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Association of growth differentiation factor-15 level with adverse outcomes in patients with stable coronary artery disease: A meta-analysis

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ABSTRACT

Background and aims: Studies on the association between growth-differentiation factor-15 (GDF-15) level and adverse outcomes have yielded conflicting results in patients with stable coronary artery disease (CAD). This meta-analysis aimed to evaluate the association of baseline GDF-15 level with adverse outcomes in stable CAD patients.

Methods: Two authors independently searched PubMed and Embase databases from inception to May 31, 2021 for available studies that investigated the association of baseline GDF-15 level with all-cause mortality, cardiovascular mortality, or major adverse cardiovascular events (MACEs) in stable CAD patients. Pooled multivariable adjusted hazard ratio (HR) with 95% confidence interval (CI) was calculated for the highest vs. the lowest GDF-15 level.

Results: Seven studies that involved 28,765 stable CAD patients were identified and analyzed. The meta-analysis showed that the highest GDF-15 level was associated with higher risk of MACEs (HR 1.42; 95% CI 1.29−1.57; $p < 0.001$), cardiovascular mortality (HR 1.64: 95% CI 1.25−2.14; $p < 0.001$), and all-cause mortality (HR 2.01; 95% CI 1.67−2.42; $p < 0.001$) when compared the lowest GDF-15 level. Moreover, the values of GDF-15 level in predicting MACEs were consistently observed in each named subgroup.

Conclusions: Elevated blood GDF-15 level is an independent predictor of MACEs, cardiovascular mortality, and all-cause mortality in stable CAD patients. The baseline GDF-15 level may play an important role in the risk stratification of stable CAD patients.

1. Introduction

Coronary artery disease (CAD) is generally classified into acute coronary syndrome (ACS) and stable CAD. Stable CAD usually refers to a history of ACS or presence of plaque documented by catheterization or angiography [1]. Patients are considered stable if they have controlled angina or are asymptomatic. Despite advance in medical care, stable CAD remains a global public health burden [2]. Patients with stable CAD are threatened by recurrent cardiovascular events and premature mortality [3,4]. Therefore, early risk stratification for adverse outcomes is still crucial in stable CAD patients.

Biomarkers of inflammation, oxidative stress, and myocardial injury are important tools for risk stratification of stable CAD [5]. Growth-differentiation factor-15 (GDF-15) belongs to the transforming growth factor-β cytokine family [6]. Blood GDF-15 level has been identified as a novel systemic biomarker of oxidative stress, inflammation, and cellular aging [7]. Induction of GDF-15 expression in the heart may protect from ischemia/reperfusion injury [8]. Accumulating evidence suggests that elevated GDF-15 level is an independent predictor of all-cause mortality and recurrent myocardial infarction in patients with ACS [9,10]. However, studies regarding the association of elevated GDF-15 level with cardiovascular events, cardiovascular death, and all-cause mortality have yielded conflicting results in stable CAD patients [11–14].

To the best of our knowledge, no previous meta-analysis has evaluated the predictive value of GDF-15 level in patients with stable CAD. The value of blood GDF-15 level in predicting adverse

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outcomes has not been well-established in stable CAD patients. To address these knowledge gaps, we performed a meta-analysis to investigate the association of elevated GDF-15 level at baseline with adverse outcomes in patients with stable CAD.

2. Methods

This meta-analysis was conducted and reported according to the guidelines of the Meta-analysis Of Observational Studies in Epidemiology statement [15]. We did not register this topic in the PROSPERO international database but prospectively designed a protocol. Two independent authors searched PubMed and Embase databases from inception to May 31, 2021 using the following keywords in combination: “coronary disease” OR “stabilized myocardial infarction” OR “stabilized acute coronary syndrome” AND “growth-differentiation factor-15”. The reference lists of pertinent reviews and eligible studies were manually scanned to identify additional studies.

The inclusion criteria were as follows: 1) full-text articles (cohort studies or post hoc analysis of randomized controlled trials) published in peer-reviewed journals; 2) enrolling patients with stable CAD; 3) investigating the association between blood GDF-15 level at baseline and adverse outcomes; 4) all-cause mortality, cardiovascular death, or major adverse cardiovascular events ([MACEs] defined as a composite of death, stroke, non-fatal myocardial infarction, revascularization, or heart failure re-hospitalization) as outcome measures; and 5) reporting at least age-adjusted risk ratio (RR) or hazard ratio (HR) with 95% confidence interval (CI) of the outcomes of interest for the highest *vs.* the lowest category of GDF-15 level. All-cause mortality or cardiovascular death was determined by the death certificates and International Classification of Diseases code. For multiple articles from the same population that reported different outcomes, we deemed them as separate study. When multiple articles from the same population reported the same outcomes, we only selected the article with the most complete data or the longest follow-up duration. Exclusion criteria included:1)

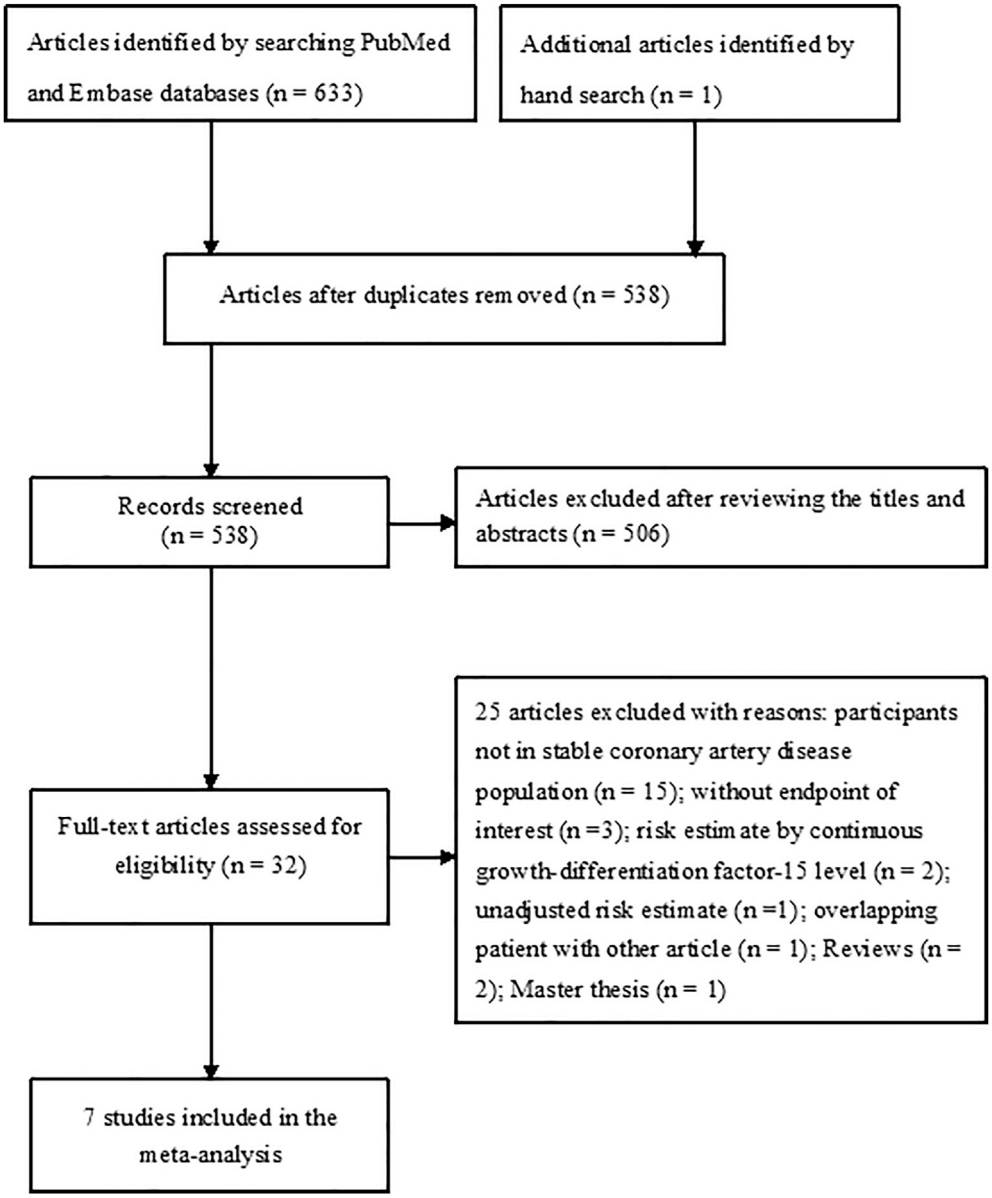

Fig. 1. Flow chart showing the study selection process.

Table 1
Baseline characteristics of the included studies.

Author/ year	Region	Design	Sample sizes (% male)	Age (years)	GDF-15 cutoff (ng/ L)	Definition of MACEs	Follow-up (years)	Outcome measures HR (95% CI)	Adjustment for variables	Total NOS
Bonaca 2011 [10]	Multination	Post hoc analysis	3501(78.9)	58.1 ± 11.1	Tertile 3 vs. 1; >1800 vs. <1200	Death, MI, chronic HF	2.0	Total death 1.91 (0.84 −4.32) MACEs 1.79 (1.28 −2.50)	Age, sex, BMI, DM, hypertension, current smoking, prior MI, qualifying event, creatinine clearance, BNP, hsCRP	7
Schopfer 2014 [11]	USA	Prospective	984 (81.5)	66.7 ± 11.0	Tertile 3 vs. 1; >2660 vs. <1770	MI, stroke, CV death	8.9	CV death 1.49 (0.77 −2.87) Total death 2.73 (1.80 −4.15) MACEs 1.59 (0.99 −2.55)	Age, sex, race, smoking, hypertension, DM, eGFR, stroke, LDL, cardiac disease severity, NT-proBNP, C-reactive protein	8
Dallmeier 2016 [12]	Germany	Prospective	1073 (84.7)	59 ± 8	Tertile 3 vs. 1; >1800 vs. <1200	Nonfatal MI/ stroke	10	Total death 1.73 (1.02 −2.94) MACEs 1.54 (0.97 −2.44)	Age, sex, BMI, smoking, DM, hypertension, TC, HDL, use of statins, cystatin C, NT-proBNP, hs-CRP, hs-cTnT	8
Hagström 2017 [18]	Multination	Post hoc analysis	14,577 (81.5)	53−75	Quartile 4 vs.1; ≥1827 vs. <915	CV death, nonfatal MI/stroke	3.7	CV death 1.53 (1.09 −2.16) Total death 1.85 (1.41 −2.44) MACEs 1.35 (1.09 −1.67)	Age, sex, previous MI, geographic region, BMI, SBP, PCI, CABG, multivessel disease, smoking, hemoglobin, white blood cell, eGFR, LDL, HDL, TG, hs-cTnT, NT-proBNP, hs-CRP	8
Qamar 2019 [19]	Multination	Post hoc analysis	7195 (75.3)	63.8 (57.4 −71.3)	Quartile 4 vs.1; ≥1827 vs. <875.8	CV death, MI, stroke	6.0	MACEs 1.65 (1.34 −2.02)	Age, DM, hypertension, PAD, prior stroke, prior CABG, history of HF, active smoking, eGFR	7
Wang 2020 [20]	China	Prospective	541 (67.5)	59.5 ± 9.9	Quartile 4 vs.1	Death, non-fatal MI, revascularization, angina pectoris.	5.3	MACEs 1.24 (1.05 −1.48)	Age, sex, BMI, SBP, DM, smoking, TC, C-reactive protein, use of statin and aspirin	7
Mayer Jr 2021 [13]	Czech Republic	Prospective	894 (79)	64.3 ± 9.0	Quartile 4 vs. 1−3; ≥1339 vs. <1339	MI, stroke, revascularization	7.6	CV death 2.09 (1.20 −3.63) Total death 2.00 (1.26 −3.19) MACEs 1.30 (0.88 −1.92)	Age, sex, survey, revascularization, current smoking, BMI, blood pressure, LDL, glycemic control, eGFR, BNP, beta-blockers, statins, renin-angiotensin-aldosterone system blockers, antidiabetics or warfarin	8

Abbreviations: GDF-15, growth differentiation factor 15; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; MI, myocardial infarction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; CV, cardiovascular; PAD, peripheral artery disease; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI, angiotensin converting enzyme inhibitors; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; NOS, Newcastle-Ottawa Scale.

patients with ACS; 2) reporting risk summary by per unit or standard deviation changes of GDF-15 level; and 3) meeting abstract, review, or dissertation.

Two authors independently extracted the following information from the included studies: surname of the first author, year of publication, country, study design, sample sizes, gender distribution, baseline age of patients, threshold of GDF-15 level elevation, definition of MACEs, follow-up duration, study endpoints, most fully adjusted HR with 95% CI (top *vs*. bottom tertile/quartile group of GDF-15 level), and adjusted variables in the statistical analysis. Two authors independently evaluated the methodological quality of the included studies using a nine-point Newcastle−Ottawa Scale (NOS) [16], which assessed the selection of the study, comparability of the groups, and ascertainment of outcomes. Studies with scores of 7−9 points are considered as of high quality. Discrepancy in the process of data extraction and quality evaluation was settled through consensus.

All data were analyzed by STATA 12.0 (Stata Corporation, College Station, TX, USA). The HR was used as the common measure for comparison of patients with the highest and lowest GDF-15 level

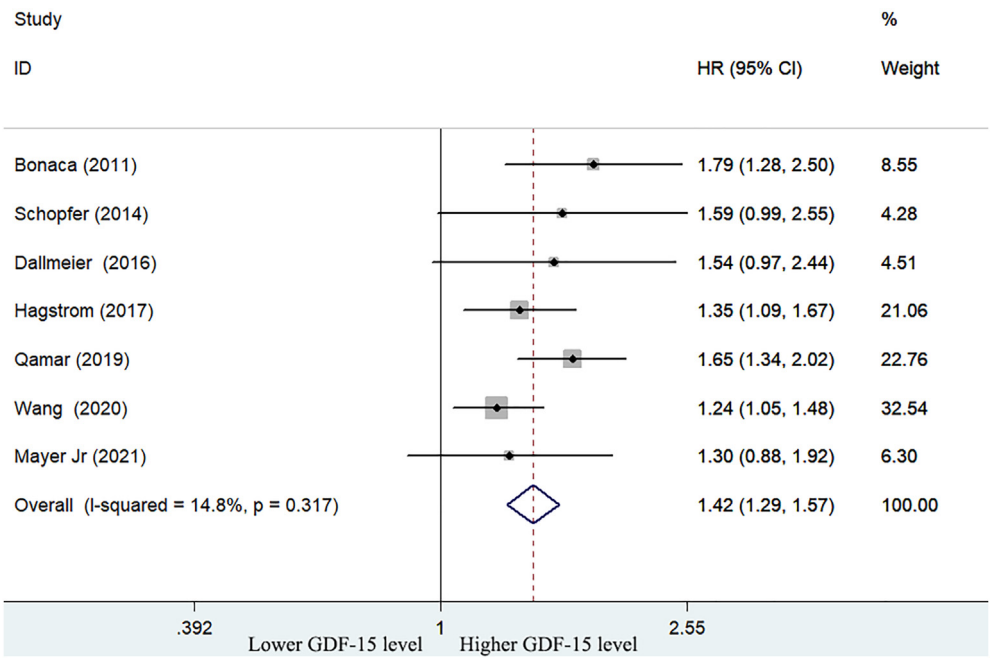

Fig. 2. Forest plots showing the pooled HR and 95% CI of major adverse cardiovascular events for the highest *vs* the lowest growth differentiation factor 15 level in a fixed-effect model. The sizes of the squares are proportional to the weights of the individual studies. The diamond symbol represents the pooled risk estimates. Horizontal lines show the ranges of 95% CI.

Table 2
Pooled risk estimate of MACEs by GDF-15 level in each subgroup.

Subgroup	No. of studies	Pooled HR	95%CI	Heterogeneity between studies
Publication year				
Before 2018	4	1.49	1.27–1.74	$p = 0.559$; $I^2 = 0.0\%$
After 2018	3	1.38	1.22–1.57	$p = 0.106$; $I^2 = 55.5\%$
Sample size				
≥1000	4	1.54	1.35–1.76	$p = 0.455$; $I^2 = 0.0\%$
<1000	3	1.28	1.10–1.49	$p = 0.623$; $I^2 = 0.0\%$
Study design				
Prospective	4	1.30	1.13–1.50	$p = 0.681$; $I^2 = 0.0\%$
Post hoc analysis	3	1.54	1.35–1.77	$p = 0.263$; $I^2 = 25.2\%$
Follow-up time				
>5 years	5	1.41	1.25–1.58	$p = 0.292$; $I^2 = 19.3\%$
≤5 years	2	1.46	1.22–1.75	$p = 0.164$; $I^2 = 48.5\%$

Abbreviations: GDF-15, growth differentiation factor 15; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events.

across the studies. –15 level. When the incidence of an outcome is low (<10%), the reported RR or odds ratio is directly treated as HR to facilitate the meta-analysis. The degree of heterogeneity was explored using Cochrane Q test ($p < 0.10$ suggesting statistically significant) and I^2 statistic ($I^2 \geq 50\%$ suggesting statistically significant). A random effect model was selected if the heterogeneity was statistically significant. Otherwise, we used a fixed-effect model. Subgroup analysis was conducted to investigate the impact of publication year, study design (prospective or post hoc analysis), sample sizes, and follow-up duration on the pooling risk summary. Sensitivity analysis was conducted by sequentially removal of single study each time to recalculate the risk summary. Begg's test [17], Egger's test [18], and funnel plot were applied to evaluate the likelihood of publication bias. Moreover, cumulative analyses were performed to investigate how the subsequent literature data influence the overall effect.

3. Results

Our initial literature search yielded 634 relevant records. After exclusion of duplicates and scanning the titles and abstracts, 32 articles were retrieved for full-text assessment. Twenty-four articles were further excluded because these studies did not meet the inclusion criteria. Thus, 7 studies [11–14,19–21] were finally included in this meta-analysis (Fig. 1).

Table 1 summarizes the main features of the included studies. These eligible studies were published between 2011 and 2021. Three studies [11,19,20] were post hoc analysis of clinical trials and others were prospective cohort studies. A total of 28,765 patients with stable CAD were identified. The sample size of each study ranged from 541 to 14,577 patients. The median/mean length of follow-up ranged from 2.0 to 10 years. On the basis of NOS, these eligible studies were awarded seven points or greater, indicating high methodological quality.

All the included studies reported the value of GDF-15 level in predicting MACEs. As shown in Fig. 2, no significant heterogeneity was observed between studies ($I^2 = 14.8\%$, $p = 0.317$). The pooled HR of MACEs was 1.42 (95% CI 1.29–1.57; $p < 0.001$) for the highest *vs.* the lowest GDF-15 level in a fixed-effect model. Leave–one–out sensitivity analysis indicated that the pooled risk estimates were still statistically significant (pooled HR ranged from 1.36 to 1.52 and low 95% CI ranged from 1.22 to 1.35). Cumulative meta-analyses

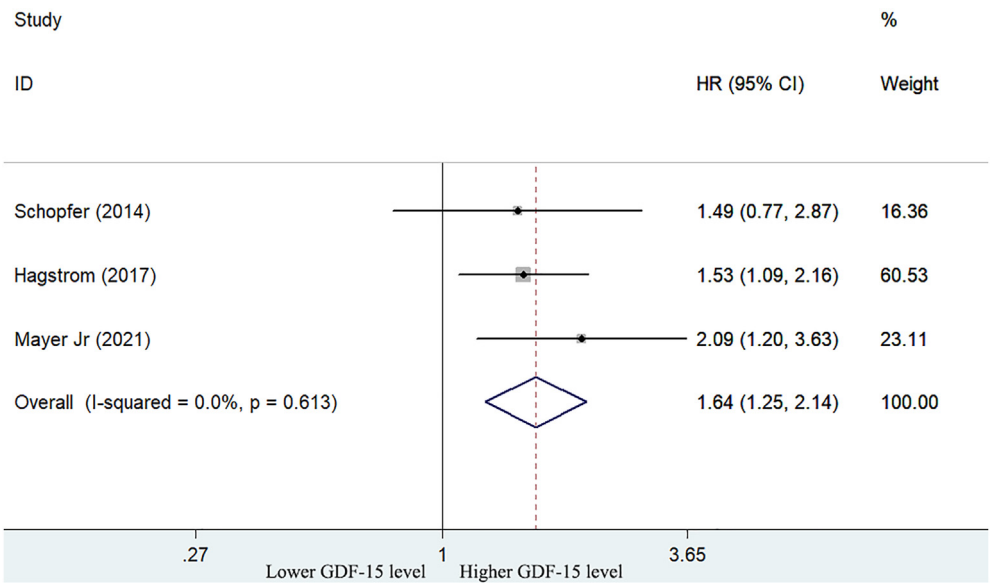

Fig. 3. Forest plots showing the pooled HR and 95% CI of cardiovascular mortality for the highest *vs* the lowest growth differentiation factor 15 level in a fixed-effect model. The sizes of the squares are proportional to the weights of the individual studies. The diamond symbol represents the pooled risk estimates. Horizontal lines show the ranges of 95% CI.

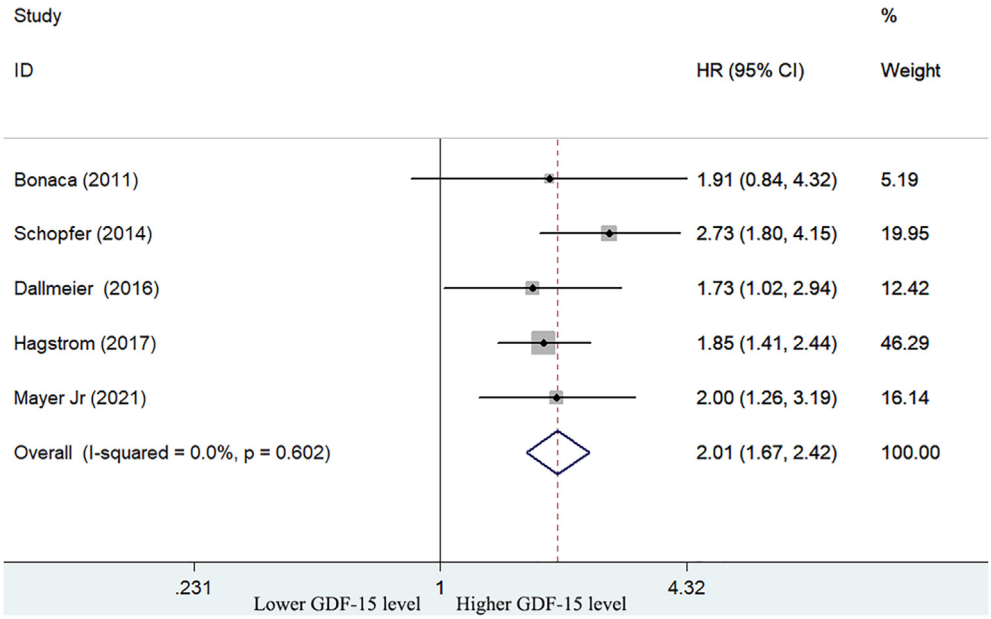

Fig. 4. Forest plots showing the pooled HR and 95% CI of all-cause mortality for the highest *vs* the lowest growth differentiation factor 15 level in a fixed-effect model. The sizes of the squares are proportional to the weights of the individual studies. The diamond symbol represents the pooled risk estimates. Horizontal lines show the ranges of 95% CI.

(Supplemental Fig. S1) suggested a consistent trend towards association after the initial discovery. Moreover, the values of GDF-15 level in prediction of MACEs were consistently found in each subgroup (Table 2). Begg's test ($p = 0.764$) Egger's test ($p = 0.488$), and funnel plot (Supplemental Fig. S2) revealed no evidence of publication bias.

Three studies [12,14,19] reported the value of GDF-15 level in predicting cardiovascular mortality. As shown in Fig. 3, no significant heterogeneity was found between studies ($I^2 = 0.0\%$, $p = 0.613$). The pooled HR of cardiovascular mortality was 1.64 (95% CI 1.25–2.14; $p < 0.001$) for the highest *vs.* the lowest GDF-15 level in a fixed-effect model.

Five studies [11–14,19] reported the value of GDF-15 level in predicting all-cause mortality. As shown in Fig. 4, no significant heterogeneity was observed across studies ($I^2 = 0.0\%$, $p = 0.602$). The pooled HR of all-cause mortality was 2.01 (95% CI 1.67–2.42; $p < 0.001$) for the highest *vs* the lowest GDF-15 level. Leave–one–out sensitivity analysis demonstrated that the pooled risk estimates were still statistically significant (pooled HR ranged from 1.86 to 2.16 and low 95% CI ranged from 1.51 to 1.68). Cumulative meta-analyses (Supplemental Fig. S3) showed a consistent trend towards association after the initial discovery. Begg's test ($p = 1.000$), Egger's test ($p = 0.864$), and funnel plot (Supplemental Fig. S4) revealed no evidence of likelihood of publication bias.

4. Discussion

The main findings of the current meta-analysis indicated that elevated blood GDF-15 level at baseline was significantly associated with an exaggerated risk of MACEs, cardiovascular mortality, and all-cause mortality in stable CAD patients. Compared with those in the lowest GDF-15 group, stable CAD patients with the highest GDF-15 level had a 42%, 64%, and 2.01-fold higher risk of MACEs, cardiovascular mortality, and all-cause mortality, respectively. These results revealed that baseline GDF-15 level may serve as a promising prognostic biomarker in stable CAD patients.

Previous meta-analysis [9] have confirmed that elevated GDF-15 level is associated with 6.75-fold and 2.08-fold higher risk of all-cause mortality and recurrent myocardial infarction in patients with ACS, respectively. By contrast, our meta-analysis focused on patients with stable CAD or stabilized after ACS. Apart from all-cause mortality, elevated GDF-15 level at baseline also significantly predicted cardiovascular mortality and MACEs in stable CAD patients. However, the value of blood GDF-15 level in predicting all-cause mortality was lower in stable CAD patients than ACS patients. Of note, patients with ACS, especially ST-elevation myocardial infarction exhibited the highest GDF-15 level than those with stable CAD [22].

Alternatively, the predictive value of elevated GDF-15 level was also supported by the dose-response analysis. The AtheroGene cohort study concluded that per unit increase in GDF-15 level was associated with a 59% higher risk of MACEs after adjusting conventional cardiovascular risk factors [23]. Each doubling increase in GDF-15 level independently predicted 44%, 61%, and 91% higher risk of MACEs, cardiovascular mortality, and all-cause mortality in stable CAD patients, respectively [12]. In addition, per standard deviation increase in GDF-15 level was associated with a 2.4-fold higher risk of CAD death in patients with stable angina [24]. Taken together, GDF-15 level may provide important predictive information in patients with stable CAD.

Several potential mechanisms may contribute to the predictive value of GDF-15 level in patients with stable CAD. First, elevated GDF-15 level may reflect the degree of inflammation and oxidative stress. Second, GDF-15 was expressed in human atherosclerotic plaque tissue [25], suggesting participation in the initiation and progression of atherosclerosis. In addition, elevated GDF-15 level may also reflect chronic disease burden in these patients [11].

This meta-analysis has important implications for clinical practice. The determination of blood GDF-15 level has potential to identify high-risk CAD patients. Correspondingly, stable CAD patients with elevated GDF-15 level may potentially benefit from anti-inflammatory and antioxidant therapies [26]. Nevertheless, further well-designed clinical trials are necessary to support these hypotheses.

Our meta-analysis has several potential limitations. Firstly, blood GDF-15 level was only determined at baseline rather than dynamic monitor. Single measurement of GDF-15 level may result in misclassification of patients' category. Secondly, the included studies reported different cutoff values of GDF-15 elevation, which prevented the clinicians to identify those in need of aggressive treatment. Thirdly, we did not analyze the predictive value of GDF-15 level by continuous data due to insufficient of such studies. Fourthly, results of publication tests are potentially unreliable because of less than the recommended arbitrary minimum number of 10 studies [27]. Finally, our meta-analysis only focused on stable CAD patients. Therefore, the generalizability of the current findings to acute stage CAD patients and other populations should be with caution.

5. Conclusions

Elevated blood GDF-15 level is an independent predictor of MACEs, cardiovascular mortality, and all-cause mortality in patients with stable CAD. The baseline GDF-15 level may play an important role in the risk stratification of stable CAD patients.

Funding

None.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athplu.2021.11.003.

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