Growth differentiation factor-15 and the risk of cardiovascular diseases and all-cause mortality: A meta-analysis of prospective studies

Shanhui Xie | Liping Lu | Liwei Liu

Background and Aim: Previous studies have documented that the association between growth differentiation factor-15 (GDF-15) and the risk of patients with cardiovascular diseases (CVDs). In this meta-analysis, our main objective is to explore the associations between GDF-15 and the risk of CVD or all-cause mortality.

Methods: PubMed and ISI Web of Science (up to January 2018) electronic databases were browsed for eligible studies. The studies provided relevant data depicted as hazard ratio (HR) with 95% confidence interval (CI), with regard to the association between GDF-15 levels and subsequent risk of CVDs or all-cause mortality. A random-effect model was applied to pool the HR and 95% CI.

Results: Thirty-one prospective studies met the eligibility criteria involving 53,706 subjects with 7,020 adverse outcome events. It was concluded that GDF-15 levels were associated with an incremental risk of CVDs or all-cause mortality. Highest GDF-15 category was associated with greater risk of cardiovascular mortality (HR, 2.66; 95% CI, 1.69-3.63), all-cause mortality (HR, 2.52; 95% CI, 2.06-2.97), and complex adverse outcome (HR, 1.81; 95% CI, 1.42-2.21). As each log-unit increment in GDF-15 concentration, the corresponding risk of adverse events also escalated, cardiovascular mortality (HR, 2.11; 95% CI, 1.57-2.66), all-cause mortality (HR, 2.70; 95% CI, 2.29-3.12), and complex adverse outcome (HR, 1.96; 95% CI, 1.64-2.29).

Conclusions: Judging from the results of the data analysis, GDF-15 levels may increase the risk of CVDs or all-cause mortality.

KEYWORDS
all-cause mortality, cardiovascular diseases, growth differentiation factor-15, meta-analysis

INTRODUCTION

Growth differentiation factor-15 (GDF-15), first named as macrophage inhibitory cytokine-1 (MIC-1), was a stress-response member of transforming growth factor-β cytokine superfamily. It was found that GDF-15 messenger RNA (mRNA) expressing increased during macrophage activation. Normally GDF-15 is weakly expressed in most tissues under physiological conditions but its expression level may sharply upregulate in response to ischemia-reperfusion injury, reactive oxygen species, and mechanical stretch, possibly mediated through pro-inflammatory cytokine and oxidative stress dependent signaling pathways. Moreover, it had suggested that elevated GDF-15 was a cardioprotective cytokine when exposed to cardiovascular injury in an animal model. In humans, increased GDF-15 had been observed in atherosclerotic plaque macrophages.

To date, cardiovascular diseases (CVDs), a leading cause of mortality worldwide, have brought heavy burden to social healthcare and individuals. Thus, intensive investigation has been focused on controlling the risk factors aimed at lowering CVD risks. Plenty of clinical research has been conducted to explore the relationship between...
GDF-15 levels and CVDs. These experiments conclusively demonstrate that GDF-15 levels link to the adverse cardiovascular events across a spectrum of CVD conditions including heart failure (HF), chest pain, acute coronary syndromes (ACS), stable ischemic heart disease, stroke, and atrial fibrillation.5–8 The potential ability of GDF-15 may attribute to the earlier diagnosis, risk stratification and prognosis assessment. However, no systematic review and meta-analysis have analyzed the available data pertaining to the association between GDF-15 levels and CVDs or all-cause mortality. Hence, we perform a meta-analysis for the purpose of qualitatively and quantitatively assessing the relationship between GDF-15 levels and CVDs or all-cause mortality.

2 | MATERIALS AND METHODS

2.1 | Literature Search

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline, we searched PubMed and ISI Web of Science databases from January 1, 1950 to December 31, 2017 for the terms “growth differentiation factor-15” or “macrophage inhibitory cytokine 1” or “placental transforming growth factor beta” or “non-steroidal anti-inflammatory drug-activated gene-1” or “prostate-derived factor” and “cardiovascular disease” or "coronary heart disease" or "ischemic heart disease" or "myocardial infarction" or "heart failure" or "stroke" or "all-cause mortality" or "acute coronary syndrome" or "troponin." The retrieval process was independently completed by two authors (S. Xie and L. Liu). In addition, we also retrieved the reference list of the selected studies and recent reviews for obtaining further information. The literature search was restricted to human studies and published in English language.

2.2 | Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (a) prospective cohort study, (b) follow-up duration of at least 3 months, (c) reported at least one of the interesting outcomes: major cardiovascular endpoints (cardiovascular death, myocardial infarction, stroke, and HF) or all-cause mortality, (d) provided relative risk (RR) or hazard ratio (HR) with 95% confidence interval (CI) for GDF-15 levels comparing the highest levels to the lowest or definite increases for risk factor as a continuous variable (data after logarithmic transformation). Studies were excluded if the study design was review articles, case-controlled studies, retrospective cohort studies, commentaries, editorials, or case report; studies concerning ecological, animal, or cell culture, genetic variation in GDF-15 relevant genes were not selected; we also excluded the study population based on non-adult.

2.2.1 | Data extraction

Two investigators (S. Xie and L. Liu) performed the relevant data extraction with discrepancies reconciled through deliberation with a third investigator (L. Lu). The information was extracted as follows: authors, publication year, sample size, characteristics of the baseline population, mean age of the participants, study location, mean levels of GDF-15, detective method, follow-up, study endpoints, total number of related events, RR or HR with 95% CI, covariates adjusted for in multivariable analyses. The data from different sub-cohort of the same study was extracted separately.

2.3 | Assessment of study quality

According to the Newcastle-Ottawa quality assessment scale (for cohort study), the assessment of including study quality was performed following three aspects: participants selection, comparability of groups, and ascertainment of outcome. A study can be awarded a maximum of one score for each numbered item within the selection. A maximum of two scores can be given for comparability and selection. Higher scores of studies represented better quality.

2.4 | Statistical analyses

Various studies reported the results in different patterns and presented the effect sizes for comparison between groups or for a given unit of increase in GDF-15 levels. To display the results more concise and understandable, we assessed the association between GDF-15 categorical level and the risk of CVD mortality or all-cause mortality or complex adverse outcome (composite of death or cardiovascular events), by comparing the highest category of GDF-15 with the lowest. We also analyzed GDF-15 level as a continuous variable to evaluate the risk of CVD mortality or all-cause mortality or complex adverse outcome based on per log-unit increase of GDF-15. Pooled HR with 95% CI was presented as an effect size for estimating the association between GDF-15 levels and the risk of CVD mortality or all-cause mortality or complex adverse outcome in the process of handling the data, the SD of log-GDF-15 was estimated from the Framingham Heart Study, Framingham, MA.9 A random-effect model was applied to pool the data across studies.10 For assessing the extent of divergence, the heterogeneity of trials was examined by Q-statistic and quantified by the I$^2$ statistic. It was considered that a relatively larger extent of I$^2$ represented greater heterogeneity. We undertook meta-regression analysis to explore the possible reason resulted in heterogeneity. According to the different characteristics of including studies, subgroup analyses were performed, respectively, stratified by the sample size (≤1000 or >1000), duration of follow-up (≤5 years or>5 years), assay method (enzyme-linked immunosorbent assay, radioimmunoassay, or others), whether to adjust the variable, and baseline population (general population, coronary heart disease, others). Sensitivity analysis was performed to appraise an excessive estimate of a single study by way of eliminating each study individually. An estimation of potential publication bias was performed by both Egger’s linear regression test. All statistical analysis was performed with software package Stata version 12.0 (STATA Corp LP, Texas). P < 0.05 was identified with a statistical significance.

3 | RESULTS

3.1 | Identification of studies

The procedures of literature retrieval and selection were present in Figure 1. We initially retrieved 886 relevant publications from the PubMed and ISI Web of Science electronic databases. The majority of these were excluded after screening the titles or abstracts, because of
editorials/reviews/case reports/cross-sectional design or not related. Twenty studies did not provide interesting outcomes, 18 articles were excluded because the data provided were insufficient or unavailable, one study was excluded because of duplicate report on the same study population, and one study follow-up duration was less than 3 months. Finally, 29 studies were selected in our meta-analysis.

3.2 | Study characteristics

Table 1 displayed the baseline characteristics of participants across the 29 studies. The eligible trials involved a total of 53,706 participants. Six studies enrolled community-based populations, 17,6,11-19,27,29,31,32,34,36,37 studies were restricted to patients with coronary artery disease (CAD), five studies were on HF, and the remaining three were respectively pertaining to diabetes mellitus (DM), atrial fibrillation (AF), and intensive care unit patients. The mean age of the subjects ranged from 42 to 79 years. The median follow-up duration ranged from 0.25 to 11.3 years. The estimates of association between GDF-15 levels and risk of adverse outcomes included in the meta-analysis. Nine studies individually regarded the GDF-15 level as a continuous variable to evaluate the risk of CVDs, 7,17,22,26,28,30,34,36,37 studies only regarded the GDF-15 level as a categorical variable and 5,19,22,31,35 studies utilized both two ways. Among the 31 trials, seven reported CVD mortality as outcomes, 13 reported all-cause mortality as outcomes, and the estimate of association between GDF-15 levels and risk of adverse outcomes of included studies was yielded in the Table 2.

3.3 | GDF-15 and the risk of cardiovascular mortality

Eight studies reported cardiovascular mortality as outcomes. Four studies handling the data as a categorical variable demonstrated that the pooled HR for highest GDF-15 category vs lowest was 2.39 (95% CI, 1.36-3.41) (Figure 2A). Moreover, when regarded GDF-15 level as a continuous variable, the pooled HR for cardiovascular mortality from six studies was 2.11 (95% CI, 1.57-2.66) per log-unit ng/L increment using a random effect model. (Figure 2B).

3.4 | GDF-15 and the risk of all-cause mortality

Figure 2C showed the pooled HR for all-cause mortality comparing the highest GDF-15 category with lowest of GDF-15 level (HR, 2.54; 95% CI, 2.07-3.01). When GDF-15 concentration increased one log-unit ng/L, 2.7-fold of the risk of all-cause mortality correspondingly varied (HR, 2.70; 95% CI, 2.29-3.12 (Figure 2D).

3.5 | GDF-15 and the risk of complex adverse outcome

We observed that GDF-15 concentration was associated with an increased risk of complex adverse outcome (HR, 1.80; 95% CI, 1.38-2.23), when pooling data from six studies reporting the estimates as categorical
variables. Every log-unit ng/L increase in GDF-15 concentration was associated with a 95% increase in the risk of complex adverse outcome from pooling the nine studies reporting estimates risk as continuous variables (HR, 1.96; 95%CI, 1.64-2.29).

### 3.6 Heterogeneity measurement

As the heterogeneity inspection tools, meta-regression, analysis and sensitivity analysis were carried out aimed at exploring the potential sources of heterogeneity on all-cause mortality regarding GDF-15 as a categorical variable or continuous variable in our study. The detailed results were displayed in Table 1.

#### TABLE 1 Baseline characteristics of the identified studies

| Source                | No. of Patients | Baseline population | Nation     | Age (y) | Follow-up (y) | Events number | Assay Method | Quality score |
|-----------------------|----------------|---------------------|------------|---------|---------------|---------------|--------------|--------------|
| Wollert et al,11      | 2079           | NSTE-ACS(GUSTO-IV trial) | Germany | 66      | 1             | 143           | RIA          | 7            |
| Eitel et al,12        | 238            | STEMI (LIPSIA-N-ACC) | Germany | 67      | 0.5           | 36            | ELISA        | 6            |
| Kempf et al,13        | 741            | AMI                 | Germany   | 67      | 1             | 59            | RIA          | 6            |
| Eggers et al,14       | 950            | NSTE-ACS (FRISC II trial) | Sweden | 67.1    | 5             | 220           | RIA          | 7            |
| Kempf et al,15        | 2229           | CHD (AtheroGene Study) | Germany | 61.5    | 3.6           | 188           | RIA          | 7            |
| Khan et al,16         | 1142           | AMI                 | UK        | 67      | 1.38          | 303           | ELISA        | 6            |
| Damman et al,17       | 1151           | NSTE-ACS(ICTUS)     | The Netherlands | 62     | 5             | 236           | RIA          | 7            |
| Lin et al,18          | 216            | STEMI               | Taiwan    | 59.8    | 2.33          | 18            | ELISA        | 7            |
| Schopper et al,6      | 984            | Ischemic heart disease | USA | 66.7    | 8.9           | 478           | ELISA        | 7            |
| Bonaca et al,19       | 3501           | ACS (PROVE IT-TIMI 22 trial) | USA | 58.1    | 2             | 317           | RIA          | 7            |
| Izuimya et al,2014    | 149            | Heart Failure       | Japan     | 69.9    | 1.96          | 16            | ELISA        | 7            |
| Wang et al,9          | 3428           | General population (FHS) | USA | 59      | 11.3          | 824           | ECLIA        | 9            |
| Daniels et al,20      | 1740           | General population (RBS) | USA | 71      | 11            | 521           | ELISA        | 8            |
| Eggers et al,21       | 1004           | General population (PIVUS) | Sweden | 70      | 8             | 111           | RIA          | 8            |
| Rohatgi et al,22      | 3291           | General population (DHS) | USA | 48.7    | 7.3           | 120           | ELISA        | 9            |
| Wallentin et al,23    | 940            | General population (ULSAM) | Sweden | 71     | 9.8           | 265           | ECLIA        | 9            |
| Lok et al,24          | 209            | DEAL-HF             | The Netherlands | 71     | 8.7           | 151           | ECLIA        | 8            |
| Foley et al,2009      | 158            | Patients with heart failure undergoing CRT | UK | 68     | 2.6          | 52            | ELISA        | 7            |
| Lajer et al,26        | 891            | Type 1 diabetic patients With Nephropathy | Denmark | 42.1   | 8.1           | 229           | ECLIA        | 9            |
| Schnabel et al,27     | 1781           | CAD (AtheroGene Study) | Germany | 63      | 3.6           | 137           | ELISA        | 7            |
| Wiklund et al,28      | 876            | Male cohort (general population) | Sweden | 68      | 5.3           | 102           | ELISA        | 7            |
|                      | 324            | Twin cohort (general population) | Sweden | 78.6    | 9.1           | 214           |              |              |
| Kempf et al,5         | 455            | Chronic Heart Failure | Germany | 64      | 3.33          | 117           | RIA          | 6            |
| Widera et al,29       | 754            | NSTE-ACS             | Germany   | 70      | 0.5           | 66            | RIA          | 6            |
| Richter et al,30      | 349            | advanced systolic HF | Austria | 75      | 4.9           | 195           | ELISA        | 6            |
| Velders et al,31      | 5385           | STEMI treated with PPCI (PLATO trial) | Multicenter | 59     | 1             | 199           | ECLIA        | 5            |
| Dallmeier et al,32    | 1029           | Stable CHD           | Germany   | 59      | 10            | 162           | ECLIA        | 6            |
| Wallentin et al,33    | 14 798         | Atrial fibrillation  | Multicenter | 70     | 1.9           | 1061          | ECLIA        | 6            |
| Eggers et al,34       | 453            | Acute chest pain     | Germany   | 66      | 5.8           | 92            | RIA          | 7            |
| Dieplerger et al,35   | 530            | ICU patients         | Austria   | 68      | 0.25          | 118           | ECLIA        | 4            |
| Tzikas et al,36       | 1804           | Acute chest pain     | Sweden    | 62      | 0.5           | 63            | Other        | 6            |
| Ska et al,37          | 847            | AMI                 | Sweden    | 70      | 6.9           | 207           | Other        | 7            |

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CHD, coronary heart disease; CRT, cardiac resynchronization therapy; DEAL-HF, Deventer-Alkmaar Heart Failure study; DHS, Dallas Heart Study; ECLIA, electrochemiluminescence assay; ELISA: enzyme-linked immunosorbent assay; FHS, Framingham Heart Study; FRISC II: Framing and Fast Revascularization during Instability in Coronary artery disease II; GUSTO-IV trial: Global Utilization of Strategies to Open Occluded Arteries (GUSTO)-IV trial; ICTUS: Invasive vs Conservative Treatment in Unstable coronary Syndromes; ICU, intensive care unit; LIPSIA-N-ACC: Leipzig Immediate Percutaneous coronary Intervention Acute myocardial infarction N-Acetyl Cysteine; NSTE-ACS: Non-ST-elevation myocardial infarction; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; RBS: Rancho Bernardo Study; RIA: radioimmunoassay; STEMI: ST-elevation myocardial infarction; ULSAM: Uppsala Longitudinal Study of Adult Men; al-HeFT,Valsartan Heart Failure Trial.
| Study                  | Endpoints                                                                 | Comparison               | HR (95% CI)                  | Adjustments                                                                                           |
|-----------------------|---------------------------------------------------------------------------|--------------------------|------------------------------|--------------------------------------------------------------------------------------------------------|
| Wollert et al, 11     | All-cause mortality                                                       | Per SD                   | 1.49 (1.2-1.85)              | Age, gender, delay time, current smoking, history of HTN, hypercholesterolemia, diabetes, previous angina pectoris, MI, revascularization, history of HF, and ST-segment depression ≥ 0.5 mm |
| Eitel et al, 12       | Mortality, MACE*                                                          | Per SD                   | 2.51 (1.59-3.96)             | Unadjusted                                                                                           |
| Kempf et al, 13       | Mortality                                                                | Per SD                   | 1.55 (1.14-2.11)             | Age, gender, delay time, current smoking, hypertension, diabetes mellitus, history of myocardial infarction, and trial (ASSENT-2 vs ASSENT-plus)  |
| Eggers et al, 14      | Death, Death/recurrent MI                                                | Per log-unit             | 3.4 (2.0-5.8)                | Age, gender, diabetes, heart failure, and previous MI                                               |
| Kempf et al, 15       | Coronary heart disease mortality                                         | Per SD                   | 2.4 (1.7-3.4)*              | Age, gender, HTN, diabetes, smoking, LDL/HDL-ratio, number of diseased vessels, history of MI, and all indicated biomarkers |
| Khan et al, 16        | Death, Death or heart failure                                           | Per log-unit             | 1.83 (1.06-3.15)             | Age, gender, previous history of AMI, HF, HTN, DM, smoking history, territory of infarction, STEMI or NSTEMI, Killip class, eGFR, troponin I, therapy with ACE inhibitors, angiotensin receptor blockers and beta-blockers, NT-proBNP, and GDF-15 |
| Damman et al, 17      | Death, Death or spontaneous MI                                          | Highest level vs lowest t (>1800 ng/L vs <1200 ng/L) | 6.12 (3.45-10.9)            | Unadjusted                                                                                           |
| Lin et al, 18         | Death or HF                                                               | Per log-unit             | 13.39 (2.8-63.89)            | Age, DM                                                                                                |
| Schopfer et al, 6     | All-cause mortality, MI, stroke, or CV death                             | Highest tertile vs lowest | 2.73 (1.80-4.15)            | Age, gender, race, smoking, HTN, DM, eGFR, stroke, LDL, exercise capacity, inducible ischemia, NT-proBNP, CRP, leptin |
| Bonaca et al, 2011    | Death                                                                     | Highest level vs lowest t (>1800 ng/L vs <1200 ng/L) | 1.91 (0.84-4.32)            | Age, sex, BMI, DM, HTN, current smoking, prior MI, qualifying event, and creatinine clearance, BNP, hsCRP |
|                       | Death/MI                                                                 | Per log-unit             | 2.95 (1.65-5.26)            |                                                                                                       |
|                       | Death or MI                                                              | Highest level vs lowest t (>1800 ng/L vs <1200 ng/L) | 1.52 (1.05-2.19)            |                                                                                                       |
|                       |                                                                           | Per log-unit             | 2.14 (1.58-2.91)            |                                                                                                       |
| Izumiya et al, 7      | All-cause mortality/cardiac events*                                       | Per log-unit             | 4.74 (1.26-17.88)           | Age, atrial fibrillation, BNP                                                                       |
| Wang et al, 9         | Death                                                                     | Highest quartile vs lowest | 3.7 (2.34-5.86)          | Age, sex, BMI, SBP, HTN therapy, diabetes, cigarette smoking, total cholesterol, HDL cholesterol |
|                       | Major cardiovascular event                                               | Per SD                   | 1.66 (1.51-1.81)            |                                                                                                       |
|                       |                                                                           | Highest quartile vs lowest | 1.56 (1.03-2.36)          |                                                                                                       |
|                       |                                                                           | Per SD                   | 1.26 (1.12-1.41)            |                                                                                                       |
| Daniels et al, 20     | Coronary revascularization, MI or CVD death                              | Highest quartile vs lowest | 1.59 (0.96-2.64)          | Age, sex, DM, HTN, current smoking, SBP, total cholesterol, HDL cholesterol, creatinine clearance, BMI |
|                       | CVD death                                                                | Per log-unit             | 2.46 (1.17-5.18)            |                                                                                                       |
|                       | All-cause death                                                          | Per log-unit             | 2.56 (1.66-3.94)            |                                                                                                       |
| Eggers et al, 21      | All-cause mortality                                                      | Per log-unit             | 4.0 (2.7-6.0)               | Sex, HTN, diabetes, HDL cholesterol, LDL cholesterol, current smoking, BMI, previous CVD, ln (CRP), and ln (eGFR) |
|                       | CVD mortality                                                            | Per log-unit             | 2.3 (1.1-5.0)               |                                                                                                       |
| Rohatgi et al, 22     | All-cause mortality                                                      | Highest level vs lowest t (>1800 ng/L vs <1200 ng/L) | 3.5 (2.1-5.9)              | Age, sex, race, HTN, diabetes, current smoking, hypercholesterolemia, low HDL-cholesterol, BMI, CKD stage, LV mass/body surface area, and history of CVD |
|                       |                                                                           | Per log-unit             | 2.4 (1.7-3.4)               |                                                                                                       |
| Study                          | Endpoints                  | Comparison                                      | HR (95% CI)          | Adjustments                                                                 |
|-------------------------------|----------------------------|-------------------------------------------------|----------------------|-----------------------------------------------------------------------------|
| Wallentin et al.\(^{23}\)    | All-cause mortality       | Highest level vs lowest                         | 2.5 (1.1-5.8)        | Age, current smoking, BMI, systolic blood pressure, antihypertensive treatment, total cholesterol, HDL cholesterol, lipid-lowering treatment, type 2 diabetes, previous cancer, troponin T, NT-proBNP, Cystatin C, CRP |
|                               | CVD mortality             | Per SD                                          | 1.8 (1.1-3.2)        |                                                                            |
|                               |                            | Per log-unit                                    | 1.35 (1.18-1.53)     |                                                                            |
|                               |                            |                                                 | 1.22 (1.01-1.48)     |                                                                            |
| Lok et al.\(^{24}\)          | All-cause mortality       | Per SD                                          | 2.10 (1.63-2.73)     | Randomized treatment, previous warfarin/vitamin K antagonist treatment, geographic region, age, sex, BMI, smoking status, sBP, heart rate, atrial fibrillation type, DM, history of symptomatic congestive HF, previous stroke/systemic embolism/transient ischemic attack, HTN, previous MI, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, cTnI, NT-proBNP, cystatin C. |
| Foley et al.\(^{25}\)        | All-cause mortality       | Per SD                                          | 1.41 (1.11-1.78)     | Age, gender, eGFR HF etiology NT-proBNP GDF-15, hs-TnT, Gal-3 and/or hs-CRP |
|                               | CVD mortality             | Per log-unit                                    | 1.35 (1.18-1.53)     |                                                                            |
|                               |                            |                                                 | 1.22 (1.01-1.48)     |                                                                            |
| Lajer et al.\(^{26}\)        | All-cause mortality       | Highest quartile vs lowest                      | 4.86 (1.37-17.30)    | Sex age, smoking, A1C, systolic BP, cholesterol GFR, NT-proBNP, antihypertensive treatment, and a history of cardiovascular events at baseline |
|                               | CVD mortality             |                                                 | 5.59 (1.23-25.43)    |                                                                            |
| Schnabel et al.\(^{27}\)     | Non-fatal MI and CV       | Per SD                                          | 1.59 (1.25-2.02)     | Age, sex, BMI, LDL/HDL ratio, smoking, diabetes, hypertension, and number of diseased vessels. |
| Wiklund et al.\(^{28}\)      | All-cause mortality       | Highest level vs lowest                         | 2.61 (1.53-4.45)     | Blood draw, BMI, and smoking history                                        |
|                               |                            |                                                 | 2.20 (1.47-3.42)     |                                                                            |
| Kempf et al.\(^{5}\)         | All-cause mortality       | Per log-unit                                    | 1.59 (1.25-2.02)     |                                                                            |
|                               |                            |                                                 | 1.41 (1.11-1.78)     |                                                                            |
| Widera et al.\(^{29}\)       | Death                     | Per SD                                          | 2.26 (1.52-3.37)     |                                                                            |
| Richter et al.\(^{30}\)      | All-cause mortality       | Per SD                                          | 2.4 (1.9-3.0)        |                                                                            |
| Velders et al.\(^{31}\)      | CVD mortality             | Highest quartile vs lowest                      | 2.27 (1.32-4.09)     |                                                                            |
|                               |                            |                                                 | 1.42 (1.25-1.61)     |                                                                            |
| Dallmeier et al.\(^{32}\)    | All-cause mortality       | Highest level vs lowest                         | 1.73 (1.02-2.94)     |                                                                            |
| Wallentin et al.\(^{33}\)    | All-cause mortality       | Highest quartile vs lowest                      | 2.10 (1.63-2.73)     |                                                                            |
| Eggers et al.\(^{34}\)       | All-cause mortality       | Per SD                                          | 1.8 (1.1-3.2)        |                                                                            |
|                               |                            |                                                 | 2.20 (1.47-3.42)     |                                                                            |
heterogeneity. We conducted a sensitivity analysis based on all-cause mortality. In the sensitivity analyses, the results suggested that the pooled HRs or 95% CI did not reflect significant difference when omitting one of the studies from the analysis. (Figure S1 and S2, Supporting Information).

3.7 Publication bias

Egger test showed that no publication bias was observed (coefficient 1.772, \( P = 0.201, 95\% \text{ CI: } -1.15-4.66 \)) when considered as categorical variable. The similar results also identified the relationship as the continuous variable (coefficient 1.214, \( P = 0.121, 95\% \text{ CI: } -0.36-2.78 \)). (Figure S3 and S4).

4 DISCUSSION

CVD, one of the major causes of death, has drawn comprehensive attention worldwide. Serum biomarkers play a crucial role in diagnosing CVDs, moreover, providing the predictive value on adverse outcomes. Apart from traditional cardiac markers, some newly discovered serum biomarkers have been found from large amounts of research. The role of GDF-15 as a potential risk predictor in CVDs has been investigated popularly in recent years. To the best of our knowledge, it is probably the first attempt to analyze the data from the relative literature to evaluate the association on the risk of CVDs or all-cause mortality.

Two studies were conducted on meta-analysis of the relationship between GDF-15 and the different prognosis of acute coronary syndromes and heart failure separately. One of them, GDF-15 is classified as a categorical variable for statistical analysis, and the other is as a continuous variable. In our meta-analysis, 31 studies were included for the further integration analysis comprehensively. It was calculated that GDF-15 was significantly increased when adverse cardiovascular events occur (cardiovascular mortality, all-cause mortality, and complex adverse outcome). Meanwhile, GDF-15 was classified into categorical and continuous data for analysis, respectively. Thus, we can more clearly and intuitively infer the relationship between GDF-15 and the different outcome of CVD or all-cause mortality. Our meta-analyses summarize the results of different cohort studies and evaluate the association between GDF-15 levels and the risk of CVDs or all-cause mortality. It is indicated that higher GDF-15 levels have an adverse relationship on the risk of CVDs or all-cause mortality. In view of our results, compared with the lowest GDF-15 levels, those with the highest levels have a 139% increment in the risk of CVD mortality, 154% increment in the risk of all-cause mortality, and 80% increment in the risk of composite of death or cardiac events. When GDF-15 level was calculated as a continuous variable, there is a 111% increment in the risk of CVD mortality per log-unit increment, 170% increment in the risk of all-cause mortality per log-unit increment and 96% increment in the risk of composite of death or cardiac events. So, qualitatively and quantitatively assessment for the association between GDF-15 levels and adverse outcomes has been performed respectively to verify the hypothesis.

Plenty of clinical researches had demonstrated that GDF-15 is independently related to a variety of CVDs. Moreover, growth differentiation factor 15 provided more prognostic information in assessing the prognosis for the risk of adverse cardiac events or all-cause mortality. The majority of the included literature in this analysis had verified conclusions drawn from a large number GDF-15 prospective clinical trials, indicating that GDF-15 may play a protective role in the pathophysiological processes.

In this meta-analysis, we have fully integrated the studies on the basis of different research groups, including general population, cardiac disease patients, and various of diseases cases. Numerous studies have demonstrated that GDF-15 engaged in predicting the prognosis of the diseases of different baseline populations. HF, as the end-stage of a variety of heart disease, earlier diagnosis appears to be particularly crucial. Studies of research population of HF have showed that the concentration of GDF-15 was markedly elevated, moreover, providing prognostic information with clinical value on all-cause mortality. It
was proved by experiment that GDF-15 plays a protective role by inhibiting apoptosis, hypertrophy, and adverse remodeling in the injured heart. GDF-15 also participated in the development of cardiac remodeling in HF with a function of counterworking hypertrophy and apoptosis through PI3K-Akt, ERK1/2, and SMAD2/3 signaling pathways. A study of a large sample of AF has identified that GDF-15 is...
an indicator for the prognosis of major bleeding and death.\textsuperscript{33} Owing to the incidence trend of ischemic heart disease, the application of GDF-15 on early diagnosis and prognosis of disease is widely studied. In an animal model, it was confirmed that GDF-15 played a cardioprotective role. After the occurrence of ischemia-reperfusion (I/R), the expression of GDF-15 was sharply enhanced in the cardiomyocytes as an endogenous protective cytokine against I/R-induced cardiomyocyte apoptosis, possibly through PI3K-Akt-dependent signaling pathways. In addition, it seemed to be mediated by the approach of induction of nitric oxide (NO) synthase-2, production of NO and peroxynitrite formation. Meanwhile, some relevant pro-inflammatory cytokines (interferon-$\gamma$ and interleukin-1$\beta$) involved in the induction of GDF-15 through NO-dependent pathways.\textsuperscript{3} Besides, GDF-15, has provided more valuable information for risk stratification and prognosis in CVDs.\textsuperscript{11} An epidemiological research demonstrates that GDF-15 levels are associated with carotid artery intima-media thickness, plaque burden, and endothelial dysfunction in elderly individuals, which may provide insight into disparate mechanism of GDF-15 pathophysiology.\textsuperscript{40} Some studies included in our meta-analysis demonstrate that GDF-15 has performed well both in identifying stable and unstable CAD and in evaluating the prognosis, and likewise, independent of traditional clinical risk biomarkers, such as troponin T, NT-proBNP, and hs-CRP.\textsuperscript{6,13,15} To find the potential heterogeneity, we did meta-regression analysis and sensitivity analysis to identify conceivable sources of the discrepancy from the studies that reported all-cause mortality as endpoints. Several probable aspects were filtered for the subgroup analyses. Paradoxically, the results of meta-regression analysis and sensitive analysis was failed to elucidate that where the heterogeneity stems from genuinely. It was inexplicit that which was the initiator of the difference. Furthermore, the results of the sensitivity analysis also indicated that the elimination of any study did not make a significant alteration in the pooled HR.

In conclusion, it can be noted that the present study has stated the association between GDF-15 and adverse prognosis of CVDs and all-cause mortality. A large number of research need to be done until GDF-15 could contribute to clinical and bring more valuable information for clinician.

5 | LIMITATION

We delimit the studies published in the English language as one of the eligible criteria, which may be a limiting factor. First based on prospective study data, the result of our meta-analysis is subject to potential bias. Although potential confounders, such as age, sex, and body mass index have been adjusted in most studies, residual confounding cannot be precluded. Second, some studies of small sample size resulting in extremely strong associations may have an impact on pooled estimates. Third, the characteristics of baseline participants differ across included studies which cause the initial production of heterogeneity. Fourth, on account of disparate adjusted variables of each study it is arduous to unify the diverse adjustments for all studies. Fifth, a dose-effect relationship between the GDF-15 level and all-cause mortality or adverse cardiac events is failed to be conducted owing to the lack of indispensable data. In addition, the indefinite cutoff point of GDF-15 and the various assay methods may influence the results. The relative small sample sizes of studies attenuate the strength of this meta-analysis. Furthermore, larger numbers of studies are expected to strengthen our results, which may provide more vital information on the diagnosis and prognosis for CVDs.

6 | CONCLUSION

Elevated GDF-15 may increase risk of all-cause mortality and adverse cardiovascular events. Further and more detailed clinical investigations are needed to conduct to identify whether measurement of
GDF-15 can be applied to clinical patients for an effective earlier diagnosis, risk stratification, and prognosis assessment.

**Author contributions**

Conceived and designed the experiments: L. Lu Retrieved literature: (S. Xie and L. Liu); Analyzed the data: (S. Xie). Contributed to data analyses: (L. Liu). Wrote the manuscript: S. Xie.

**ORCID**

Shanhui Xie https://orcid.org/0000-0001-5056-7310

**REFERENCES**

1. Bootcov MR, Bauskin AR, Valenzuela SM, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. *Proc Natl Acad Sci U S A*. 1997;94:11514-11519.
2. Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and antiatherosclerotic factor released from the myocardium in association with SMAD protein activation. *Circ Res*. 2006;98:342-350.
3. Kempf T, Eden M, Strelau J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res*. 2006;98:351-360.
4. Schlittenhardt D, Schober A, Strelau J, et al. Involvement of growth differentiation factor-15/macrophase inhibitory cytokine-1 (GDF-15/MIC-1) in oxLDL-induced apoptosis of human macrophages in vitro and in atherosclerotic lesions. *Cell Tissue Res*. 2004;318:325-333.
5. Kempf T, von Haehling S, Peter T, et al. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol*. 2007;50:1054-1060.
6. Schopfer DW, Ku IA, Regan M, Whooley MA. Growth differentiation factor 15 and cardiovascular events in patients with stable ischemic heart disease (The Heart and Soul Study). *Am Heart J*. 2014;167:186-192.e1.
7. Izumiya Y, Hanatani S, Kimura Y, et al. Growth differentiation factor-15 is a useful prognostic marker in patients with heart failure with preserved ejection fraction. *Can J Cardiol*. 2014;30:338-344.
8. Hu XF, Zhan R, Xu S, et al. Growth differentiation factor 15 is associated with left atrial/left atrial appendage thrombus in patients with non-valvular atrial fibrillation. *Circ Cardiol*. 2018;41:34-38.
9. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation*. 2012;126:1596-1604.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
11. Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. *Circulation*. 2007;115:962-971.
12. Eitel I, Blase P, Adams V, et al. Growth-differentiation factor 15 as predictor of mortality in acute reperfused ST-elevation myocardial infarction: insights from cardiovascular magnetic resonance. *Heart*. 2011;97:632-640.
13. Kempf T, Bjorklund E, Olofsson S, et al. Growth-differentiation factor-15 improves risk stratification in ST-segment elevation myocardial infarction. *Eur Heart J*. 2007;28:2858-2865.
14. Eggers KM, Kempf T, Lagerqvist B, et al. Growth-differentiation factor-15 for long-term risk prediction in patients stabilized after an episode of non-ST-segment-elevation acute coronary syndrome. *Circ Cardiovasc Genet*. 2010;3:88-96.
15. Kempf T, Sinning JM, Quint A, et al. Growth-differentiation factor-15 for risk stratification in patients with stable and unstable coronary heart disease: results from the AtheroGene study. *Circ Cardiovasc Genet*. 2009;2:286-292.
16. Khan SQ, Ng K, Dhillon O, et al. Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction. *Eur Heart J*. 2009;30:1057-1065.
17. Danman P, Kempf T, Windhausen F, et al. Growth-differentiation factor-15 for long-term prognostication in patients with non-ST-elevation acute coronary syndrome: an Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) substudy. *Int J Cardiol*. 2014;172:356-363.
18. Lin JF, Wu S, Hsu SY, et al. Growth-differentiation factor-15 and major cardiac events. *Am J Med Sci*. 2014;347:305-311.
19. Bonaca MP, Morrow DA, Braunwald E, et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2011;31:203-210.
20. Daniels LB, Clapton P, Laughlin GA, Maisel AS, Barrett-Connor E. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo Study. *Circulation*. 2011;123:2101-2110.
21. Eggers KM, Kempf T, Wallentin L, Wollert KC, Lind L. Change in growth differentiation factor 15 concentrations over time independently predicts mortality in community-dwelling elderly individuals. *Clin Chem*. 2013;59:1091-1098.
22. Rohatgi A, Patel P, Das SR, et al. Association of growth differentiation factor-15 with coronary atherosclerosis and mortality in a young, multi-ethnic population: observations from the Dallas Heart Study. *Clin Chem*. 2012;58:172-182.
23. Wallentin L, Zethelius B, Berglund L, et al. GDF-15 for prognostication of cardiovascular and cancer morbidity and mortality in men. *PLoS One*. 2013;8:e78797.
24. Lok DJ, Klip IT, Lok SI, et al. Incremental prognostic power of novel biomarkers (growth-differentiation factor-15, high-sensitivity C-reactive protein, galectin-3, and high-sensitivity troponin-T) in patients with advanced chronic heart failure. *Am J Cardiol*. 2013;112:831-837.
25. Foley PWX, Stegemann B, Ng K, et al. Growth differentiation factor-15 predicts mortality and morbidity after cardiac resynchronization therapy. *Eur Heart J*. 2009;30:2749-2757.
26. Lajer M, Jorsal A, Tarnow L, Parving HH, Rossing P. Plasma growth differentiation factor-15 independently predicts all-cause and cardiovascular mortality as well as deterioration of kidney function in type 1 diabetic patients with nephropathy. *Diabetes Care*. 2010;33:1567-1572.
27. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. *Eur Heart J*. 2010;31:3024-3031.
28. Wiklund FE, Bennet AM, Magnusson PKE, et al. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. *Aging Cell*. 2010;9:1057-1064.
29. Widera C, Pencina MJ, Meisinger A, et al. Adjustment of the GRACE score by growth differentiation factor 15 enables a more accurate appreciation of risk in non-ST-elevation acute coronary syndrome. *Eur Heart J*. 2012;33:1095-1104.
30. Richter B, Koller L, Hohensinner PJ, et al. A multi-biomarker risk score improves prediction of long-term mortality in patients with advanced heart failure. *Int J Cardiol*. 2013;168:1251-1257.
31. Velders MA, Wallentin L, Becker RC, et al. Biomarkers for risk stratification of patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention: Insights from the Platelet Inhibition and Patient Outcomes trial. *Am Heart J*. 2015;169:879-889.e7.
32. Dallmeier D, Brenner H, Mons U, Rottbauer W, Koenig W, Rothenbacher D. Growth Differentiation Factor 15, Its 12-Month Relative Change, and Risk of Cardiovascular Events and Total Mortality in Patients with Stable Coronary Heart Disease: 10-Year Follow-up of the KAROLA Study. *Clin Chem*. 2016;62:982-992.
33. Wallentin L, Hijazi Z, Andersson U, et al. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;130:1847-1858.
34. Eggers KM, Kempf T, Venge P, Wallentin L, Wollert KC, Lindahl B. Improving long-term risk prediction in patients with acute chest pain: the Global Registry of Acute Coronary Events (GRACE) risk score is enhanced by selected nonnecrosis biomarkers. *Am Heart J*. 2010;160:88-94.
35. Dieplinger B, Egger M, Leitner I, et al. Interleukin 6, galectin 3, growth differentiation factor 15, and soluble ST2 for mortality prediction in critically ill patients. J Crit Care. 2016;34:38-45.

36. Tzikas S, Palapies L, Bakogiannis C, et al. GDF-15 predicts cardiovascular events in acute chest pain patients. PLoS One. 2017;12:e0182314.

37. Skau E, Henriksen E, Wagner P, Hedberg P, Siegbahn A, Leppert J. GDF-15 and TRAIL-R2 are powerful predictors of long-term mortality in patients with acute myocardial infarction. Eur J Prev Cardiol. 2017;24:1576-1583.

38. Zhang S, Dai D, Wang X, et al. Growth differentiation factor-15 predicts the prognoses of patients with acute coronary syndrome: a meta-analysis. BMC Cardiovasc Disord. 2016;16:82.

39. Zeng X, Li L, Wen H, Bi Q. Growth-differentiation factor 15 as a predictor of mortality in patients with heart failure: a meta-analysis. J Cardiovasc Med (Hagerstown). 2017;18:53-59.

40. Lind L, Wallentin L, Kempf T, et al. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. Eur Heart J. 2009;30:2346-2353.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Xie S, Lu L, Liu L. Growth differentiation factor-15 and the risk of cardiovascular diseases and all-cause mortality: A meta-analysis of prospective studies. Clin Cardiol. 2019;42:513–523. [https://doi.org/10.1002/clc.23159](https://doi.org/10.1002/clc.23159)