Growth differentiation factor 15 is associated with cardiovascular outcomes in patients with coronary artery disease

Man Li 1,2, Lei Duan 2, Yu-Lun Cai 1,2, Hui-Ying Li 1,2, Ben-Chuan Hao 1,2, Jian-Qiao Chen 1,2, Hong Bin-Liu 2,3*

Full list of author information is available at the end of the article

Corresponding author: Hong Bin-Liu
Email: singlesail@126.com

Abstract

Background: Growth differentiation factor-15 (GDF-15) is a marker of inflammation, oxidative stress and it is associated with adverse prognosis in cardiovascular disease. The aim of the present cohort study is to investigate the prognostic value of GDF-15 in patients with coronary artery disease (CAD) during long-term follow up.

Method: A total of 3641 consecutive patients with CAD were prospectively enrolled into the study and followed up for all cause death and major adverse cardiovascular events (MACEs) up to 6.4 years. Plasma GDF-15 was measured and clinical data and long-term events were registered. The patients were subsequently divided into three groups by the levels of GDF-15 and the association of GDF-15 level with MACEs was evaluated.

Result: After a median follow-up at 6.4 years later, 775 patients (event rate of 21%) had developed MACEs and 275 patients died (event rate of 7.55%). Kaplan–Meier analysis indicated that the patients with GDF-15 > 1800 ng/L were significantly associated with an increased risk of MACEs and all cause death. After adjustment for potential confounders, GDF-15 > 1800 ng/L were independently associated with the composite of major adverse cardiovascular events (MACEs) (HR 1.74; 95% CI: 1.44–2.02; p < 0.001) and all-cause death (HR 2.04; 95% CI 1.57–2.61; p < 0.001). For MACEs a significant increase of receiver operator characteristic curve (ROC)curve was seen after addition of GDF-15 to a clinical model 0.628(95% CI 0.605–0.651; p < 0.001).For long-term all-cause death a significant increase of ROC curve was seen after addition of GDF-15 to a clinical model 0.817(95% CI 0.787–0.846; p < 0.001).

Conclusions: In the setting of CAD, GDF-15 is associated with long-term all-cause death, MACEs and provides incremental prognostic value beyond traditional risks factors.

Keywords: Growth differentiation factor-15, Major adverse cardiovascular outcomes, Coronary
Coronary artery disease (CAD) remains the leading cause of death of the world [1]. Patients with previous coronary heart disease have a high probability of major adverse cardiac events (MACEs). Stratification for subsequent coronary events among patients with CAD is of considerable importance because of the potential to guide secondary preventive therapies. Identifying high-risk patients prone to future major adverse cardiovascular events may direct more potent systemic and local approaches for pre-emptive treatment. Growth and differentiation factor 15 (GDF15), previously known as macrophage inhibitory cytokine 1 (MIC-1), is a divergent transforming growth factor b (TGF-b) family member historically associated with cancer cachexia, cardiovascular disease, and a host of other diseases with inflammatory etiologies [2]. Growth differentiation factor-15 is expressed in most tissues only at very low levels [3], the only human organ that expresses high levels of GDF-15 in healthy conditions is the placenta [4]. However, GDF15 could be markedly increased in the case of cardiovascular injury, such as pressure overload, myocardial infarction, heart failure, and atherosclerosis [5]. In the past decade, accumulating evidence has demonstrated that the GDF-15 serve as a potential prognostic factor in patients in with acute coronary syndrome [6]. However, these studies did not elucidate the prognostic value of MACEs in CAD patients. Moreover, at present, whether GDF15 has a long-term prognostic value of MACEs in CAD patients remains unknown. There are no large-scale studies on Chinese people. Therefore, the aim of the present study was to investigate the long term prognostic value of plasma GDF-15 on all cause death and major cardiovascular events (MACEs) in patients with established CAD in hospitalized patients.

2. Methods

2.1 Study population

The present study was designed as a single-center, observational cohort study. As described in the flowchart (Fig. 1), from March 2011 to December 2015, 4078 patients who underwent coronary angiography examination because of angina-like chest pain or positive noninvasive tests (such as treadmill exercise test or coronary computed tomography angiography) at the Chinese PLA General Hospital were recruited in the study. Then, 83 patients with the detailed data lost and 112 patients without angiographically determined CAD were excluded. 56 Patients with congestive
heart failure, systematic inflammatory disease, hemodynamically significant valvar heart disease, surgery or trauma within the previous month, known cardiomyopathy, known cancer, febrile conditions were also excluded from the study. 187 patients lost to follow-up were also excluded. Ultimately, 3641 patients were included in the final analysis.

All subjects gave written informed consent. This study was approved by the Ethics Board of the Chinese PLA General Hospital and written informed consent was obtained from each patient.

2.2 Baseline Examinations
All enrolled patients were required to complete a standardized questionnaire to collect comprehensive data on medical and family history, medication use, smoking status, and body weight, height, and systolic and diastolic blood pressure. Hypertension was defined as blood pressure ≥140/90 mm Hg or receiving antihypertensive treatment. Hyperlipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. Diabetes mellitus was defined as known untreated diabetes and/or use of insulin or oral hypoglycemic agents. Patients were defined as current smoker if they reported any tobacco use in the last 30 days. Diabetes mellitus was defined as a fasting blood glucose >7 mmol/L or current use of diet or medication to lower blood glucose.

2.3 Laboratory Analyses
Blood samples were drawn from patients early in the morning after hospital admission. Serum was centrifuged within 30 minutes, and plasma was stored at -80°C for subsequent analysis. Concentration of GDF-15 was routinely measured by an established available enzyme linked immunosorbent assay kit (pre-commercial Elecsys® assay, measuring range 400–40 000 ng/L; Roche Diagnostics, GmbH, Mannheim, Germany). The detection limit is of 400 ng/ml, and The intra and inter-assay imprecisions were< 0.9% and< 2.3%, respectively. All GDF-15 measurements were performed by investigators in blinded. As previously reported, GDF-15 risk categories were defined as low risk (< 1200 ng/L), intermediate (1200–1800 ng/L) and high risk (> 1800 ng/L) [6-9]. Other routine measurements were performed at the participating study centers using standard laboratory techniques.

2.4 Follow up and study endpoints
All data were prospectively collected and entered into a database. All patients were followed up semiannually through telephone interviews or clinic visits. The primary endpoint was the occurrence
of major adverse cardiac events. MACEs was determined as a composite of all-cause mortality, nonfatal such as ACS, or unplanned revascularization treatment. All deaths were considered cardiac unless a definitive non cardiac cause was established. ACS was defined as the clinical diagnosis of ST-segment elevation myocardial infarction (STEMI), non STEMI, or unstable angina pectoris in accordance with the guidelines of the European Society of Cardiology. Unplanned coronary revascularization was defined as unplanned repeated percutaneous coronary intervention (PCI) or unplanned coronary artery bypass grafting (CABG), with at least 1 of the following: 1) recurrence of angina; 2) positive noninvasive test; and 3) positive invasive physiological test. The second outcome of this study was all-cause death.

2.5 Statistical analysis

Continuous variables were presented as means ± SDs, while categorical variables were described as percentages. Comparisons between groups were performed by using unpaired Student’s t test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Spearman’s correlation coefficients were calculated to evaluate the relations between the levels of GDF-15 and baseline clinical materials and biomarkers. Multiple linear regression was used to evaluate the association of GDF-15 as the dependent variable with other predictors. For patients who experienced more than one event, the first was considered. Kaplan-Meier analysis was used for stratified analysis of time-to-event for 2 event types: 1) MACEs; 2) overall mortality; and statistical assessment was performed using the log-rank test. The differences in proportions in outcome events in the different strata of GDF-15 levels were judged by Fisher’s exact test. The relation of GDF-15 levels to each clinical outcome is presented as cumulative Kaplan–Meier curves and analyzed with Cox proportional hazards models [hazard ratios (HRs) with 95% CIs] with GDF-15 both with GDF-15 concentration as a continuous variable and with GDF-15 group (G1–G3) as a categorical variable. Simple Cox-regression analysis was used to identify predictors of each clinical outcome during the follow up. A multivariate Cox proportional hazards regression model was used to identify independent predictors of clinical events. Covariates that were either statistically significant on univariate analysis or clinical risk factors were considered candidate variables. Model 1: Clinical background characteristics included age, sex, smoking, hypertension, diabetes mellitus, and hyperlipidemia. Model 2 includes model 1, with the addition of GDF-15. For illustrative purposes, receiver operating characteristics (ROC) plots were derived from univariable
binary logistic regression models.
All probability values were 2-sided, and p values <0.05 were considered statistically significant.

STATA 14.2 (Stata Corp, College Station, Texas, USA) was used for statistical analysis.

3. Result
3.1 Patient characteristics
A total of 3641 patients diagnosed as CAD admitted to our hospital were enrolled in the present study. The median age was 64 years; 56.1% were male, the median GDF 15 level was 1884 ng/L. The enrolled patients were divided into three groups upon the levels of serum GDF-15 (G1: GDF-15 < 1200 ng/L, G2: GDF-15:1200-1800 ng/L, G3: GDF-15 > 1800 ng/L). During 6.4 years of follow-up (median follow-up of 6.4 [interquartile range 5.3–7.6] years), 775 patients had an occurrence of MACEs. In those patients, 158 (15.9%) had values of GDF-15 below 1200 ng/L, 134 (17.8%) between 1200 and 1800 ng/L and 483 (25.2%) above 1800 ng/L. The baseline characteristics of two groups were shown in Table 1.

Patients with a higher level of GDF-15 were older, higher level of total cholesterol (TC), had a history of myocardial infarction and percutaneous coronary intervention or coronary artery bypass graft; and had a higher rate of hypertension, hyperlipidemia, diabetes, treatment with aspirin.

There were no differences between patients included and not included in the analysis regarding other background variables: sex, body mass index (BMI), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), smoking, treatment with angiotensin-converting enzyme inhibitor, and treatment with β-blocker).

| Table 1 Baseline clinical and laboratory characteristics of the study patients according to status of GDF-15 |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Total n=3641 | Low GDF-15 ( < 1200 ng/L) | Medium GDF-15 (1200-1800 ng/L) | High GDF-15 (> 1800 ng/L) | p value for trend |
| Age, years | 61.4 (27-95) | 57.2 (26-95) | 59.9 (30-92) | 64.3 (27-95) | < 0.001 |
| Male, n% | 2632 (72.29) | 735 (74.17) | 540 (53.33) | 1357 (71.42) | 0.484 |
| BMI (kg/m2) | 25.64 (13.3–41) | 26.02 (13.3–41) | 25.82 (16.5–37.4) | 25.38 (17.5-32.1) | 0.074 |
| Current smokers, n (%) | 1668 (45.82) | 473 (47.72) | 345 (46.00) | 850 (44.70) | 0.304 |
| Hypertension, n (%) | 2370 (65.09) | 592 (59.74) | 474 (63.20) | 1304 (68.63) | < 0.001 |
| Hyperlipidemia, n (%) | 1120 (30.76) | 282 (28.5%) | 230 (30.70) | 608 (32.0) | 0.034 |
| Diabetes mellitus, n (%) | 1163 (31.94) | 223 (22.50) | 226 (30.13) | 714 (37.58) | < 0.001 |
| Previous MI, n (%) | 254 (6.98) | 54 (5.45) | 44 (5.89) | 156 (8.21) | < 0.001 |
| Previous PCI/CABG, n (%) | 299 (8.21) | 66 (6.66) | 57 (7.58) | 176 (9.26) | < 0.001 |
3.2 Correlations of serum GDF15 levels with other clinical biochemical factors

Increasing levels of GDF-15 at presentation were associated with increased age, diabetes, hypertension, hyperlipidemia and a history of previous myocardial infarction and previous PCI /CABG. GDF-15 levels were also related to a higher rate of aspirin use (Table 2). By multiple regression analysis that included all patients’ characteristics shown in Table 2, used the natural logarithm of GDF-15 as the dependent variable, GDF-15 was independently associated with age (P < 0.001), diabetes (P < 0.001).

| TC(mmol/L) | 4.03±1.0 | 3.97±1.02 | 4.03±1.09 | 4.10±1.14 | 0.046 |
| HDL-C (mmol/L) | 1.07±0.68 | 1.06±0.43 | 1.09±0.94 | 1.07±0.67 | 0.624 |
| LDL-C (mmol/L) | 2.40±0.91 | 2.36±0.84 | 2.44±0.90 | 2.40±0.96 | 0.201 |
| TG (mmol/L) | 1.62±1.21 | 1.65±1.11 | 1.66±1.05 | 1.60±1.32 | 0.326 |

**Medications**

| Aspirin, n (%) | 3415(93.79%) | 942(95.06%) | 718(95.73%) | 1755(92.37%) | 0.001 |
| ACEI, n (%) | 1503(41.28%) | 403(40.67%) | 305(40.67%) | 822(43.26%) | 0.289 |
| β-blocker, n (%) | 1629(44.74%) | 744(75.08%) | 533(71.07%) | 1352(71.16%) | 0.070 |
| Statins, n (%) | 3442(94.53%) | 944(95.25%) | 716(95.47%) | 1782(93.79%) | 0.070 |

| GDF15 < 1200 (n=991) | 1200-1800 (n=750) | GDF15 > 1800 (n=190) | spearman correlation | p |
| Age, years | 57.2(26-95) | 59.9(30-92) | 64.3(27-95) | 0.267 | < 0.001 |
| Male, n% | 735(74.17) | 540(53.33) | 1357(71.42) | -0.025 | 0.133 |
| BMI(kg/m2) | 26.02(13.3-41) | 25.82(16.5-37.4) | 25.38(17.5-32.1) | -0.024 | 0.100 |
| Current smokers, n (%) | 473(47.72) | 345(46.00) | 850(44.70) | -0.025 | 0.127 |
| Hypertension, n (%) | 592(59.74) | 474(63.20) | 1304(68.63) | 0.079 | < 0.001 |
| Hyperlipidemia, n (%) | 282(28.5) | 230(30.70) | 608(32.0) | 0.053 | 0.031 |
| Diabetes mellitus, n (%) | 223(22.50) | 226(30.13) | 714(37.58) | 0.137 | < 0.001 |
| Previous MI, n (%) | 54(5.45) | 44(5.89) | 156(8.21) | 0.064 | < 0.001 |
| Previous PCI/CABG, n (%) | 66(6.66) | 57(7.58) | 176(9.26) | 0.096 | < 0.001 |
| TC (mmol/L) | 3.97±1.02 | 4.03±1.09 | 4.10±1.14 | 0.017 | 0.315 |
| HDL-C (mmol/L) | 1.06±0.43 | 1.09±0.94 | 1.07±0.67 | 0.007 | 0.656 |
| LDL-C (mmol/L) | 2.36±0.84 | 2.44±0.90 | 2.40±0.96 | 0.014 | 0.403 |
| TG (mmol/L) | 1.65±1.11 | 1.66±1.05 | 1.60±1.32 | -0.022 | 0.192 |

**Table 2: Spearman’s correlation coefficients between GDF15 and clinical and biochemical parameters**
3.3 Clinical Outcomes

Primary endpoint

A composite of major adverse cardiovascular events was analyzed during follow-up (Figure 1). In this way, 775 patients had an occurrence of MACE. Of those patients, 158 (15.9%) had values of GDF-15 below 1200 ng/L, 134 (17.8%) between 1200 and 1800 ng/L and 483 (25.2%) above 1800 ng/L. The MACEs rate was significantly higher in the group of patients with GDF-15 values > 1800 ng/L compared with those with GDF-15 values < 1200 ng/L and patients with GDF-15 levels between 1200 and 1800 ng/L (25.2% vs 17.8% vs 15.9%, p < 0.001). Kaplan–Meier curve of the incidence of the primary endpoint is presented in Fig. 2a. The incidence of the primary endpoint in the G3 group was significantly higher than that in the G1, G2 group (P log-rank < 0.001). Univariate Cox proportional analyses revealed that GDF-15 values > 1800 ng/L were significantly associated with the incidence of MACEs (unadjusted HR = 1.92; 95% CI 1.37–2.52; p < 0.001). After adjusted for basic clinical risk factors (age, sex, smoking hypertension, body mass index, diabetes mellitus and hyperlipidemia). In univariate analysis, GDF-15 values > 1800 ng/L was associated with an HR of 1.74 (95% CI 1.44–2.02; P < 0.001) (Table 3)

| Independent Predictors of Major Adverse Cardiac Events | Univariate Models | Multivariate Models |
|---------------------------------------------------------|------------------|-------------------|
| Age                                                     | 1.02             | 1.009-1.022       | 0.00             |
| Sex                                                     | 0.00             | 0.001-0.028       | 0.00             |
| Smoking                                                 | 1.10             | 0.933-1.296       | 0.23             |
| BMI                                                     | 0.98             | 0.959-1.000       | 0.05             |
| Hypertension                                            | 1.03             | 0.646-0.880       | 0.00             |
| Hyperlipidemia                                          | 1.15             | 0.98-1.34         | 0.09             |
| DM                                                      | 0.79             | 0.680-0.911       | 0.00             |
| GDF-15 ≤ 1200 ng/L                                      | 1.05             | 0.87-1.44         | 0.16             |
| GDF-15 > 1200 ng/L                                      | 1.92             | 1.37–2.52         | < 0.001          |

Secondary endpoint

During 6.4 years of follow-up (median follow-up of 6.4 [interquartile range 5.3–7.6] years),
275 patients died. Patients with GDF-15 levels < 1200 ng/L had a low mortality rate of 3.2% (32). Patients with GDF-15 levels between 1200 and 1800 ng/L had the same mortality rate of 3.2% (24). whereas those with GDF-15 levels > 1800 ng/L had a very high mortality rate of 11.3% (219 P < 0.001). Kaplan–Meier curve of the incidence of the primary endpoint is presented in Fig. 2b. The incidence of all-cause death the G3 group was significantly higher than that in the G1, G2 group (P log-rank < 0.001). Univariate Cox proportional analyses revealed that GDF-15 values >1800 ng/L were significantly associated with the incidence of all-cause death. (Table 3). After adjustment for potential confounders, higher GDF-15 values >1800 ng/L were still independently associated with all-cause death (adjusted HR 2.04; 95% CI 1.57–2.61; p < 0.001) (Table 4).

**Table 4** Relation of the GDF-15 level and all-cause death in univariate and multivariate survival analysis

| Independent Predictors of All-cause death | Univariate Models | Multivariate Models |
|------------------------------------------|-------------------|-------------------|
|                                          | HR | 95% CI | p    | HR | 95% CI | p    |
| Age                                      | 1.97 | 1.04-1.12 | < 0.001 | 1.07 | 1.01-1.09 | 0.01 |
| Sex                                      | 1.23 | 0.98-1.37 | 0.09   | -   | -       | -    |
| Smoking                                  | 0.87 | 0.80-1.17 | 0.39   | -   | -       | -    |
| BMI                                      | 0.99 | 0.95-1.02 | 0.48   | -   | -       | -    |
| Hypertension                             | 0.98 | 0.74-1.28 | 0.87   | -   | -       | -    |
| Hyperlipidemia                           | 1.54 | 1.38-1.76 | 0.02   | 1.48 | 1.38-1.86 | 0.03 |
| DM                                       | 1.11 | 0.87-1.42 | 0.42   | -   | -       | -    |
| GDF-15≤1200ng/L                          | 1.11 | 0.87-1.42 | 0.42   | -   | -       | -    |
| GDF-15≤1800 ng/L                         | 1.33 | 0.94-1.56 | 0.13   | -   | -       | -    |
| GDF-15 > 1800ng/L                        | 2.54 | 1.99-3.09 | < 0.001 | 2.04 | 1.57–2.61 | < 0.001 |

**3.4 Incremental value of GDF-15 over conventional risk factors for MACE**

We analyzed the predictive value of GDF-15 by ROC curve. For MACEs, ROC curve analyses indicated that AUC (area under the curve) were 0.583 (95% CI 0.559–0.606) for clinical model (model1), 0.595 (95% CI 0.594–0.641) for GDF-15 alone, 0.628 (95% CI 0.605–0.651) for clinical model including GDF-15 (model2). ROC curve analysis showed non-significant differences in the clinical model alone compared to the clinical model with GDF-15 alone (p=0.093), however there was a significant difference compared to the clinical model with GDF-15 (p < 0.001) (Figure 3a).

For all-cause mortality: ROC curve analyses indicated that AUC were 0.728 (95% CI 0.694–
0.761) for clinical model (model1), 0.766 (95% CI 0.735–0.798) for GDF-15 alone, and 0.817 (95% CI 0.787–0.846) for clinical model including GDF-15. ROC curve analysis showed significant differences in the clinical model alone compared to the clinical model with GDF-15 alone (p < 0.001), and there was a significant difference compared to the clinical model with GDF-15 (p < 0.001) (Figure 3b).

**Discussion**

In this study, we found that GDF15 concentrations higher than 1800 ng/L were associated with an increased risk of all-cause death, MACEs in patients with established CAD. After adjusting for both established risk factors for cardiovascular (CV) disease and these other prognostic biomarkers, GDF-15 remained an independent indicator of MACEs and all-cause death (Figure 4). Even more, we observed that GDF-15 had an incremental prognostic value beyond a clinical model for MACEs and all-cause death. ROC curve analysis showed compared with clinical model there was a significant difference compared to the clinical model with GDF-15. Finally, higher GDF-15 concentrations in the setting of established CAD were consistently related with an increased prevalence of cardiovascular risk factors, the result is in consistent with previous studies [10]. Our results provide updated information on the long-term prognostic role of GDF-15 in CAD, our result indicates that the addition of plasma GDF-15 measurements to information from clinical characteristics and established CV risk factors might further improve risk stratification.

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β (TGF-β)/bone morphogenetic protein (BMP) super family [5]. It is highly expressed in cardiac myocytes [11], adipocytes [12], macrophages [13], endothelial cells [14], and vascular smooth muscle cells [15] in normal and pathological condition. GDF-15 increases during tissue injury and inflammatory states and is associated with cardiovascular risk. Increased GDF-15 levels are associated with cardiovascular diseases such as hypertrophy [16], heart failure [17-19], atherosclerosis [20], endothelial dysfunction [21], obesity [22]. Increasing evidence suggests that inflammation plays an important role in atherosclerosis. A large number of studies showed that GDF-15 increases in response to various stressors including reactive oxygen species and proinflammatory cytokines. GDF-15 highly expressed in response to different kinds of cytokines and growth factors like interleukin-1β (IL-1β), TNF-α, angiotensin II, macrophage colony stimulating factor (M-CSF), and TGF-β. Tumor suppressor protein p53 also induces GDF-15 and
thus acts as a growth inhibitory molecule in tissue [5] [13] [23] [24]. It has been reported that GDF-15 induced proinflammatory factors such as IL-1b, tumor necrosis factor-a, and CRP induce GDF-15 expression in macrophage cells through the regulation of p53 binding sites in the GDF-15 promoter [25]. The above studies shows that elevated GDF-15 has been shown to promote inflammation implying that GDF-15 may play an important role in the pathogenesis of atherosclerosis [25-27].

The prognostic value of GDF15 has been reported for various cardiovascular diseases, such as acute coronary syndrome (ACS), atrial fibrillation, heart failure. Lindholm D had reported a study included 17 095 patients with acute coronary syndrome, GDF-15 was the strongest marker associated with all-cause death with adjusted HRs:2.65[8]. According to Kempf T’s research GDF-15 provided prognostic information in STEMI[6]. The predictive value of GDF-15 in ACS has been confirmed in the 2 large non-ST-segment-elevation ACS (NSTEMIACS) trials: the GUSTO-IV (Global Utilization of Strategies to Open Occluded Arteries IV) and FRISC II (Fast Revascularization during Instability in Coronary Artery Disease II) cohorts[6] [9]. Walter J found that GDF-15 concentrations at emergency department presentation have a high predictive accuracy for all-cause death in patients with suspected acute myocardial infarction (AMI) [26]. Sharma A reported in the ARISTOTLE trial which included 18 201 patients with atrial fibrillation that GDF-15 was the strongest marker associated with bleeding death (HR: 1.72) [27]. Ho JE found that 3523 Framingham Heart Study participants growth differentiation factor 15 (GDF15) was associated with all cause death in the community [28]. According to Bouabdallaoui N’s research baseline GDF-15 and changes in GDF-15 at both 1 month and 8 months were associated with subsequent mortality and CV events in patients with heart failure in the PARADIGM-HF trial[29].

However, the current study is the first to report the long-term value of GDF15 in the prediction of MACEs or all cause death in patients with CAD in a large population. Our study provides a unique and renewed prognostic information that could be extrapolated to the patients who GDF-15 has been diagnosed as CAD. According to GDF15 levels, patients were divided into three groups: <1200, 1200-1800, and >1800 ng/L [6] [9], our research also divided our patients into three groups according to the GDF15 levels, however, our result revealed that only GDF-15 values>1800 ng/L were significantly associated with the incidence of MACEs in CAD patients. A
research measured plasma GDF-15 in 3219 participants of the Dallas Heart Study, their result showed that GDF-15≥1800 ng/L was associated with all-cause mortality (hazard ratio 3.5; 95% CI 2.1-5.9, P<0.0001), and cardiovascular mortality (hazard ratio 2.5; 95% CI 1.1-5.8, P=0.03). Our study is consistent with the results of this study [10]. we add new evidence that GDF-15≥1800 ng/L maybe a high risk critical range for patients with coronary heart disease.

In conclusion, GDF-15 reveals the pathophysiological pathways underlying CAD. Higher level of GDF-15 can predict the MACEs events and mortality for CAD patients, GDF-15 values>1800 ng/L may be a critical value with a strong prognostic value. Although GDF-15 has been shown to be associated with the risk of future cardiovascular events in individuals with and without CAD, their clear clinical utility remains not fully elucidated. Proper reference ranges of GDF-15 need to be established to identify the disease severity and risk stratification of the diseases. Our study provides evidence for the high risk values range.

**Conclusion**

In conclusion, this large sample size and long-term follow-up study for the first time indicated that elevated plasma GDF-15 could predict worse outcomes in patients with CAD.

**List of abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| GDF-15       | growth differentiation factor-15 |
| CAD          | coronary artery disease |
| MACEs        | major adverse cardiovascular events |
| CV           | cardiovascular |
| AMI          | myocardial infarction |
| ACS          | acute coronary syndrome |
| STEMI        | ST-segment elevation myocardial infarction |
| M-CSF        | macrophage colony stimulating factor |
| TGF-β        | transforming growth factor-β |
| IL-1β        | interleukin-1β |
| TNF-α        | tumor necrosis factor-α |
| MIC-1        | macrophage inhibitory cytokine 1 |
| HR           | hazard ratios |
Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Board of the Chinese PLA General Hospital and written informed consent was obtained from each patient.

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests

Funding
This work was supported by the Key Projects of Logistics Scientific Research Project of Chinese PLA (17BJZ48)

Authors' contributions
HL and ML designed the study and provided methodological expertise. ML drafted the manuscript. LD, YC, BH, HL, JC drafted the tables and figures and performed statistical analysis. All authors read and approved the final manuscript.

Acknowledgements
Not applicable

Author details
1 Medical School of Chinese PLA
2 Department of Cardiology, the second Medical Center, Chinese PLA General Hospital
3 Beijing key laboratory of chronic heart failure precision medicine

References
1. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. Eur Heart J. 2018;39(7):508-79.
2. Luan HH, Wang A, Hilliard BK, Carvalho F, Rosen CE, Ahasic AM, et al. GDF15 Is an Inflammation-Induced Central Mediator of Tissue Tolerance. Cell. 2019;178(5).
3. Xu J, Kimball TR, Lorenz JN, Brown DA, Bauskin AR, Klevitsky R, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res. 2006;98(3):342-50.
4. Lawton LN, Bonaldo MF, Jelenc PC, Qiu L, Baumes SA, Marcelino RA, et al. Identification of a novel member of the TGF-beta superfamily highly expressed in human placenta. Gene. 1997;203(1):17-26.
5. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers 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(3):351–60.
6. Kempf T, Björklund E, Olofsson S, Lindahl B, Allhoff T, Peter T, et al. Growth–differentiation factor–15 improves risk stratification in ST-segment elevation myocardial infarction. Eur Heart J. 2007;28(23):2858–65.
7. Damman P, Kempf T, Windhausen F, van Straalen JP, Guba-Quint A, Fischer J, et al. Growth–differentiation factor 15 for long–term prognostic in patients with non–ST-elevation acute coronary syndrome: an Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) substudy. International journal of cardiology. 2014;172(2):356–63.
8. Lindholm D, James SK, Gabrysch K, Storey RF, Himmelmann A, Cannon CP, et al. Association of Multiple Biomarkers With Risk of All–Cause and Cause–Specific Mortality After Acute Coronary Syndromes: A Secondary Analysis of the PLATO Biomarker Study. JAMA Cardiol. 2018;3(12):1160–6.
9. Wollert KC, Kempf T, Peter T, Olofsson S, James S, Johnston N, et al. Prognostic value of growth–diferentiation factor–15 in patients with non–ST-elevation acute coronary syndrome. Circulation. 2007;115(8):962–71.
10. Rohatgi A, Patel P, Das SR, Ayers CR, Khera A, Martinez-Rumayor A, et al. Association of growth differentiation factor-15 with coronary atherosclerosis and mortality in a young, multiethnic population: observations from the Dallas Heart Study. Clin Chem. 2012;58(1):172–82.
11. Wang T, Liu J, McDonald C, Lupino K, Zhai X, Wilkins BJ, et al. GDF15 is a heart–derived hormone that regulates body growth. EMBO Mol Med. 2017;9(8):1150–64.
12. Lu W, Wan Y, Li Z, Zhu B, Yin C, Liu H, et al. Growth differentiation factor 15 contributes to marrow adipocyte remodeling in response to the growth of leukemic cells. J Exp Clin Cancer Res. 2018;37(1):66.
13. Koopmann J, Buckhaults P, Brown DA, Zahren ML, Sato N, Fukushima N, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res. 2004;10(7):2386–92.
14. Schlittenhardt D, Schober A, Strelau J, Bonaterra GA, Schmiedt W, Unsicker K, et al. Involvement of growth differentiation factor-15/macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in oxLDL-induced apoptosis of human macrophages in vitro and in arteriosclerotic lesions. Cell Tissue Res. 2004;318(2):325-33.
15. Bermúdez B, López S, Pacheco YM, Villar J, Muriana FJG, Hoheisel JD, et al. Influence of postprandial triglyceride-rich lipoproteins on lipid-mediated gene expression in smooth muscle cells of the human coronary artery. Cardiovascular research. 2008;79(2):294-303.
16. Xu X-y, Nie Y, Wang F-f, Bai Y, Lv Z-z, Zhang Y-y, et al. Growth differentiation factor (GDF)-15 blocks norepinephrine-induced myocardial hypertrophy via a novel pathway involving inhibition of epidermal growth factor receptor transactivation. J Biol Chem. 2014;289(14):10084-94.
17. Magnussen C, Blankenberg S. Biomarkers for heart failure: small molecules with high clinical relevance. J Intern Med. 2018;283(6):530-43.
18. Stenemo M, Nowak C, Byberg L, Sundström J, Giedraitis V, Lind L, et al. Circulating proteins as predictors of incident heart failure in the elderly. Eur J Heart Fail. 2018;20(1):55-62.
19. Kimmoun A, Cotter G, Davison B, Takagi K, Addad F, Celutkiene J, et al. Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study. Eur J Heart Fail. 2018;21(11):1459-67.
20. Wang J, Wei L, Yang X, Zhong J. Roles of Growth Differentiation Factor 15 in Atherosclerosis and Coronary Artery Disease. Journal of the American Heart Association. 2019;8(17):e012826.
21. Andersson C, Enserro D, Sullivan L, Wang TJ, Januzzi JL, Benjamin EJ, et al. Relations of circulating GDF-15, soluble ST2, and troponin-I concentrations with vascular function in the community: The Framingham Heart Study. Atherosclerosis. 2016;248:245-51.
22. Mullican SE, Rangwala SM. Uniting GDF15 and GFRAL: Therapeutic Opportunities in Obesity and Beyond. Trends Endocrinol Metab. 2018;29(8):560-70.
23. Tan M, Wang Y, Guan K, Sun Y. PTGF-beta, a type beta transforming growth factor (TGF-beta) superfamily member, is a p53 target gene that inhibits tumor cell growth via TGF-beta signaling pathway. Proc Natl Acad Sci USA. 2000;97(1):109-14.
24. Bauskin AR, Brown DA, Junankar S, Rasiah KK, Eggleton S, Hunter M, et al. The propeptide mediates formation of stromal stores of PROMIC-1: role in determining prostate cancer outcome. Cancer Res. 2005;65(6):2330-6.
25. Jung S-B, Choi MJ, Ryu D, Yi H-S, Lee SE, Chang JY, et al. Reduced oxidative capacity in macrophages results in systemic insulin resistance. Nat Commun. 2018;9(1):1551.
26. Walter J, Nestelberger T, Boeddinghaus J, Twerebold R, Croton L, Badertscher P, et al. Growth differentiation factor-15 and all-cause mortality in patients with suspected myocardial infarction. International journal of cardiology. 2019;292:241-5.
27. Sharma A, Hijazi Z, Andersson U, Al-Khatib SM, Lopes RD, Alexander JH, et al. Use of Biomarkers to Predict Specific Causes of Death in Patients With Atrial Fibrillation. Circulation. 2018;138(16):1666-76.
28. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, et al. Protein Biomarkers of Cardiovascular Disease and Mortality in the Community. Journal of the American Heart Association. 2018;7(14).
29. Bouabdallaoui N, Claggett B, Zile MR, McMurray J, O'Meara E, Packer M, et al. Growth
differentiation factor-15 is not modified by sacubitril/valsartan and is an independent marker of risk in patients with heart failure and reduced ejection fraction: the PARADIGM-HF trial. Eur J Heart Fail. 2018;20(12):1701-9.