Systematic Review and Meta-Analysis

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# Predictive value of baseline C-reactive protein level in patients with stable coronary artery disease

## A meta-analysis

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**Abstract**

**Background:** Conflicting results have been reported on the association of C-reactive protein (CRP) level with adverse outcomes in patients with stable coronary artery disease (CAD). The objective of this meta-analysis was to evaluate the predictive value of baseline CRP level in stable CAD patients.

**Methods:** Two reviewers independently searched PubMed and Embase databases from their inception to November 28, 2021 to identify studies assessing the value of baseline CRP level in predicting adverse outcomes in stable CAD patients. The endpoints of interest included cardiovascular mortality, all-cause mortality, or major adverse cardiovascular events (MACEs). The predictive value of CRP level was estimated by pooling the multivariable adjusted risk ratio with 95% confidence intervals (CI) compared the highest to the lowest CRP level.

**Results:** Twenty-six studies involving of 22,602 patients with stable CAD satisfied the inclusion criteria. In a comparison of the highest with the lowest CRP level, the pooled multivariable adjusted risk ratio was 1.77 (95% CI 1.60–1.96) for MACEs, 1.64 (95% CI 1.13–2.33) for cardiovascular mortality, and 1.62 (95% CI 2.62–5.12) for all-cause mortality, respectively. Subgroup analyses indicated that the values of elevated CRP level in predicting MACEs were consistently observed in each subgroup.

**Conclusion:** Elevated baseline CRP level was an independent predictor of MACEs, cardiovascular mortality, and all-cause mortality in patients with stable CAD. Baseline CRP level can provide important predictive information in stable CAD patients.

**Abbreviations:** CAD = coronary artery disease, CI = confidence intervals, CRP = C-reactive protein, MACEs = major adverse cardiovascular events, RR = risk ratio.

**Keywords:** C-reactive protein, major adverse cardiovascular events, meta-analysis, mortality, stable coronary artery disease

## 1. Introduction

Coronary artery disease (CAD) is generally divided into acute coronary syndrome (including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction or unstable angina) and stable angina. Stable CAD usually refers to the patients stabilized after acute coronary syndrome, or the presence of plaque documented by angiography or catheterization.[1] Stable CAD is the most common type of ischemic heart disease. Despite widely use of evidence-based therapies, stable CAD remains a significant cause of morbidity and mortality worldwide.[2] CAD patients at stable stage are still threatened by recurrent cardiovascular events and higher risk of mortality.[3,4] Therefore, risk stratification is very important for secondary prevention in stable CAD patients.

Inflammation plays a pivotal role in the progress of atherosclerosis.[5,6] Low-grade inflammation is deemed as an important factor in the development of CAD.[7] C-reactive protein (CRP), an acute-phase reactant produced by hepatocytes, has been recognized as a biomarker of systemic inflammation. Inflammatory biomarkers including CRP level can provide prognostic information in stable coronary artery disease.[8] There is convincing evidence that elevated CRP level was independently associated with higher risk of adverse outcomes in patients with acute coronary syndrome.[9,10] However, studies on the association of elevated CRP level with adverse outcomes have produced inconsistent findings in patients with stable CAD.[11–28]

An early well-designed meta-analysis has examined the effect of CRP level in predicting fatal and nonfatal events in stable

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

*The available data and materials section refers to the raw data used in this study are included in manuscript.*

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CAD patients.[29] However, the quality of published evidence was not sufficient to recommend routine usefulness of CRP. To summarize the available evidence, we performed the current meta-analysis to evaluate the value of baseline CRP level in predicting adverse outcomes in patients with stable CAD in terms of cardiovascular mortality, all-cause mortality, or major adverse cardiovascular events (MACEs).

## 2. Methods

### 2.1. Data sources and Searches

The current meta-analysis was conducted in accordance with the guidelines of the Meta-analysis Of Observational Studies in Epidemiology statement.[30] Two independent authors searched PubMed and Embase databases from their inception to November 28, 2021 using the following items in combination: "C-reactive protein" AND "stable coronary disease" OR "stabilized acute coronary syndrome" OR "stabilized myocardial infarction" OR "mortality" OR "death" OR "cardiovascular events" AND "follow-up". Furthermore, reference lists of the included studies and pertinent reviews were also manually checked for additional studies. Ethical approval was not required because this study analyzed the study-level data.

### 2.2. Study selection

Two independent authors selected studies when they fulfilled all the following inclusion criteria: post hoc analysis of randomized controlled trials (placebo arm) or cohort studies; enrollment of CAD patients at stable stage; assessing the value of baseline CRP level in predicting all-cause mortality, cardiovascular mortality, or major adverse cardiovascular events ([MACEs] defined as a composite of death, non-fatal myocardial infarction, revascularization, refractory angina, arrhythmia, stroke, or unstable angina pectoris readmission); and providing multivariable adjusted risk estimate of outcomes for the highest versus the lowest CRP category. For multiple publication from the same population, we chose the study with the longest follow-up. Exclusion criteria included: patients at acute stage of coronary disease; reporting risk estimate by each unit changes or per standard deviation of CRP level; and without report the value of CRP in predicting clinical outcomes.

### 2.3. Data extraction and quality evaluation

Data extraction and quality assessment were conducted by two independent authors. Disagreement between the authors was resolved by consensus. Data extracted from the eligible studies included: name of first author, publication year, origin of study, study design, sample size, gender distribution, age of patients, threshold of elevated CRP level, assessment of MACEs, length of follow-up, outcomes of interest, fully adjusted risk summary, and adjusted covariates. We evaluated the methodological quality of included studies according to the Newcastle–Ottawa Scale,[31] which checked the selection of the study, comparability of the groups, and ascertainment of outcomes. Study awarding seven points or more was deemed to be high-quality.

### 2.4. Statistical analysis

STATA 12.0 (Stata Corporation, College Station, TX) was used to perform the meta-analysis. We pooled the risk ratio (RR) and 95% confidence interval (CI) for the highest versus the lowest CRP category. Cochran Q test ($P < .10$ indicating statistically significant) and $I^2$ statistic ($I^2 \geq 50\%$ indicating statistically significant) were used to investigate the degree of heterogeneity between studies. We adopted a random effect model when there was significant heterogeneity. Otherwise, a fixed-effect model was chosen. We performed the subgroup analysis according to study design, mean/median age, sample sizes, region, category of CRP level, and follow-up duration. Sensitivity analysis was conducted by excluding studies one by one to recalculate the risk estimate. Publication bias was evaluated by the combination of Begg test[32] and Egger test.[33] The trim-and-fill analysis was conducted to investigate the potential impact of publication bias on the overall risk estimate.

## 3. Results

### 3.1. Search results and study characteristics

Our literature search yielded 1050 potentially relevant articles. After removal of duplicates and evaluation of titles or/and abstracts, 74 full-text articles were retrieved for detailed evaluation. Forty-eight articles were excluded because these studies did not fulfil the inclusion criteria. Finally, 26 studies[11–28,34–41] were ultimately included in this meta-analysis (Fig. 1).

Table 1 summarizes the characteristics of the selected studies. The eligible studies were published between 2002 and 2019. Seven studies[20–22,26,34,38,40] were retrospective designs and others were prospective studies. A total of 22,602 patients with stable CAD were identified, with sample sizes ranging from 75 to 3771. The median/mean length of follow-up ranged between 1.0 and 10.4 years. Based on the Newcastle–Ottawa Scale criteria, the overall scores of these eligible studies were equal to or >6, suggesting moderate to high methodological quality.

### 3.2. Major adverse cardiovascular events

Twenty-four studies[11–28,35–39,41] reported the value of CRP level in predicting MACEs. A random effect model meta-analysis showed that the pooled RR of MACEs was 1.77 (95% CI 1.60–1.96; $I^2 = 28.4\%$, $P = .093$) for the highest *vs* the lowest CRP level (Fig. 2). Sensitivity analysis showed that

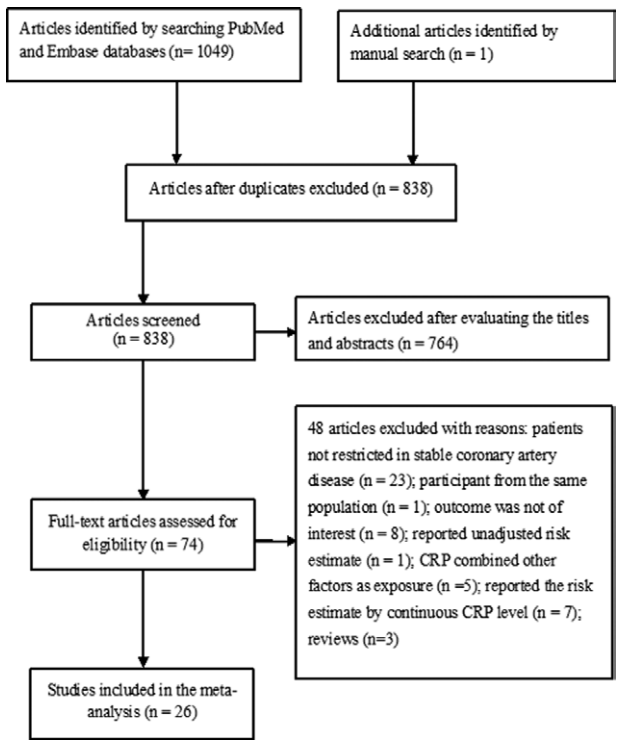


**Figure 1.** Flow chart showing the study selection process.

**Table 1**

**Main characteristics of the included studies.**

| Author/year | Region | Design | Patients (% men) | Age (yr) | CRP cutoff (mg/dL) | Definition of MACEs | Follow-up (yr) | Outcomes HR/RR (95% CI) | Adjustment for covariates | Total NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| Speidl 2002[11] | Austria | P | 119 (76.5) | 39.3 ± 5.6 | Tertile 3 vs 1 | CAD death, nonfatal MI, angina, revascularization | 4.5 | MACEs<br>2.70 (0.94–7.75) | Ae, sex, BMI, smoking, hypertension, DM, family history of CAD, TG, TC, HDL | 7 |
| Zebrack 2002[12] | USA | P | 599 (77) | 33–95 | ≥1.15 vs <1.15 | Death, AMI | 2.8 | Total death<br>5.2 (1.5–17.2)<br>MACEs<br>2.3 (1.1–4.6) | Age, sex, hypertension, hyperlipidemia, DM, tobacco, family history of CAD, treatment. TC, TG, LDL, SBP, DBP, renal failure, number of stenosis vessels, LVEF | 7 |
| de Winter 2002[13] | Netherlands | P | 501 (73.9) | 61.8 ± 11.2 | >3.0 vs ≤3.0 | Death, MI, revascularization, UAP readmission | 1.16 | MACEs<br>2.54 (1.44–4.47) | Age, sex, smoking, hypertension, DM, statin therapy, | 7 |
| Dibra 2003[14] | Germany | P | 1152 (73.4) | 66.1 ± 10.5 | >5.0 vs ≤5.0 | Death, MI | 1.0 | MACEs<br>1.8 (1.1–2.9) | Age, DM, active smoking, TC, LVEF, use of evidence-based therapies | 8 |
| Leu 2004[15] | Taiwan | P | 75 (88) | 68.1 ± 10.1 | >0.1 vs ≤0.1 | CV death, nonfatal MI, revascularization, refractory, or UAP admission | 1.5 | MACEs<br>2.78 (1.21–6.41) | Age, sex, smoking, hypertension, previous revascularization, biochemical markers, severity of CAD | 7 |
| Wu 2005[16] | China | P | 150 (90.7) | 67·8 ± 0·8 | ≥0.1 vs <0.1 | CV death, nonfatal MI, UAP admission, revascularization | 1.5 | MACEs<br>1.91 (0.98–3.74) | Multivariate adjusted | 7 |
| Hoffmeister 2005[17] | Germany | P | 312 (85.7) | 57.9 ± 7.3 | Quartiles 4 vs 1; >2.85 vs <0.69 | Non-fatal MI, ischemic stroke, revascularization, CAD death | 3.2 | MACEs<br>1.3 (0.6–2.8) | Age, sex, BMI, HDL, smoking, alcohol, years of school, DM, hypertension, use of acetylsalicylic acid, statins or diuretics, prior MI, affected vessels, intervention | 8 |
| Ikonomidis 2005[18] | Greece | P | 100 (84) | 54 ± 5 | ≥2.5 vs <2.5 | Cardiac death, AMI, UAP admission | 6.0 | MACEs<br>6.24 (1.74–22.42) | Age, sex, smoking, hypertension, hyperlipidaemia, parental CAD, previous MI, multivessel disease, non-use of evidence-based therapies, MCSF | 7 |
| Sinning 2006[19] | Germany | P | 1806 (78.7) | 61.7 ± 9.4 | Quartiles 4 vs1; >8.4 vs <1.46 | CV death, non-fatal MI | 3.5 | MACEs<br>1.41 (0.92–2.18)<br>CV death<br>1.40 (0.83–2.38) | Age, sex, BMI, hypertension, DM, smoking, HDL, number of diseased vessels, statin, beta-blocker therapies | 6 |
| Huang 2006[20] | China | R | 185 (53) | 69.4 ± 16.3 | >3.0 vs ≤3.0 | Sudden death, MI, chronic HF | 3.0 | Total death<br>4.6 (2.51–6.47)<br>MACEs<br>2.32 (1.76–2.89) | Lipids, hypertension, smoking, BMI | 7 |

*(Continued)*

**Table 1**

***(Continued)***

| Author/year | Region | Design | Patients (% men) | Age (yr) | CRP cutoff (mg/dL) | Definition of MACEs | Follow-up (yr) | Outcomes HR/RR (95% CI) | Adjustment for covariates | Total NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| Sabatine 2007[21] | USA | R | 3771 (81.1) | 63.7 ± 8.2 | >3.0 vs <1.0 | CV death, MI, stroke | 4.8 | MACEs<br>1.52 (1.15–2.02)<br>CV death<br>1.67 (1.00–2.78) | Age, sex, TC, SBP, DBP, DM, current smoking, BMI, hypertension, MI, eGFR, use of aspirin, beta-blockers, or lipid-lowering drug, treatment arm | 8 |
| Haim 2007[22] | Israel | R | 1486 (NP) | 60 ± 7 | Tertile 3 vs 1; >5.4 vs <2.3 | Fatal or nonfatal MI, sudden cardiac death | 6.2 | Total death<br>2.16 (1.18–3.98)<br>MACEs<br>1.63 (1.09–2.44) | Age, sex, history of MI, smoking, BMI, hypertension, DM, HDL, stroke, angina pectoris, study arm | 7 |
| Papa 2008[23] | Italy | P | 422 (80.1) | 64 ± 11 | >0.8 vs ≤0.8 | Cardiac death, non-fatal MI | 3.0 | MACEs<br>2.51 (1.14–5.52)<br>CV death<br>10.15 (1.26–81.8) | LVEF, white blood cell, glucose, fibrinogen, neutrophil count, Iron, HDL, prior MI, | 7 |
| Inoue 2008[24] | Japan | P | 158 (71.5) | 63 ± 8 | >median ≤ median | HF, nonfatal MI or stroke, refractory angina, arrhythmia revascularization | 7.0 | MACEs<br>1.45 (0.88–2.77) | Multi-vessel disease, DM, hypertension, hyperlipidemia, other cytokines | 7 |
| Shlipak 2008[25] | USA | P | 979 (82) | 66.8 ± 11 | >4.93 ≤ 4.93 | CAD death, nonfatal MI, stroke | 3.7 | MACEs<br>1.82 (1.24–2.67) | Age, sex, race, DM, BMI, current smoking, prior MI, cerebrovascular accident, chronic HF, LVEF, hypertension, creatinine, acetylsalicylic acid use, Nt-proBNP, albuminuria | 8 |
| Momiyama 2009[26] | Japan | R | 373 (79) | 64 ± 9 | >1.0 vs ≤1.0 | Death, MI, UAP, stroke, aortic disease, PAD, HF | 2.9 | MACEs<br>2.0 (1.1–3.4) | Age, sex, hypertension, hyperlipidemia, DM, smoking, BMI, number of >50% stenotic coronary vessels, statin, antiplatelet, ARB/ACEI | 7 |
| Arroyo-Espliguero 2009[27] | Spain | P | 790 (70.5) | 63.1 ± 9.5 | >median ≤ median | Cardiac death, nonfatal MI, UAP admission, revascularization | 1.0 | MACEs<br>1.9 (1.1–3.2) | Multivariate adjusted | 7 |
| Eschen 2010[28] | Denmark | P | 291 (69) | 59.6 ± 8.5 | Quartiles 4 vs 1 | Death, stroke, MI admission | 5.3 | MACEs<br>3.1 (1.5–6.3) | Age, sex, smoking, TC, SBP, prior MI, DM, LVEF | 7 |
| Bode 2012[34] | Austria | R | 394 (73) | 67 ± 9 | Tertile 3 vs 1 | — | 3.2 | Total death<br>3.43 (1.13–10.37) | Age, sex, bypass/PCI, gammaglutamyl transferase, NT-proBNP | 7 |
| Eldrup 2012[35] | Denmark | P | 1090 (72.7) | 49–67 | >3.0 vs ≤3.0 | UAP, MI, death | 10.4 | MACEs<br>1.4 (1.2–1.6) | Age, sex, smoking, hypertension, DM, TC, BMI, LDL, HDL, TG, degree of coronary disease | 8 |

*(Continued)*

**Table 1**

***(Continued)***

| Author/year | Region | Design | Patients (% men) | Age (yr) | CRP cutoff (mg/dL) | Definition of MACEs | Follow-up (yr) | Outcomes HR/RR (95% CI) | Adjustment for covariates | Total NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| Rothenbacher 2012[36] | Germany | P | 1056 (84.9) | 58.9 ± 8.0 | Quartiles 4 vs 1; ≥3.1 vs <0.6 | CV dreath, non-fatal MI, non-fatal ischemic stroke | 8.0 | MACEs<br>1.27 (0.76–2.10) | Smoking, history of MI, DM, severity of CAD, ACEI, allopurinol, HDL, LDL | 7 |
| Tang 2013[37] | USA | P | 3635 (65) | 63 ± 11 | >0.2 vs ≤0.2 | Death, nonfatal MI, or nonfatal stroke | 3.0 | MACEs<br>1.82 (1.46–2.28) | Age, sex, LDL, SBP, cigarette smoking, DM, history of MI, creatinine clearance | 8 |
| Pan 2015[38] | China | R | 181 (77.9) | 67 ± 12 | ≥0.1 vs <0.1 | Death, stroke, new MI, revascularization | 3.5 | MACEs<br>1.47 (1.08–1.99) | Age, sex, hypertension, DM, BMI, TC, adiponectin, Gensini score | 7 |
| Ogita 2015[39] | Japan | P | 1176 (84) | 66.5 ± 9.4 | >0.16 vs <0.05 | Death, nonfatal MI, revascularization | 3.5 | MACEs<br>1.43 (0.92–2.25)<br>2.39 (1.27–4.75) | Age, sex, BMI, waist, hypertension, DM, current smoking, family history of CAD, prior MI, LVEF, triple vessel disease, type C lesion, stent size, stent length, type of drug-eluting stent, use of evidence-based therapies | 8 |
| Luo 2019[40] | China | R | 196 (NP) | 43–98 | Quartiles 4 vs1; >2.85 vs <0.69 | — | 2.1 | Total death<br>10.02 (1.2–83.5) | Age, past smoking | 6 |
| Shitara 2019[41] | Japan | P | 1605 (83.1) | 64.9 ± 10 | Tertile 3 vs 1 | Death, non-fatal ACS | 4.7 | MACEs<br>2.14 (1.43–3.27) | Age, BMI, fasting blood glucose, CKD, statins, multivessel disease, LMT lesion, DES used | 8 |

ACS = acute coronary syndrome, AMI = acute myocardial infarction, BMI = body mass index, BNP = brain natriuretic peptide, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, CRP = c-reactive protein, CV = cardiovascular, DBP = diastolic blood pressure, DES = drug-eluting stent, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, GDF-15 = growth differentiation factor 15, HDL = high-density lipoprotein, HF = heart failure, HR = hazard ratio, LDL = low-density lipoprotein, LMT = left main trunk, Lp-PLA2 = lipoprotein-associated phospholipase A2 activity, LVEF = left ventricular ejection fraction, MACEs = major adverse cardiovascular events, MCSF = macrophage colony stimulating factor, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale, NT-proBNP = N-terminal prohormone B-type natriuretic peptide, PAD = peripheral artery disease, PCI = percutaneous coronary intervention, RR = risk ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, UAP = unstable angina pectoris.

removal of studies one by one did not alter the original statistically significance (data not shown). In addition, the values of CRP level in predicting MACEs were consistently observed in each subgroup (Table 2). However, Egger test ($P$ = .016) and Begg test ($P$ = .006) suggested the presence of publication bias. The trim-and-fill analysis indicated that the pooled risk estimate (RR 1.64; 95% CI 1.23–2.17) remained statistically significant after imputing 7 potentially missing studies (Fig. 3).

### 3.3. All-cause mortality

Five studies[12,20,22,34,40] reported the value of CRP level in predicting all-cause mortality. A fixed-effect model meta-analysis showed that the pooled RR of all-cause mortality was 3.66 (95% CI 2.62–5.12; $I^2$ = 19.7%, $P$ = .289) for the highest *vs* the lowest CRP level (Fig. 4A). Sensitivity analysis showed that the pooled risk estimate remained statistically significant (data not shown). Begg test ($P$ = .806) and Egger test ($P$ = .649) revealed unlikelihood of publication bias.

### 3.4. Cardiovascular mortality

Three studies[19,21,23] reported the value of CRP level in predicting cardiovascular mortality. A fixed-effect model meta-analysis showed that the pooled RR of cardiovascular mortality was 1.62 (95% CI 1.13–2.33; $I^2$ = 39.0%, $P$ = .194) for the highest *vs* the lowest CRP level (Fig. 4B).

## 4. Discussion

This meta-analysis assessed the value of CRP level by categorical analysis in predicting adverse outcomes among patients with stable CAD. The main finding of our meta-analysis suggested that elevated baseline CRP level significantly predicted the MACEs, cardiovascular death, and all-cause mortality in stable CAD patients. Compared with those in the lowest CRP category, stable CAD patients with the highest CRP had a 77%, 62%, and 3.66-fold higher risk of MACEs, cardiovascular death, and all-cause mortality, respectively. Together these findings, CRP level at baseline may provide an important predictive information in stable CAD patients.

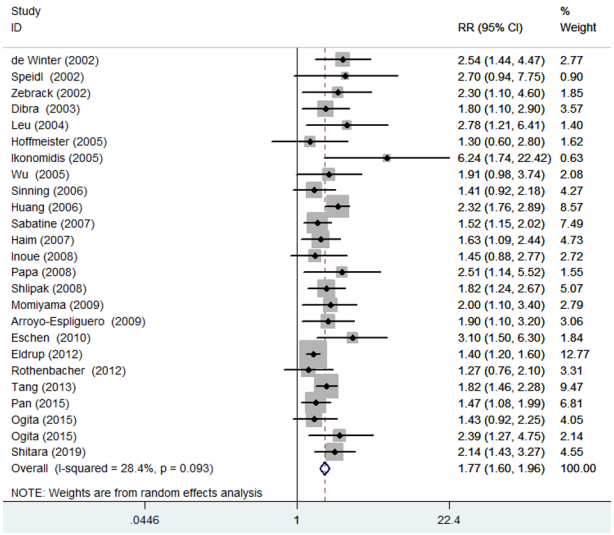


**Figure 2.** The pooled RR and 95% CI of major adverse cardiovascular events for the highest versus the lowest CRP level. 95% CI = confidence intervals, CRP = C-reactive protein, RR = risk ratio.

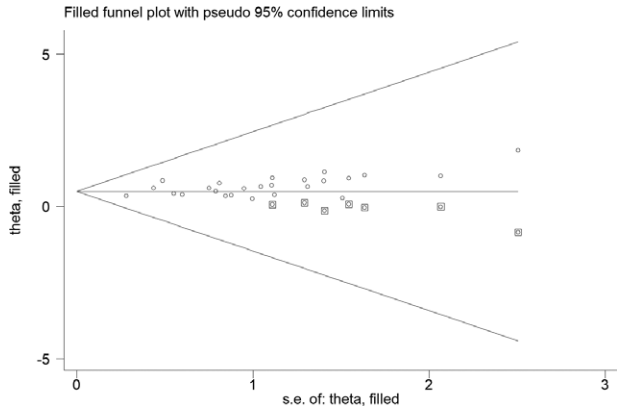


**Figure 3.** Funnel plot showing the value of elevated CRP level in predicting major adverse cardiovascular events. The circles alone are real studies and the circles enclosed in boxes are "filled" studies. CRP = C-reactive protein.

In patients with acute stage of CAD, elevated CRP level was associated with 2.5-fold exaggerated risk of MACEs after at least 3-month of follow-up.[9] Moreover, elevated preprocedural CRP level significantly predicted recurrent myocardial infarction and in-hospital target vessel revascularization in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.[10] By contrast. our meta-analysis focused on the stable CAD patients. However, the magnitude of predictive values was lower in stable patients compared with the acute coronary syndrome patients.

When analyzed the predictive value of CRP level by continuous variable, per standardized deviation in the log-transformed high-sensitivity CRP (hs-CRP) level increase was associated with 17% higher risk of MACEs in patients with stable CAD.[42] Of the 3319 patients with stable CAD, per unit log-transformed hs-CRP was associated with 52% higher risk of MACEs.[43]These findings further supported the predictive value of CRP in stable CAD patients.

The difference between measurement of CRP by conventional and high-sensitivity method is the limit of detection. High-sensitivity method can detect very low amounts of blood CRP level. Accordingly, our subgroup analysis indicated that high-sensitivity CRP level appeared to have a stronger predictive value in predicting MACEs than the conventional method. However, this finding was based on indirect comparison. It is still lack of study directly comparing the predictive value of conventional and high-sensitivity method in stable CAD patients.

Biomarkers of myocardial stretch (B-type natriuretic peptide or N-terminal portion of the prohormone of B-type natriuretic peptide), myocardial injury (cardiac troponin), inflammation (CRP, interleukin-6), or oxidative stress (myeloperoxidase) have been used to predict adverse outcomes in cardiological diseases. The predictive role of biomarkers depends on their different mechanisms. CRP representing low-grade inflammatory status

**Table 2**

**Pooled risk estimate of MACEs by CRP level in subgroup.**

| Subgroup | No. of studies | Pooled RR | 95% CI | Heterogeneity between studies |
|---|---|---|---|---|
| Region | | | | |
| Asia | 9 | 1.87 | 1.62–2.15 | $P = .372$; $I^2 = 7.6\%$ |
| Others | 15 | 1.73 | 1.51–1.98 | $P = .115$; $I^2 = 31.8\%$ |
| Sample size | | | | |
| ≥1000 | 9 | 1.56 | 1.41–1.72 | $P = .414$; $I^2 = 2.7\%$ |
| <1000 | 15 | 2.01 | 1.75–2.30 | $P = .413$; $I^2 = 3.5\%$ |
| Study design | | | | |
| Prospective | 19 | 1.78 | 1.57–2.01 | $P = .148$; $I^2 = 25.2\%$ |
| Retrospective | 5 | 1.76 | 1.43–2.16 | $P = .114$; $I^2 = 46.3\%$ |
| Follow-up time | | | | |
| >5 yr | 6 | 1.65 | 1.26–2.16 | $P = .073$; $I^2 = 50.4\%$ |
| ≤5 yr | 18 | 1.84 | 1.67–2.03 | $P = .622$; $I^2 = 0.0\%$ |
| Type of biomarker | | | | |
| CRP | 12 | 1.67 | 1.43–1.94 | $P = .199$; $I^2 = 24.9\%$ |
| hs-CRP | 12 | 1.86 | 1.64–2.10 | $P = .316$; $I^2 = 12.9\%$ |
| Category of CRP | | | | |
| Single cutoff | 14 | 1.76 | 1.54–2.01 | $P = .175$; $I^2 = 25.9\%$ |
| ≥ category | 10 | 1.78 | 1.51–2.10 | $P = .150$; $I^2 = 31.2\%$ |

CI = confidence interval, CRP = c-reactive protein, hs-CRP = high-sensitivity C-reactive protein, MACEs = major adverse cardiovascular events, RR = risk ratio.

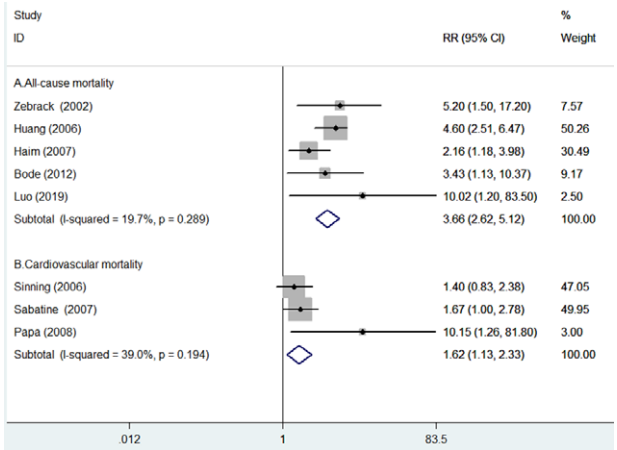


**Figure 4.** The pooled RR and 95% CI of all-cause mortality (A) and cardiovascular mortality (B) for the highest versus the lowest CRP level. CI = confidence intervals, CRP = C-reactive protein, RR = risk ratio.

associated with atherothrombosis could predict adverse outcomes in stable coronary artery disease patients. It should be noted that multiple-biomarker approach may improve risk classification of stable CAD patients.

Several potential mechanisms may contribute to the predictive value of CRP level in stable CAD patients. First, elevated CRP level may reflect the degree of inflammation and oxidative stress associated with atherosclerosis. Second, elevated CRP level may also reflect chronic disease burden in these patients. Our meta-analysis has an important clinical implication. Measurement of CRP level at baseline has potential to identify high-risk group of patients who need an early invasive treatment. Correspondingly, patients with higher CRP level may potentially benefit from anti-inflammatory and antioxidant therapies. However, future well-designed clinical trials are warranted to support these hypotheses.

Several potential limitations should be addressed in our meta-analysis. First, blood CRP level was only measured at baseline rather than dynamic monitor. Single determination of CRP level may have led to misclassification of patients' category. Second, the selected studies reported the different cutoff of CRP elevation, which prevents the clinicians to identify those in need of aggressive management. Third, the definition of MACEs was not consistent with the one used in each study. Particularly, predictive value for the MACEs may be mainly driven by the special outcomes. Fourth, our meta-analysis did not analyze the predictive role of CRP level by continuous data because of different value of CRP reported (unit, standard deviation, or logarithmically transformed CRP). Finally, both of Egger test and Begg test indicated the likelihood of publication bias in pooling MACEs. However, the pooled risk estimate of MACEs was only slightly reduced under the trim-and-fill analysis.

## 5. Conclusions

Elevated CRP level at baseline is significantly associated with higher risk of MACEs, cardiovascular death, and all-cause mortality in patients with stable CAD. Baseline CRP level can provide important predictive information in stable CAD patients. Stable CAD with elevated CRP level may be identified as a high-risk group and receive more intensive management.

## Author contributions

Study conception/design and interpretation of data: HW. Literature search, data extraction, quality assessment, and statistical analysis: SYL and JZ. Drafting the manuscript: BL. All the authors approved the final version of the manuscript.
**Conceptualization:** Hui Wu.
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## References

[1] Fox KAA, Metra M, Morais J, et al. The myth of "stable" coronary artery disease. Nat Rev Cardiol. 2020;17:9–21.
[2] Braun MM, Stevens WA, Barstow CH. Stable coronary artery disease: treatment. Am Fam Physician. 2018;97:376–84.
[3] Ruiz Ortiz M, Ogayar C, Romo E, et al. Long-term survival in elderly patients with stable coronary disease. Eur J Clin Invest. 2013;43:774–82.
[4] Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016;388:2142–52.
[5] Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–74.
[6] Corrado E, Rizzo M, Coppola G, et al. An update on the role of markers of inflammation in atherosclerosis. J Atheroscler Thromb. 2010;17:1–11.
[7] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685–95.
[8] McCarthy CP, McEvoy JW, Januzzi JL Jr. Biomarkers in stable coronary artery disease. Am Heart J. 2018;196:82–96.
[9] Correia LC, Esteves JP. C-Reactive protein and outcomes in acute coronary syndromes: a systematic review and meta-analysis. Arq Bras Cardiol. 2011;97:76–85.
[10] Mincu RI, Janosi RA, Vinereanu D, et al. Preprocedural C-reactive protein predicts outcomes after primary percutaneous coronary intervention in patients with ST-elevation myocardial Infarction a systematic meta-analysis. Sci Rep. 2017;7:41530.
[11] Speidl WS, Graf S, Hornykewycz S, et al. High-sensitivity C-reactive protein in the prediction of coronary events in patients with premature coronary artery disease. Am Heart J. 2002;144:449–55.
[12] Zebrack JS, Anderson JL, Maycock CA, et al. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol. 2002;89:145–9.
[13] de Winter RJ, Heyde GS, Koch KT, et al. The prognostic value of pre-procedural plasma C-reactive protein in patients undergoing elective coronary angioplasty. Eur Heart J. 2002;23:960–6.
[14] Dibra A, Mehilli J, Braun S, et al. Association between C-reactive protein levels and subsequent cardiac events among patients with stable angina treated with coronary artery stenting. Am J Med. 2003;114:715–22.
[15] Leu HB, Lin CP, Lin WT, et al. Risk stratification and prognostic implication of plasma biomarkers in nondiabetic patients with stable coronary artery disease: the role of high-sensitivity C-reactive protein. Chest. 2004;126:1032–9.
[16] Wu TC, Leu HB, Lin WT, et al. Plasma matrix metalloproteinase-3 level is an independent prognostic factor in stable coronary artery disease. Eur J Clin Invest. 2005;35:537–45.
[17] Hoffmeister A, Rothenbacher D, Kunze M, et al. Prognostic value of inflammatory markers alone and in combination with blood lipids in patients with stable coronary artery disease. Eur J Intern Med. 2005;16:47–52.
[18] Ikonomidis I, Lekakis J, Revela I, et al. Increased circulating C-reactive protein and macrophage-colony stimulating factor are complementary predictors of long-term outcome in patients with chronic coronary artery disease. Eur Heart J. 2005;26:1618–24.
[19] Sinning JM, Bickel C, Messow CM, et al. Impact of C-reactive protein and fibrinogen on cardiovascular prognosis in patients with stable angina pectoris: the AtheroGene study. Eur Heart J. 2006;27:2962–8.

[20] Huang W, Chen QW, Lei H, et al. Predictive value of fibrinogen and high-sensitivity C-reaction protein for cardiovascular events in patients with stable coronary artery disease. Zhonghua Xin Xue Guan Bing Za Zhi. 2006;34:718–21.
[21] Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation. 2007;115:1528–36.
[22] Haim M, Benderly M, Tanne D, et al. C-reactive protein, bezafibrate, and recurrent coronary events in patients with chronic coronary heart disease. Am Heart J. 2007;154:1095–101.
[23] Papa A, Emdin M, Passino C, et al. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta. 2008;395:27–31.
[24] Inoue T, Komoda H, Nonaka M, et al. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease. Int J Cardiol. 2008;124:319–25.
[25] Shlipak MG, Ix JH, Bibbins-Domingo K, et al. Biomarkers to predict recurrent cardiovascular disease: the Heart and Soul Study. Am J Med. 2008;121:50–7.
[26] Momiyama Y, Kawaguchi A, Kajiwara I, et al. Prognostic value of plasma high-sensitivity C-reactive protein levels in Japanese patients with stable coronary artery disease: the Japan NCVC-collaborative inflammation cohort (JNIC) Study. Atherosclerosis. 2009;207:272–6.
[27] Arroyo-Espliguero R, Avanzas P, Quiles J, et al. Predictive value of coronary artery stenoses and C-reactive protein levels in patients with stable coronary artery disease. Atherosclerosis. 2009;204:239–43.
[28] Eschen O, Christensen JH, Johnsen SP, et al. Adhesion molecules and C-reactive protein are associated to adverse events in angina pectoris. Scand Cardiovasc J. 2010;44:153–60.
[29] Hemingway H, Philipson P, Chen R, et al. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. PLoS Med. 2010;7:e1000286.
[30] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283:2008–12.
[31] Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Access date May 8,2022].
[32] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–101.
[33] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
[34] Bode E, Wuppinger T, Bode T, et al. Risk stratification in stable coronary artery disease: superiority of N-terminal pro B-type natriuretic peptide over high-sensitivity C-reactive protein, gamma-glutamyl transferase, and traditional risk factors. Coron Artery Dis. 2012;23:91–7.
[35] Eldrup N, Kragelund C, Steffensen R, et al. Prognosis by C-reactive protein and matrix metalloproteinase-9 levels in stable coronary heart disease during 15 years of follow-up. Nutr Metab Cardiovasc Dis. 2012;22:677–83.
[36] Rothenbacher D, Kleiner A, Koenig W, et al. Relationship between inflammatory cytokines and uric acid levels with adverse cardiovascular outcomes in patients with stable coronary heart disease. PLoS One. 2012;7:e45907.
[37] Tang WH, Iqbal N, Wu Y, et al. Usefulness of cardiac biomarker score for risk stratification in stable patients undergoing elective cardiac evaluation across glycemic status. Am J Cardiol. 2013;111:465–70.
[38] Pan HC, Sheu WH, Lee WJ, et al. Coronary severity score and C-reactive protein predict major adverse cardiovascular events in patients with stable coronary artery disease (from the Taichung CAD study). Clin Chim Acta. 2015;445:93–100.
[39] Ogita M, Miyauchi K, Kasai T, et al. Impact of preprocedural high-sensitive C-reactive protein levels on long-term clinical outcomes of patients with stable coronary artery disease and chronic kidney disease who were treated with drug-eluting stents. J Cardiol. 2015;66:15–21.
[40] Luo F, Feng C, Zhuo C. C-reactive protein and all-cause mortality in patients with stable coronary artery disease: a secondary analysis based on a Retrospective Cohort Study. Med Sci Monit. 2019;25:9820–8.
[41] Shitara J, Ogita M, Wada H, et al. Clinical impact of high-sensitivity C-reactive protein during follow-up on long-term adverse clinical outcomes in patients with coronary artery disease treated with percutaneous coronary intervention. J Cardiol. 2019;73:45–50.
[42] Dai W, Zhang Z, Zhao S. Baseline levels of serum high sensitivity C reactive protein and lipids in predicting the residual risk of cardiovascular events in Chinese population with stable coronary artery disease: a prospective cohort study. Lipids Health Dis. 2018;17:273.
[43] Aguilar D, Fisher MR, O'Connor CM, et al. Metabolic syndrome, C-reactive protein, and prognosis in patients with established coronary artery disease. Am Heart J. 2006;152:298–304.