups of patients with CVs and without CVs were shown in Table 1. The patients with CVs were much older (62.87 ± 10.01 vs. 56.68 ± 10.95 months, $P = 0.0026$) and had a relatively lower left ventricular ejection fraction (55.38% ± 12.36% vs. 60.49% ± 9.93%, $P = 0.0081$) than those without CVs. However, there was no statistically significant difference between the groups in terms of sex, hypertension, hyperlipidemia, diabetes mellitus, smoking, family history of coronary heart diseases, prior myocardial infarctions, prior cerebral vascular diseases, Gensini score, and medications.[13]

Comparisons of the routine laboratory examination results between groups with CVs and without CVs according to the binary classification (by the median level) and quartered (by quartiles) classification are shown in the supplementary materials [Supplementary Tables 1a and 1b]. In the binary classification, the group with CVs had a larger proportion of parameters–including left ventricular ejection fraction (79.3% vs. 49.7%, $P = 0.0013$)–below the median level than the group without CVs. Conversely, there was a smaller proportion of direct bilirubin (30.8% vs. 52.9%, $P = 0.0263$) below the median level in the group with CVs than the group without CVs. In the quartered classification, the following variables had statistical significance: the left ventricular ejection fraction, neutrophils, brain natriuretic peptide, and direct bilirubin.

Table 2 shows comparisons of the baseline characteristics between CAE patients with hs-CRP ≤3 mg/L and those with hs-CRP >3 mg/L. The patients with hs-CRP >3 mg/L showed a greater incidence of hypertension (35.6% vs. 26.9%, $P = 0.0270$) and a larger BMI (27.09 ± 3.71 vs. 26.20 ± 3.14 kg/m^2, $P = 0.0036$). In terms of medications, there was more aspirin usage in the group with hs-CRP >3 mg/L. There were no significantly statistical differences between the two groups in the other baseline characteristics.

The multivariable analysis of the association between an hs-CRP >3 mg/L vs. an hs-CRP ≤3 mg/L and CVs was obtained with Cox proportional hazard models [Table 3]. After adjustment for the prognostic factors of CAE identified by a previous study (i.e., age, diabetes mellitus and hyperlipidemia), a higher hs-CRP level (>3 mg/L) remained an independently significant predictor of CVs (*HR*: 2.33, 95% confidence interval [*CI*]: 1.13–4.81, $P = 0.0215$). After further adjustment for brain natriuretic peptide and lymphocyte, an hs-CRP level >3 mg/L was still associated with a higher risk of CVs (*HR*: 2.11, 95% *CI*: 1.02–4.38, $P = 0.0445$). Adjustment for BMI, neutrophils, left ventricle ejection fraction, direct bilirubin, and sex seemed to increase the strength of this association (*HR*: 2.99, 95% *CI*: 1.31–6.81, $P = 0.0091$).

The Kaplan–Meier analysis of CV-free survival according to the hs-CRP level (3 mg/L) is curved in Figure 1. From the curve in Figure 1a, it is apparent that the event-free survival rate of the patients with hs-CRP >3 mg/L differed from that with hs-CRP ≤3 mg/L (log-rank test for trend, $P = 0.0235$). After adjusting for the age, gender, diabetes mellitus, hyperlipidemia, BMI, lymphocyte, neutrophils, natriuretic peptide, left ventricle ejection fraction, and direct bilirubin,

Table 1: Baseline characteristics of CAE patients who had composite cardiovascular events and those who were events-free

Variables	CV events (+) (n = 30)	CV events (−) (n = 547)	Statistic value	*P*
Age (years), mean ± SD	62.87 ± 10.01	56.68 ± 10.95	3.0271*	0.0026
Male, *n* (%)	27 (90)	468 (85.6)	Fisher	0.7870
Hypertension, *n* (%)	10 (33.3)	164 (30.1)	0.1344†	0.7139
Hyperlipidemia, *n* (%)	7 (23.3)	147 (27.0)	0.2026†	0.6526
Diabetes mellitus, *n* (%)	6 (20.0)	121 (22.1)	0.0761†	0.7826
BMI (kg/m^2), *n* (%)	25.80 ± 4.52	26.77 ± 5.16	−1.0514*	0.3326
Smoking, *n* (%)	8 (26.7)	141 (25.9)	0.0082†	0.9278
Family history of CHD, *n* (%)	1 (3.3)	28 (5.1)	Fisher	1.0000
Prior MI, *n* (%)	9 (30.0)	115 (21.1)	1.2217†	0.2690
Prior CVD, *n* (%)	1 (3.3)	13 (2.4)	Fisher	0.5325
LVEF (%), mean ± SD	55.38 ± 12.36	60.49 ± 9.93	−2.6583*	0.0081
Gensini score, mean ± SD	68.50 ± 65.61	60.83 ± 60.27	−0.0676*	0.4998
Medications, *n* (%)				
Aspirin	14 (77.8)	444 (91.0)	Fisher	0.0807
ACEIs/ARBs	9 (50.0)	143 (29.2)	3.2932†	0.0696
β-blocker	8 (44.4)	227 (46.3)	0.0248†	0.8749
Statins	13 (72.2)	384 (78.4)	Fisher	0.5620

*t-test value; †Chi-square test value. ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; BMI: Body mass index; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cerebral vascular disease; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction.

Table 2: Comparison of the baseline characteristics of the CAE patients with hs-CRP ≤3 mg/L and hs-CRP >3 mg/L

Variables	hs-CRP		Statistic value	*P*
	≤3 mg/L (*n* = 361)	>3 mg/L (*n* = 216)		
Age (years), mean ± SD	57.45 ± 11.02	56.25 ± 10.90	1.2745*	0.2030
Male, *n* (%)	311 (86.1)	184 (85.2)	0.1026†	0.7487
Hypertension, *n* (%)	97 (26.9)	77 (35.6)	4.8905†	0.0270
Hyperlipidemia, *n* (%)	99 (27.4)	55 (25.5)	0.2667†	0.6056
Diabetes mellitus, *n* (%)	79 (21.9)	48 (22.2)	0.0090†	0.9244
Smoking, *n* (%)	88 (24.4)	61 (28.2)	1.0456†	0.3065
BMI (kg/m^2), mean ± SD	26.20 ± 3.14	27.09 ± 3.71	−2.9316*	0.0036
Family history of CHD, *n* (%)	18 (5.0)	11 (5.2)	0.0088†	0.9251
Prior MI, *n* (%)	75 (20.8)	49 (23.0)	0.3907†	0.5320
Prior CVD, *n* (%)	9 (2.5)	5 (2.3)	0.0120†	0.9127
Prior CABG, *n* (%)	21 (5.8)	15 (6.9)	0.2898†	0.5903
CABG this time, *n* (%)	43 (12.0)	33 (15.3)	1.2049†	0.2723
LVEF (%), mean ± SD	60.36 ± 8.96	60.08 ± 11.23	0.3127*	0.7547
Multivessel disease, *n* (%)	278 (77.0)	183 (84.7)	5.2858†	0.0712
Gensini score, mean ± SD	61.24 ± 60.81	61.23 ± 60.19	0.0017*	0.9987
Medications, *n* (%)				
Aspirin	284 (88.2)	174 (94.6)	5.9769†	0.0145
ACEI/ARBs	95 (29.4)	57 (30.8)	0.1095†	0.7407
β-blocker	150 (46.4)	85 (45.9)	0.0115†	0.9145
Statins	247 (76.5)	150 (81.1)	1.4872†	0.2226
Nitrates	151 (46.7)	93 (50.3)	0.5841†	0.4447
Warfarin	7 (2.2)	2 (1.1)	Fisher	0.4977

**t*-test value; †Chi-square test value. ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blockers; BMI: Body mass index; CABG: Coronary artery bypass graft; CHD: Coronary heart disease; CVD: Cerebral vascular disease; MI: Myocardial infarction.

Table 3: *HRs* (95% *CI*) of cardiovascular events in relation to baseline hs-CRP (>3 mg/L vs. ≤3 mg/L) among CAE patients

Items	Composite cardiovascular events		Cardiac death		Nonfetal myocardial infarction	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Model 1	2.25 (1.09–4.64)	0.0275	2.34 (0.74–7.39)	0.1458	2.16 (0.85–5.49)	0.1040
Model 2	2.33 (1.13–4.81)	0.0215	2.46 (0.78–7.78)	0.1251	2.20 (0.87–5.57)	0.0973
Model 3	2.10 (1.01–4.37)	0.0456	2.28 (0.71–7.30)	0.1655	1.95 (0.76–5.02)	0.1647
Model 4	2.11 (1.02–4.38)	0.0445	2.30 (0.72–7.36)	0.1614	1.98 (0.77–5.08)	0.1573
Model 5	2.64 (1.22–5.72)	0.0137	3.89 (1.08–13.98)	0.0375	2.22 (0.83–5.99)	0.1138
Model 6	2.67 (1.23–5.82)	0.0134	4.06 (1.12–14.77)	0.0335	2.20 (0.82–5.94)	0.1191
Model 7	2.99 (1.31–6.81)	0.0091	4.97 (1.03–23.95)	0.0456	2.73 (0.95–7.88)	0.0629

BMI: Body mass index; CAE: Coronary artery ectasia; hs-CRP: High-sensitivity C-reactive protein; *HRs*: Hazard ratios; *CI*: Confidence interval. Model 1 diabetes mellitus and hyperlipidemia; Model 2 adjusted for the above variables plus age; Model 3 adjusted for the above variables plus brain natriuretic peptide; Model 4 adjusted for the above variables plus lymphocyte; Model 5 adjusted the above variables plus BMI, neutrophils and left ventricle ejection fraction; Model 6 adjusted for the above variables direct bilirubin; Model 7 adjusted for the above variables and plus gender.

the cumulative 66-month event-free survival rate of CAE patients with hs-CRP ≤3 mg/L remained considerably better than that of patients with hs-CRP >3 mg/L [*HR* = 2.66, 95% *CI*: 1.22–5.77, *P* = 0.014; Figure 1b].

The reclassification was assessed to further explore whether the hs-CRP added to the predictive value of traditional risk factors for the outcomes of CAE [Table 4]. Unexpectedly, the NRI for hs-CRP was merely 0.01 (*P* = 0.8798). However, the hs-CRP yielded an IDI of 0.02 (*P* = 0.033). The *P* value improved from 0.344 to 0.897 in the Hosmer–Lemeshow test, which quantifies the extent to which the predicted probabilities match the actual experience. However, there was no improvement in the reclassification of hs-CRP for the prediction of cardiovascular death or of nonfatal myocardial infarction.

Discussion

The present study assessed the prognostic value of hs-CRP for patients with CAE. The major finding of this study is that the hs-CRP on admission is an independent predictor of the cardiovascular outcomes in CAE patients.

There has been relatively limited research on the outcome of CAE and the prognosis for patients with the condition

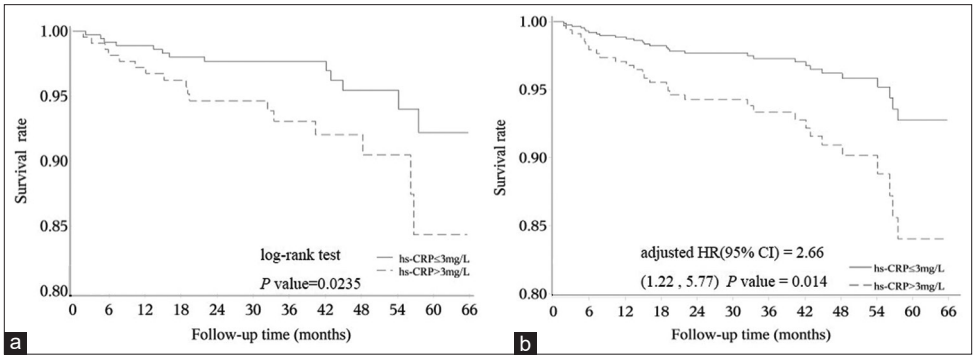

Figure 1: Kaplan–Meier curve for composite cardiovascular events by hs-CRP (>3 mg/L vs. ≤3 mg/L) in CAE. (a) The survival rate of the patients with hs-CRP >3 mg/L notably distinguished from those counterpart (log-rank test, $P = 0.0235$). (b) The cardiovascular events risk of patients with hs-CRP >3 mg/L was still much higher than those with hs-CRP ≤3 mg/L (*HR* = 2.66, 95% *CI*: 1.22–5.77, $P = 0.014$). The adjusting variables include age, gender, diabetes mellitus, hyperlipidemia, body mass index, lymphocyte, neutrophils, natriuretic peptide, left ventricle ejection fraction, and direct bilirubin. hs-CRP: High-sensitivity C-reactive protein; *HR*: Hazard ratio; *CI:* Confidence interval; CAE: Coronary artery ectasia.

Table 4: Net reclassification improvement and integrated discrimination improvement for hs-CRP

Events	NRI	*P*	IDI	*P*	Hosmer–Lemeshow test *P* value	
					Baseline	Addition
Composite	0.01	0.8798	0.020	0.033	0.344	0.897
Cardiovascular death	0.09	0.3066	0.014	0.237	0.928	0.909
Nonfatal MI	0.08	0.5513	0.010	0.161	0.991	0.650

MI: Myocardial infarction; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; NRI: Net reclassification improvement; IDI: Integrated discrimination improvement; The basic model comprised age, sex, BMI, LDL/HDL ratio, smoking, diabetes, hypertension, and number of diseased vessels.

remained. Three decades ago, the largest cohort study of CAE to date found that the aneurysmal patients had a 5-year mortality rate of 26%.[1] In 2004, Baman *et al.* reported a 5-year mortality rate of 29.1% in a cohort of 276 CAE patients.[2] However, in another study of 258 CAE patients, the cardiovascular deaths over the follow-up period of 49 ± 21 months only represented 2%.[14] In the present study, we obtained follow-up data for 540 CAE patients over a median follow-up period of 36 (37.41 ± 15.88) months, and observed 12 (2.22%) cardiac deaths and 18 (3.33%) nonfatal myocardial infarctions. In light of these numbers, it appeared that the prognosis of CAE patients has improved over time—a phenomenon that might be partially explained by the advances in medical therapy.

In the present analysis, hs-CRP >3 mg/L was identified as an independent predictor of poor prognosis in patients with CAE. However, there has been conflicting information about the ideal and incremental level of hs-CRP for the prediction of CVs. In several studies, a median hs-CRP value of 2 mg/L was regarded as the appropriate cutoff point for the identification of increased risks of CVs.[15] However, more than 50% of adults and 41% of 20-year-olds in the United States have an hs-CRP level >2 mg/L.[16] Therefore, an hs-CRP of 2 mg/L might not be an ideal cutoff point for risk stratification. The clinically applied threshold of hs-CRP >3 mg/L might be more suitable for the identification of high risks of future cardiovascular complications. In a study, patients with coronary artery disease were followed for a median of 5.0 years (5.1 ± 0.3 years), and those with an hs-CRP >3 mg/L had a significantly higher coronary events risk than those with an hs-CRP level ≤3 mg/L.[17] Patients with stable angina whose hs-CRP exceeded 3 mg/L were subjected to more frequent subsequent cardiovascular death, myocardial infarctions, and strokes.[18] In the present study, we applied the CDC/AHA hs-CRP cutoff point (>3 mg/L) for the identification of the higher risk group and demonstrated that an elevated level of hs-CRP was associated with an increased risk of cardiovascular death and nonfetal myocardial infarction in CAE patients.

The isolated CAE bears high-risk of mortality and myocardial infarction.[1] CAE is commonly concomitant with O-CAD. But the survival rate of CAE patients is similar during 5-year's follow-up, no matter with O-CAD or not.[2] Consistent with this result, there was no significant difference of Gensini score between the group with CVs and without CVs [Table 1], indicating that the poor prognosis of CAE was not associated with the severity of the concomitant O-CAD.

The present study demonstrated that an elevated level of hs-CRP was associated with a higher risk of CVs, indicating that CRP might be involved in the progression of CAE. Previous investigators have shown an increase in plasma CRP in CAE patients,[4] and several reports have suggested that CRP might contribute to the adverse CVs. At first, systematic inflammation–as reflected in the concentration of CRP–preceded the onset of CVs rather than being a result of ischemia.[19] Second, CRP could increase monocyte adhesion to endothelial cells and the secretion of matrix metalloproteinases, leading to endothelial dysfunction and medial destruction.[20] Third, the pro-thrombotic effects of CRP were demonstrated in human[21] as well as transgenic mouse.[22] Finally, the therapeutic inhibition of CRP could counteract the increase in infarct size and cardiac dysfunction produced by the injection of human CRP in rats.[23] Thus, CRP might play a role in the progression of CAE.

Besides demonstrating the prognostic role of CRP in CAE patients, this study also had its clinical implications. Consideration of hs-CRP level could be used in the risk stratification of CAE patients. Irrespective of LDL cholesterol concentration, a higher hs-CRP concentration has previously been associated with a higher coronary event rates.[24] Similarly, in this study, a higher hs-CRP level indicated a poor prognosis in CAE patients. Therefore, consideration of hs-CRP level might be helpful in tailoring the therapy to individual CAE patients.

Several limitations of this study must be mentioned. First, the number of observed CVs in the present study was relatively small. This might have influenced the accuracy of the multivariable Cox models and might limit the generalizability of the results. Nevertheless, the present results suggested that CRP might contribute to the progression of CAE. Further and broader investigations will be needed to confirm and refine this hypothesis. Second, the small value of the hs-CRP NRI for the outcomes might have resulted from the relatively small sample size and limited follow-up time. However, we found an IDI of 0.02 ($P = 0.033$) and P value improvement in the Hosmer–Lemeshow test; these results were similar to those observed in cases of stable O-CAD.[12] Finally, as we only used the hs-CRP level on admission in the analyses, there was a lack of the longitudinal detection and continuous observation. However, considering the decade-to-decade consistency in CRP values,[25] the CRP has been sufficiently suitable for the long-term prediction of CAE patients' prognosis.

In conclusion, the hs-CRP on admission was an independent predictor of CAE patients' adverse CVs in. In addition, this study suggested that the CRP may play a role in CAE, as a relationship was found between elevated hs-CRP levels and poor CAE prognosis. An hs-CRP cutoff point of 3 mg/L might be considered for risk stratification in patients with CAE.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1a: Comparisons for composite cardiovascular events by the median of various routine laboratory examination results

Variables	CV events (+)	CV events (−)	*P*
Age (years)			
≤57	7 (23.3%)	289 (52.8%)	0.0013
>57	23 (76.7%)	258 (47.2%)	
LVEF (%)			
≤61	23 (79.3%)	258 (49.7%)	0.0013
>61	6 (20.7%)	261 (50.3%)	
Neutrophils ($\times 10^9$)			
≤4.1	17 (63.0%)	287 (53.1%)	0.3148
>4.1	10 (37.0%)	253 (46.9%)	
Lymphocyte ($\times 10^9$)			
≤1.9	17 (63.0%)	267 (49.4%)	0.1680
>1.9	10 (37.0%)	273 (50.6%)	
Monocyte ($\times 10^9$)			
≤0.45	13 (48.1%)	274 (50.7%)	0.7926
>0.45	14 (51.9%)	266 (49.3%)	
BNP (ng/L)			
≤617.1	8 (32.0%)	235 (51.1%)	0.0603
>617.1	17 (68.0%)	225 (48.9%)	
DBil (μmol/L)			
≤2.5	8 (30.8%)	277 (52.9%)	0.0263
>2.5	18 (69.2%)	247 (47.1%)	
Glucose (mmol/L)			
≤5.25	13 (48.1%)	267 (50.4%)	0.8212
>5.25	14 (51.9%)	263 (49.6%)	
HsCRP (mg/L)			
≤2.12	9 (34.6%)	272 (51.0%)	0.0995
>2.12	17 (65.4%)	261 (49.0%)	
LDL-C (mmol/L)			
≤2.5	14 (53.8%)	263 (50.1%)	0.7087
>2.5	12 (46.2%)	262 (49.9%)	

BNP: Brain natriuretic peptide; CV: Cardiovascular events; Dbil: Direct bilirubin; Hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low density lipiproten-cholesteral; LVEF: Left ventricular ejection fraction.

Supplementary Table 1b: Comparison for composite cardiovascular events by the quartile of various routine laboratory examination results

Variables	CV events (+)	CV events (−)	*P*
Age (years)			
≤49	3 (10.0%)	150 (27.4%)	
(49,57)	4 (13.3%)	139 (25.4%)	0.0105
(57,65)	10 (33.3%)	135 (24.7%)	
>65	13 (43.3%)	123 (22.5%)	
LVEF (%)			
≤56	14 (48.3%)	128 (24.7%)	
(56,61)	9 (31.0%)	130 (25.0%)	0.0022
(61,65)	1 (3.4%)	137 (26.4%)	
>65	5 (17.2%)	124 (23.9%)	
Neutrophilis ($\times 10^9$)			
≤3.3	11 (40.7%)	146 (27.0%)	
(3.3,4.1)	6 (22.2%)	141 (26.1%)	0.0315
(4.1,5.2)	1 (3.7%)	122 (22.6%)	
>5.2	9 (33.3%)	131 (24.3%)	
Lymphocyte ($\times 10^9$)			
≤1.49	8 (29.6%)	135 (25.0%)	
(1.49,1.9)	9 (33.3%)	132 (24.4%)	0.4970
(1.9,2.37)	6 (22.2%)	136 (25.2%)	
>2.37	4 (14.8%)	137 (25.4%)	
Monocyte ($\times 10^9$)			
≤0.35	6 (22.2%)	137 (25.4%)	
(0.35,0.45)	7 (25.9%)	137 (25.4%)	0.4161
(0.45,0.58)	4 (14.8%)	135 (25.0%)	
>0.58	10 (37.0%)	131 (24.3%)	
BNP (ng/L)			
≤487.5	1 (4.0%)	121 (26.3%)	
(487.5,617.1)	7 (28.0%)	114 (24.8%)	0.0007
(617.1,894.1)	3 (12.0%)	118 (25.7%)	
>894.1	14 (56.0%)	107 (23.3%)	
≤1.9	6 (23.1%)	150 (28.6%)	
Dbil (mmol/L)			
(1.9,2.5)	2 (7.7%)	127 (24.2%)	0.0397
(2.5,3.3)	6 (23.1%)	124 (23.7%)	
>3.3	12 (46.2%)	123 (23.5%)	
≤4.73	8 (29.6%)	135 (5.5%)	
Glucose (mmol/L)			
(4.73,5.25)	5 (18.5%)	132 (24.9%)	0.8154
(5.25,5.97)	6 (22.2%)	132 (24.9%)	
>5.97	8 (29.6%)	131 (24.7%)	
≤1.1	4 (15.4%)	135 (25.3%)	
Hs-CRP (mg/L)			
(1.1,2.12)	5 (19.2%)	137 (25.7%)	0.2290
(2.12,5.63)	6 (23.1%)	132 (24.8%)	
>5.63	11 (42.3%)	129 (24.2%)	
≤1.9	5 (19.2%)	133 (25.3%)	
LDL-C (mmol/L)			
(1.9,2.5)	9 (34.6%)	130 (24.8%)	0.4421
(2.5,3.09)	8 (30.8%)	130 (24.8%)	
>3.09	4 (15.4%)	132 (25.1%)	

BNP: Brain natriuretic peptide; CV: Cardiovascular; Dbil: Direct bilirubin; Hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low density lipiproten-cholesteral; LVEF: Left ventricular ejection fraction.