C-Reactive Protein and All-Cause Mortality in Patients with Stable Coronary Artery Disease: A Secondary Analysis Based on a Retrospective Cohort Study

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Background: The association between C-reactive protein (CRP) and all-cause mortality (ACM) in patients with stable coronary artery disease (CAD) is unclear. Therefore, the aim of the present study was to explore the correlation between CRP and ACM in stable CAD patients.

Material/Methods: This study was a secondary analysis. Between October 2014 and October 2017, 196 patients aged 43 to 98 years who had a first diagnosis of stable CAD were recruited into this study. We divided the patients into 4 groups (Quartile 1: 0.01–0.03 mg/dL; Quartile 2: 0.04–0.11 mg/dL; Quartile 3: 0.12–0.33 mg/dL; and Quartile 4: 0.34–9.20 mg/dL) according to the concentration of CRP. The indicator surveyed in this research was ACM.

Results: During a median follow-up of 783 days, ACM occurred in 18 patients, with a mortality rate of 9.18% (18/196). Univariate analysis showed that elevated CRP was closely related to ACM in stable CAD patients (P<0.005). After controlling for potential confounding factors by multivariate logistic regression analysis, this relationship still existed. Pearson correlation analysis showed that elevated CRP log10 transform was associated with LVEF (r=–0.1936, P=0.0067). Receiver operating characteristic (ROC) curve analysis showed that the optimal concentration of CRP for the diagnosis of ACM was 0.345, and the area under the curve (AUC) was 0.735.

Conclusions: Elevated CRP is associated with ACM in stable CAD patients, and the best diagnostic threshold is 0.345.

MeSH Keywords: C-Reactive Protein • Coronary Vessels • Hospital Mortality

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Background

Stable coronary artery disease (CAD) [1–4] is a global medical problem that increases the risk of cardiovascular events. Patients with stable CAD also have significantly higher risks of cardiac arrest and ischemic stroke. Our results demonstrated that the potential pathophysiology of adverse reactions in patients with atherosclerosis is the rupture or erosion of atherosclerotic plaques, resulting in endothelial matrix exposure to blood circulation [5,6], thus activating platelet aggregation and coagulation cascade reaction in the body, which ultimately leads to the occurrence of arterial occlusive events.

C-reactive protein (CRP) [7–9] is a systemic inflammatory response factor synthesized and released in the liver. It is one of the first acute-phase proteins discovered by humans. CRP is so named because it can react with pneumococcal type C polysaccharides in the presence of calcium ions. Under physiological conditions, the content of CRP in the human body is very low. When acute stress reaction or tissue injury occurs, the concentration of CRP increases sharply, so CRP is mainly used to detect and evaluate the severity of acute injury and inflammation in vivo. Researchers have found that the increase of CRP can be used to predict the risk of coronary artery events [10–12], which has attracted the attention and recognition of clinicians, especially cardiovascular physicians. In addition, a series of epidemiological investigations and experimental studies [13–15] support that CRP is a reliable predictor of adverse events. Nonetheless, it is unclear whether elevated CRP is correlated with all-cause mortality (ACM) in patients with stable CAD, and the optimal threshold for CRP to predict ACM is unknown.

In this research, we examined CRP level and ACM events in stable CAD patients, and explored the optimal threshold of CRP for predicting ACM, so as to provide a reference basis for refining the risk profile of patients with stable CAD.

Material and Methods

Data source

The data used in this study were available free of charge from “datadryad” websites (http://datadryad.org/). On datadryad, authors have licensed ownership of the original data to datadryad, and other medical researchers can these data for secondary data analysis based on different research assumptions. This study is a secondary analysis based on a retrospective cohort study [16] (https://doi.org/10.1371/journal.pone.0219044) and the Dryad data package (https://doi.org/10.5061/dryad.frn6730).

In general, the Suzuki study [16] was a retrospective cohort study conducted in a single hospital in Japan. The subjects were newly diagnosed stable CAD patients hospitalized in Shinonoi General Hospital, the time range was from October 2014 to October 2017, and all patients received standard elective percutaneous coronary intervention (EPCI) treatment from cardiologists. Inclusion criteria were: 1) Age ≥18 years; 2) Patients met the diagnostic criteria of stable CAD, as defined in the Suzuki study [16]; and 3) Patients received elective PCI. Exclusion criteria were: 1) Patients with old myocardial infarction; 2) Patients diagnosed as having malignant tumors. In the Suzuki study [16], 204 patients were included, but 8 were missing CRP data, so the data from these 8 patients were eliminated from the present study. Eventually, 196 patients were included in the present study. From the original data by Suzuki, we obtained data on patient age, sex, body mass index (BMI), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A1c (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), and history of medication and disease. The present study is a secondary analysis based on the Suzuki study, and all patient information was anonymous; therefore, it was not necessary to obtain patient informed consent or ethics committee approval.

Primary endpoint and treatments

The primary endpoint of our study was all-cause mortality (ACM). Treatment regimens were administered in accordance with standard protocols and guidelines, including aspirin, statin, ACEI, or ARB. Similarly, coronary angiography and PCI are performed commensurate with standard guidelines.

Statistical analysis

We used software to divide patients into 4 groups. (Quartile 1: 0.01–0.03 mg/dL; Quartile 2: 0.04–0.11 mg/dL; Quartile 3: 0.12–0.33 mg/dL; and Quartile 4: 0.34–9.20 mg/dL) according to the concentration of C-reactive protein at admission. Among them, there were 34 patients in Quartile 1 group, 62 patients in Quartile 2 group, 51 patients in Quartile 3 group, and 49 patients in Quartile 4 group. Because continuous variables were expressed by median and interquartile range (IR) in the Suzuki study, we also represent our data in this way in the present study. Continuous variables were compared between groups by analysis of variance, the classification variables are represented by the number (%), and the chi-square test was used for comparison between groups. In this study, we compared the results with odds ratio (OR) and 95% confidence intervals (CI).
Table 1. Baseline characteristics of the 4 groups of patients.

| C-reactive protein | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P value |
|--------------------|------------|------------|------------|------------|---------|
| N                  | 34         | 62         | 51         | 49         |         |
| BMI (kg/m²)        | 22.48      | 23.69      | 24.05      | 22.84      | 0.577   |
| (20.67–24.51)      | (21.35–25.73) | (21.11–25.74) | (20.44–25.41) |           |
| Age (year)         |            |            |            |            | 0.267   |
| <45                | 0 (0.00%)  | 0 (0.00%)  | 1 (1.96%)  | 0 (0.00%)  |         |
| 45–65              | 7 (20.59%) | 16 (25.81%)| 8 (15.69%) | 5 (10.20%) |         |
| ≥65                | 27 (79.41%)| 46 (74.19%)| 42 (82.35%)| 44 (89.80%)|         |
| Albumin (g/dL)     |            |            |            |            | <0.001  |
| <4.0               | 6 (17.65%) | 20 (32.26%)| 25 (49.02%)| 35 (71.43%)|         |
| ≥4.0               | 28 (82.35%)| 42 (67.74%)| 26 (50.98%)| 14 (28.57%)|         |
| EGFR (mL/min/1.73 m²)|        |            |            |            | 0.061   |
|                   | 6 (17.65%) | 20 (32.26%)| 25 (49.02%)| 35 (71.43%)|         |
| AST (U/L)          | 23.50      | 22.50      | 21.00      | 24.00      | 0.213   |
| (20.00–28.00)      | (18.00–27.00)| (18.00–29.00)| (19.00–30.00)|           |
| ALT (U/L)          | 18.50      | 19.00      | 18.00      | 18.00      | 0.836   |
| (14.00–24.75)      | (14.00–24.75)| (13.00–24.50) | (14.00–27.00) |           |
| Total cholesterol (mg/dL) | 188.50 | 189.50 | 176.50 | 180.00 | 0.162 |
| (169.75–208.50)    | (173.00–204.75)| (154.25–206.25)| (152.00–205.50)|           |
| Triglyceride (mg/dL)| 103.00 | 106.00 | 106.00 | 106.00 | 0.408 |
| (84.00–148.00)     | (78.00–149.00)| (95.25–190.75)| (60.00–157.00)|           |
| HDL (mg/dL)        | 57.00      | 52.00      | 45.00      | 45.00      | <0.001  |
| (46.00–65.00)      | (46.00–57.00)| (35.25–54.75) | (39.00–54.00) |           |
| LDL (mg/dL)        | 112.00     | 109.00     | 105.50     | 108.00     | 0.613   |
| (97.00–131.00)     | (93.00–126.00)| (87.25–130.75)| (87.00–125.25)|           |
| HbA1c (%)          | 6.00       | 6.10       | 6.00       | 5.90       | 0.407   |
| (5.70–6.43)        | (5.80–6.90)| (5.60–6.50)| (5.62–6.77) |           |
| SBP (mmHg)         | 137.00     | 136.00     | 136.00     | 138.00     | 0.915   |
| (123.75–143.00)    | (123.25–147.75)| (120.00–150.50)| (124.00–147.00) |           |
| DBP (mmHg)         | 75.00      | 76.00      | 78.00      | 79.00      | 0.578   |
| (71.25–85.75)      | (69.25–85.00)| (69.50–86.50)| (69.00–89.00) |           |
| LVEF (%)           | 67.80      | 66.00      | 65.00      | 65.40      | 0.077   |
| (64.00–69.00)      | (63.10–68.00)| (61.00–68.00)| (62.00–68.00)|           |
| Sex (Male)         |            |            |            |            | 0.932   |
| No                 | 27 (79.41%)| 47 (75.81%)| 38 (74.51%)| 34 (69.39%)|         |
| Yes                | 10 (29.41%)| 20 (32.26%)| 14 (27.45%)| 16 (32.65%)|         |
| OCI (%)            |            |            |            |            | 0.635   |
| No                 | 28 (82.35%)| 53 (85.48%)| 44 (86.27%)| 38 (77.55%)|         |
| Yes                | 6 (17.65%) | 9 (15.52%) | 7 (13.73%) | 11 (22.45%)|         |
| PAD (%)            |            |            |            |            | 0.762   |
| No                 | 27 (79.41%)| 47 (75.81%)| 38 (74.51%)| 34 (69.39%)|         |
| Yes                | 7 (20.59%) | 15 (24.19%)| 13 (25.49%)| 15 (30.61%)|         |
| Dyslipidemia (%)   |            |            |            |            | 0.309   |
| No                 | 29 (85.29%)| 56 (90.32%)| 45 (88.24%)| 40 (81.63%)|         |
| Yes                | 5 (14.71%) | 6 (9.68%)  | 6 (11.76%) | 9 (18.37%) |         |
| Dyslipidemia (%)   |            |            |            |            | 0.023   |
| No                 | 21 (60.60%)| 42 (65.60%)| 22 (42.31%)| 27 (55.10%)|         |
| Yes                | 14 (39.40%)| 26 (35.40%)| 28 (57.69%)| 22 (44.90%)|         |
### Table 1 Continued. Baseline characteristics of the 4 groups of patients.

| C-reactive protein | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P value |
|--------------------|------------|------------|------------|------------|---------|
| Past smoking (n, %) |            |            |            |            | 0.707   |
| No                 | 15 (44.12%) | 33 (53.23%) | 24 (47.06%) | 27 (55.10%) |         |
| Yes                | 19 (55.88%) | 29 (46.77%) | 25 (52.94%) | 23 (44.90%) |         |
| Diabetes mellitus (n, %) |          |            |            |            | 0.620   |
| No                 | 20 (58.82%) | 38 (61.29%) | 33 (64.71%) | 35 (71.43%) |         |
| Yes                | 14 (41.18%) | 24 (38.71%) | 18 (35.29%) | 14 (28.57%) |         |
| Aspirin (n, %)     |            |            |            |            | 0.660   |
| No                 | 0 (0.00%)  | 1 (1.61%)  | 0 (0.00%)  | 1 (2.04%)  |         |
| Yes                | 34 (100.00%) | 61 (98.39%) | 51 (100.00%) | 48 (97.96%) |         |
| Thienopyridines (n, %) |        |            |            |            | 0.722   |
| No                 | 1 (2.94%)  | 1 (1.61%)  | 0 (0.00%)  | 1 (2.04%)  |         |
| Yes                | 33 (97.06%) | 61 (98.39%) | 51 (100.00%) | 48 (97.96%) |         |
| Warfarin (n, %)    |            |            |            |            | <0.001  |
| No                 | 31 (91.18%) | 58 (93.55%) | 45 (88.24%) | 41 (83.67%) |         |
| Yes                | 3 (8.82%)  | 4 (6.45%)  | 6 (11.76%) | 5 (10.20%) |         |
| DOAC (n, %)        |            |            |            |            | 0.395   |
| No                 | 31 (91.18%) | 58 (93.55%) | 45 (88.24%) | 41 (83.67%) |         |
| Yes                | 3 (8.82%)  | 4 (6.45%)  | 6 (11.76%) | 5 (10.20%) |         |
| Ezetimibe (n, %)   |            |            |            |            | 0.106   |
| No                 | 32 (94.12%) | 62 (100.00%) | 51 (100.00%) | 48 (97.96%) |         |
| Yes                | 2 (5.88%)  | 0 (0.00%)  | 0 (0.00%)  | 1 (2.04%)  |         |
| MRA (n, %)         |            |            |            |            | 0.235   |
| No                 | 20 (58.82%) | 36 (58.06%) | 25 (49.02%) | 22 (44.90%) |         |
| Yes                | 30 (81.25%) | 48 (80.62%) | 33 (64.08%) | 25 (50.98%) |         |
| ACEI (n, %)        |            |            |            |            | 0.072   |
| No                 | 30 (88.24%) | 45 (90.32%) | 38 (89.80%) | 34 (68.77%) |         |
| Yes                | 4 (11.76%) | 4 (8.68%)  | 6 (11.76%) | 5 (10.20%) |         |
| ARB (n, %)         |            |            |            |            | 0.178   |
| No                 | 20 (58.82%) | 39 (62.90%) | 30 (58.82%) | 21 (42.86%) |         |
| Yes                | 14 (41.18%) | 23 (37.10%) | 14 (41.18%) | 13 (57.14%) |         |
| Beta blocker (n, %)|            |            |            |            | 0.034   |
| No                 | 29 (85.29%) | 44 (70.97%) | 35 (68.33%) | 36 (73.47%) |         |
| Yes                | 5 (14.71%) | 18 (29.03%) | 16 (31.37%) | 13 (26.53%) |         |
| MRA (n, %)         |            |            |            |            | 0.001   |
| No                 | 34 (100.00%) | 58 (90.32%) | 49 (96.08%) | 46 (93.88%) |         |
| Yes                | 0 (0.00%)  | 0 (0.00%)  | 0 (0.00%)  | 0 (0.00%)  |         |
| All-cause mortality (n, %) | | | | | <0.001 |
| No                 | 33 (97.06%) | 59 (95.16%) | 49 (96.08%) | 37 (75.51%) |         |
| Yes                | 1 (2.94%)  | 3 (4.84%)  | 2 (3.92%)  | 12 (24.49%) |         |

Data are represented by median, interquartile range, or number (%). ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin-receptor blocker; BMI – body mass index; DOAC – direct oral anticoagulants; eGFR – estimated glomerular filtration rate; HbA1c – hemoglobin A1c; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; OCI – old cerebral infarction; PAD – peripheral artery disease; PPI – proton pump inhibitor.
In univariate analysis, the factors related to all-cause mortality were screened by taking all-cause mortality of patients as the dependent variable and other variables as covariates. In addition, because there are more covariates selected in single-factor analysis, we use least absolute shrinkage and selection operator (LASSO) [17] regression analysis for feature variable selection and data dimensionality reduction. In multivariate logistic regression analysis, we used all-cause mortality of patients as the dependent variable, C-reactive protein was an independent variable, and the variables selected by LASSO regression were used as adjustment variables to observe the independent effect of CRP on all-cause mortality.

Considering the skewed distribution of CRP, we transformed CRP into log10 transform and used Pearson correlation analysis to observe the relationship between CRP log10 transform and left ventricular ejection fraction (LVEF). In addition, the receiver operating characteristic (ROC) [18] curve was used to explore the optimal threshold of CRP for predicting all-cause mortality, and the area under the curve (AUC), sensitivity, and specificity were applied to evaluate the reliability of the predicted results. P<0.05 is set as the level of statistical significance and we used SPSS 24 statistics (IBM Corp., Armonk, NY, USA) and EmpowerStats (http://www.empowerstats.com) to analyze and collate the data.

**Results**

**Baseline characteristics of the 4 groups of patients**

There were statistically significant differences in HDL and serum albumin among the 4 groups (all P<0.05). However, no differences were observed in age, BMI, eGFR, AST, ALT, total cholesterol, TG, HDL, HbA1c, SB, DBP, LVEF, or history of medication and disease among groups (Table 1).

**Comparison of all-cause mortality in the 4 groups of patients**

After 783 days of follow-up, ACM occurred in 18 patients, with a mortality rate of 9.18% (18/196). The all-cause mortality rates of the 4 groups were 2.94%, 4.84%, 3.92%, and 24.49%, respectively (P for trend<0.001) (Table 1, Figure 1).

**Univariate analysis of all-cause mortality**

Taking the ACM event of the patient as the dependent variable and the other variables as the covariates to observe which factors are interrelated to ACM event, we found that BMI (OR=0.73, 95% CI 0.62 to 0.87), eGFR (OR=0.98, 95% CI 0.96 to 1.00), ALT (OR=0.90, 95% CI 0.84 to 0.98), total cholesterol (OR=0.98, 95% CI 0.96 to 0.99), LDL (OR=0.98, 95% CI 0.96 to 1.00), dyslipidemia (OR=0.11, 95% CI 0.02 to 0.50), past smoking (OR=0.26, 95% CI 0.08 to 0.82), statins (OR=0.31, 95% CI 0.11 to 0.92), CRP (Quartile 2 vs. Quartile 1: OR=1.35, 95% CI 0.12 to 15.46; Quartile 4 vs. Quartile 1: OR=10.70, 95% CI 1.32 to 86.82, P for trend<0.05), and albumin (OR=0.04, 95% CI 0.00 to 0.29) were associated with all-cause mortality. However, other variables were not associated with all-cause mortality between groups (all P>0.05) (Table 2).

**Lasso regression analysis of factors related to all-cause Mortality**

Lasso regression analysis demonstrated that 6 factors were associated with all-cause mortality: ALT, peripheral artery disease (PAD), DLP, past smoking, CRP, and age. The formula used for calculating score (not including the intercept) was: 

\[ -0.01395 \times \text{ALT} - 0.31697 \times \text{PAD} + 0.81429 \times \text{DLP} + 0.05077 \times \text{past smoking} + 1.03099 \times \text{CRP} - 0.01984 \times \text{age} \] 

(Figures 2, 3).

**Multivariate logistic regression analysis of the relationship between C-reactive protein and all-cause mortality**

In multivariate logistic regression analysis, all-cause death events were taken as dependent variables, C-reactive protein was an independent variable, and the variables selected by Lasso regression analysis were adjusted as covariates. In addition, combined with the actual clinical situation, it is considered that ALT, PAD, and DLP have little influence on the results, so these 3 variables were eliminated from the covariates. Age was adjusted in adjust I model, and the results showed that CRP was significantly correlated with all-cause mortality (Quartile 2 vs. Quartile 1: OR=1.81, 95% CI 0.18 to 18.37; Quartile 3 vs. Quartile 1: OR=1.30, 95% CI 0.11 to 15.08; Quartile 4 vs. Quartile 1: OR=9.75, 95% CI 1.19 to 79.99, P for trend<0.05). Similarly, age and past smoking were adjusted in adjust II model, and the results showed
Table 2. Univariate analysis of all-cause mortality.

| Variables                  | All-cause mortality |
|----------------------------|---------------------|
| Sex (Male)                 |                     |
| 0                          | Reference           |
| 1                          | 0.87 (0.31, 2.44) 0.7928 |
| Age (year)                 |                     |
| <45                        | Reference           |
| 45–65                      | –                   |
| >65                        | –                   |
| Albumin (g/dL)             |                     |
| <4.0                       | Reference           |
| ≥4.0                       | 0.04 (0.00, 0.29) 0.0016 |
| BMI (kg/m²)                |                     |
| 0.73 (0.62, 0.87) 0.0003   |                     |
| EGFR (mL/min/1.73 m²)      |                     |
| 0.98 (0.96, 1.00) 0.0183   |                     |
| AST (U/L)                  |                     |
| 0.99 (0.94, 1.04) 0.6698   |                     |
| ALT (U/L)                  |                     |
| 0.90 (0.84, 0.98) 0.0096   |                     |
| Total cholesterol (mg/dL)  |                     |
| 0.98 (0.96, 0.99) 0.0092   |                     |
| Triglyceride (mg/dL)       |                     |
| 0.99 (0.98, 1.00) 0.1346   |                     |
| HDL (mg/dL)                |                     |
| 0.97 (0.93, 1.01) 0.1497   |                     |
| LDL (mg/dL)                |                     |
| 0.98 (0.96, 1.00) 0.0353   |                     |
| HbA1c (%)                  |                     |
| 0.64 (0.30, 1.37) 0.2516   |                     |
| SBP (mmHg)                 |                     |
| 1.32 (0.98, 1.79) 0.0723   |                     |
| DBP (mmHg)                 |                     |
| 1.00 (0.98, 1.02) 0.9152   |                     |
| LVEF (%)                   |                     |
| 1.00 (0.97, 1.04) 0.8655   |                     |
| EGFR (mL/min/1.73 m²)      |                     |
| 0.97 (0.93, 1.01) 0.1246   |                     |
| OCI (n,%)                  |                     |
| No                         | Reference           |
| Yes                        | 1.07 (0.45, 2.50) 0.3526 |
| PAD (n,%)                  |                     |
| No                         | Reference           |
| Yes                        | 2.59 (0.96, 6.99) 0.0600 |
| Dyslipidemia (n,%)         |                     |
| No                         | Reference           |
| Yes                        | 2.03 (0.61, 6.71) 0.2478 |
| Past smoking (n,%)         |                     |
| No                         | Reference           |
| Yes                        | 0.26 (0.08, 0.82) 0.2020 |
| Aspirin (n,%)              |                     |
| No                         | Reference           |
| Yes                        | 0.10 (0.01, 1.61) 0.1030 |
| Thienopyridines (n,%)      |                     |
| No                         | Reference           |
| Yes                        | 0.19 (0.02, 2.24) 0.1887 |
| Warfarin (n,%)             |                     |
| No                         | Reference           |
| Yes                        | 2.56 (0.27, 24.21) 0.4125 |
| DOAC (n,%)                 |                     |
| No                         | Reference           |
| Yes                        | 1.05 (0.22, 4.90) 0.9545 |
| PPI (n,%)                  |                     |
| No                         | Reference           |
| Yes                        | 0.00 (0.00, Inf) 0.9918 |
| Statins (n,%)              |                     |
| No                         | Reference           |
| Yes                        | 0.31 (0.11, 0.92) 0.0343 |
| ACEI (n,%)                 |                     |
| No                         | Reference           |
| Yes                        | 1.18 (0.25, 5.59) 0.8313 |
| ARB (n,%)                  |                     |
| No                         | Reference           |
| Yes                        | 2.16 (0.80, 5.93) 0.1290 |
| Beta-blocker (n,%)         |                     |
| No                         | Reference           |
| Yes                        | 2.16 (0.80, 5.93) 0.1290 |
| MRA (n,%)                  |                     |
| No                         | Reference           |
| Yes                        | 2.35 (0.47, 11.81) 0.3006 |
| C-reactive protein         |                     |
| Quartile 1                 | Reference           |
| Quartile 2                 | 1.68 (0.17, 16.79) 0.6596 |
| Quartile 3                 | 1.35 (0.12, 15.46) 0.8110 |
| Quartile 4                 | 10.70 (1.32, 86.82) 0.0265 |

Data is represented as OR (95% CI) P value. ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin-receptor blocker; BMI – body mass index; DOAC – direct oral anticoagulants; eGFR – estimated glomerular filtration rate; HbA1c – hemoglobin A1c; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; OCI – old cerebral infarction; PAD – peripheral artery disease; PPI – proton pump inhibitor.
that CRP was significantly correlated with all-cause mortality (Quartile 2 vs. Quartile 1: OR=1.81, 95% CI 0.18 to 18.55; Quartile 3 vs. Quartile 1: OR=1.46, 95% CI 0.12 to 17.18; Quartile 4 vs. Quartile 1: OR=10.02, 95% CI 1.20 to 83.54, P for trend<0.05) (Table 3).

### Pearson correlation analysis of CRP log10 transform and left ventricular ejection fraction

Considering the skewed distribution of CRP, we converted CRP into log10, and then used Pearson correlation analysis to observe the relationship between CRP log10 transform and LVEF. The results showed that there was a negative correlation between CRP log10 transform and LVEF (r=-0.1936, P=0.0067) (Figure 4).

### ROC curve used by CRP to predict all-cause mortality

We used ROC curve analysis to determine the optimal threshold of CRP to forecast ACM. The results showed that the optimal threshold of CRP for diagnosing all-cause mortality was 0.345. At this time, the area under the curve (AUC) was 0.735 (95% CI 0.597 to 0.872), the sensitivity was 0.667, and the specificity was 0.803 (Figure 5).

### Discussion

In this study, we explored whether CRP was associated with ACM in stable CAD patients, and assessed the optimal threshold for predicting ACM. The results showed that CRP was closely related to all-cause death in patients with stable CAD, although the potential confounding factors were adjusted. In addition, in Pearson correlation analysis, we explored the correlation between CRP log10 transform and LVEF. The results showed that increased CRP log10 transform is closely related to decreased LVEF, indicating that the increase of CRP could be used to judge the decrease of LVEF. In further analysis, we used the ROC curve to determine the optimal threshold of CRP for predicting all-cause death events. The results showed...
that the optimal threshold of CRP was 0.345. The AUC was 0.735, sensitivity was 0.667, and specificity was 0.803, indicating that CRP has high reliability in predicting ACM events in stable CAD patients.

The results of previous studies have been shown that CRP plays an essential role in the occurrence of cardiovascular events. Lin et al. assessed the value of CRP in predicting ACM and adverse cardiovascular events, and included 1023 Taiwanese subjects. After a 11.2-year follow-up, 351 patients had died, 82 of which were due to cardiovascular causes. After potential confounding factors were controlled, CRP was still associated with higher ACM (HR=2.31, 95% CI: 1.62–3.29). These findings further support the important role of inflammatory markers in deteriorating health [19]. Similarly, the Copenhagen City Heart Study recruited 10 388 persons from the general population to investigate whether increased CRP was closely related to all-cause mortality; 3124 persons died during the 16-year clinical follow-up, and the increased level of CRP was strongly associated with higher ACM (HR=1.25, 95% CI: 1.21–1.29) [20]. In the Cardiovascular Health Study [21], a relationship between CRP and cardiovascular events was found only in participants with atherosclerosis, suggesting that CRP is involved with atherosclerosis and cardiovascular events. In addition, other researches have illustrated that elevated CRP could also predict an increase in deaths in various groups of patients [22–27]. The mechanism may be that biomarkers of inflammation reflect the ultimate common biochemical pathway of poor human health (which may be triggered by cytokines), leading to an increase in CRP levels [28]. The change of this pathophysiological mechanism can easily to lead to cardiovascular and non-cardiovascular death events. As an acute response protein, CRP can not only reflect the immune, inflammatory, and stress state of the body, but also predict the independent risk of cardiovascular events. In addition, CRP at pathological levels may also be directly involved in the formation, development, and evolution of atherosclerosis and the process of ischemia-reperfusion injury. Previous studies have shown that the interaction between leukocytes and endothelial cells induced by oxidants has a strong effect on microvascular dysfunction caused by atherosclerosis [29,30]. This chemotaxis of neutrophils can lead to the formation of thromboembolism and the release of oxygen free radicals during the development of arteriosclerosis. Intercellular adhesion molecule-1 (ICAM-1) [31] can promote the above chemotaxis, while CRP can increase the production of ICAM-1, thus aggravating the inflammatory response. On the other hand, CRP can stimulate the production of tissue factors, and then initiate the coagulation process and promote thrombosis [32,33]. Increased CRP levels are independently correlated with in-stent thrombosis and the risk of major cardiovascular events, suggesting that CRP may be involved in atherosclerosis by promoting thrombosis.

This study has the following strengths. First, we use Lasso regression analysis to screen out the covariables that needed to be adjusted in multivariate regression analysis, and the statistical efficiency is obviously better than that of univariate analysis. Secondly, we made 2 adjustment models (adjust I and adjust II), and the results were thus more reliable. Third, this study observed the relationship between CRP log10 transform and LVEF. We found that LVEF showed a downward trend with the increase of CRP log10 transform. Finally, our study illustrated that the best threshold for predicting all-cause mortality in stable CAD patients by CRP was 0.345 mg/dL. This suggests that CRP can predict the occurrence of all-cause mortality within a very small concentration range, and this topic warrants attention in clinical practice.

This study has the following limitations. First, due to the nature of retrospective cohort studies, there was inevitably selection bias or regression bias. Secondly, the population analyzed in our study was Japanese and the conclusions need to
be confirmed in further studies. Thirdly, this study is a secondary analysis based on a previous study. We could not accurately obtain the specific causes of death (cardiovascular or non-cardiovascular causes); therefore, we could not carry out subgroup analysis according to the causes of death.

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Conclusions

CRP is positively correlated with ACM in patients with stable CAD, and the best diagnostic threshold is 0.345. However, more research is needed to verify our results.