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.[11-20]

An early well-designed meta-analysis has examined the effect of CRP level in predicting fatal and nonfatal events in stable CAD patients.
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 MACs, 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 criteria, the overall scores of these eligible studies were 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.

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 ($I^2 \geq 50\%$ indicating statistically significant) and $I^2$ statistic ($P \geq 50\%$ 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 fulfill 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...
| 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 2.70 (0.94–7.75) | Age, 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          | MACEs 5.2 (1.5–17.2) | Age, sex, smoking, hypertension, hyperlipidemia, DM, tobacco, family history of CAD, treatment.  | 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 2.54 (1.44–4.47) | Age, DM, active smoking, TC, LVEF, use of evidence-based therapies | 7        |
| Dibra 2003[14] | Germany    | P      | 1152 (73.4)      | 66.1 ± 10.5 | >5.0 vs ≤5.0 | Death, MI          | 1.0          | MACEs 1.8 (1.1–2.9) | Age, sex, smoking, hypertension, previous revascularization, biochemical markers, severity of CAD | 7        |
| 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 2.78 (1.21–6.41) | Age, sex, smoking, hypertension, DM, smoking, TC, LVEF, number of diseased vessels, LVEF, number of affected vessels, intervention | 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 1.91 (0.98–3.74) | Age, sex, BMI, HDL, smoking, alcohol, years of school, DM, hypertension, use of acetylsalicylic acid, statins or diuretics, prior MI, affected vessels, intervention | 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 1.3 (0.6–2.8) | Age, sex, smoking, hypertension, hyperlipidemia, parental CAD, previous MI, multivessel disease, non-use of evidence-based therapies, MCSF | 8        |
| Ikonomidis 2005[18] | Greece     | P      | 100 (84)         | 54 ± 5    | ≥2.5 vs <2.5 | Cardiac death, AMI, UAP admission | 6.0          | MACEs 6.24 (1.74–22.42) | Age, sex, BMI, hypertension, DM, smoking, HDL, number of treated vessels, statin, beta-blocker therapies | 7        |
| Sinning 2006[19] | Germany    | P      | 1806 (78.7)      | 61.7 ± 9.4 | Quartiles 4 vs 1; >8.4 vs <1.46 | CV death, non-fatal MI | 3.5          | MACEs 1.41 (0.92–2.18) | CV death | 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 4.6 (2.51–6.47) | Lipids, hypertension, smoking, BMI | 7        |

(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 | 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 | 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 | 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 | Multi-vessel disease, DM, hypertension, hyperlipidemia, other cytokines | 7 |
| Shipak 2008[25] | USA P | 979 (82) | 66.8 ± 11 | >4.93 ≤ 4.93 | CAD death, nonfatal MI, stroke | 3.7 | MACEs | 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 | Age, sex, hypertension, hyperlipidemia, DM, smoking, BMI, number of >50% stenotic coronary vessels, statin, antiplatelet, ARB/ACEI | 7 |
| Arroyo-Espiguero 2009[27] | Spain P | 790 (70.5) | 63.1 ± 9.5 | >median ≤ median | Cardiac death, nonfatal MI, UAP admission, revascularization | 1.0 | MACEs | 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 | Age, sex, smoking, TC, SBP, prior MI, DM, LVEF | 7 |
| Bode 2010[29] | Austria R | 394 (73) | 67 ± 9 | Tertile 3 vs 1 | — | 3.2 | MACEs | Age, sex, bypass/PCI, gamma-glutamyl transferase, NT-proBNP | 7 |
| Eldrup 2012[30] | Denmark P | 1090 (72.7) | 49–67 | >3.0 vs ≤3.0 | UAP, MI, death | 10.4 | MACEs | Age, sex, smoking, hypertension, DM, TC, BMI, LDL, HDL, TG, degree of coronary disease | 8 |
| (Continued) |
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; $P = .39$, $P = .194$) 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.
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. 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. 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.

Of the 3319 patients with stable CAD, per unit log-transformed hs-CRP was associated with 52% higher risk of MACEs. 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

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**Table 2**

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

CI = confidence interval, CRP = c-reactive protein, hs-CRP = high-sensitivity C-reactive protein, MACEs = major adverse cardiovascular events, 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 different value of CRP reported (unit, standard deviation, or log-
arithmically 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.

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