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Repeated measurement of growth-differentiation factor-15 in Chinese Han patients with post-myocardial infarction chronic heart failure

Ji-Xuan LIU[1, 2, 3], Yan-Ping LI[4, 5], Bo-Han LIU[1, 2, 3], Xiao-Jing ZHAO[1, 2], Ze-Yu ZHANG[1, 2, 3], Jin-Da WANG[3], Qian JIA[1, 2], Chun-Lei LIU[1, 2], Xiao-Jian GAO[1, 2, 3], Zhen-Guo XU[1, 2, 3], Hua-Wei ZHANG[3], Lin-Nan SONG[6], Zhi-Jun SUN[3], Kun-Lun HE[1, 2]

[1]*Beijing Key Laboratory of Chronic Heart Failure Precision Medicine, Chinese PLA General Hospital, Beijing, China*
[2]*Transformation Medicine Centre, Chinese PLA General Hospital, Beijing, China*
[3]*Department of Cardiovascular, Chinese PLA General Hospital, Beijing, China*
[4]*Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China*
[5]*Outpatient Department of North China Military Materials Procurement Bureau, Tianjin, China*
[6]*Queen Mary College of Nanchang University, Nanchang, China*

Abstract

Background Growth-differentiation factor-15 (GDF-15) is a promising prognostic biomarker in patients with chronic heart failure (CHF). Comparatively little is known about the value of repeated measurement of GDF-15 with CHF in Chinese Han population. This study sought to identify the clinical value of repeated measurement of GDF-15 in Chinese Han patients with post-myocardial infarction CHF. **Methods** In total, 232 consecutive Chinese Han patients with post-myocardial infarction CHF were enrolled prospectively from January 2014 to June 2016.The plasma concentration of GDF-15 was determined on admission and over 12 months. Patients were followed up for all-cause death and a composite outcome of major adverse cardiac events (MACE) included all-cause death, myocardial infarction and first heart failure (HF) re-hospitalization. Association with other clinical variables and adverse outcomes of repeated measurement of GDF-15 was explored. **Results** The median baseline GDF-15 level was 2025 ng/L. Baseline GDF-15 was moderately associated with baseline N-terminal pro-B type natriuretic peptide (NT-proBNP) (coefficient 0.561, $P < 0.001$). During a median follow-up of 20 months, there were 53 deaths and 100MACE. GDF-15 remained an independent predictor of all-cause death (adjusted hazard ratio 1.826 per 1 Ln U, 95% CI: 1.037–8.360; $P = 0.037$) and MACE (adjusted hazard ratio 2.243 per 1 Ln U, 95% CI: 1.181–1.775; $P < 0.001$) adjusted for established risk factors. Repeated measurement of GDF-15 was performed in 173 survivals over 12months. Increase of GDF-15 over 12 months was associated with dilatation of left ventricle and acted as an independent predictor of subsequent all-cause death (adjusted HR = 3.164, 95% CI: 1.245–0.041; $P = 0.015$). In the joint model, GDF-15 was also shown to be a risk factor for all-cause death (HR = 2.749, 95% CI: 1.667–3.831; $P < 0.001$) and MACE (HR = 2.434, 95% CI: 1.425–3.443; $P < 0.001$). **Conclusions** Repeated measurements of GDF-15 have promising prognostic value of the risk of all-cause death in Chinese Han patients with CHF post-myocardial infarction. GDF-15 may influence the post-myocardial infarction CHF through the path physiological pathway of myocardial remodeling.

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Keywords: Chronic heart failure; Growth-differentiation factor-15; Left ventricular remodeling; Myocardial infarction; Prognosis

1 Introduction

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output unable to meet the body's demand. Myocardial infarction is the leading cause of HF and the prevalence of ischemic HF has increased,[1] especially in low- and medium-income countries like China.[2] In spite of modern treatment options, chronic heart failure remains associated with poor prognosis and high mortality, exceeding 50% in five years.[3] Accurate risk stratification helps decide on the appropriate type and timing of therapies (in particular, decisions about a rapid transition to advanced therapies) is crucial for the prognosis of patients with HF.[4] However, till now, there is no accurate method to prognosticate patients with HF. For that reason, a number

Correspondence to: Zhi-Jun SUN, Department of Cardiovascular, Chinese PLA General Hospital, Beijing, China; Kun-Lun HE, Transformation Medicine Centre, Chinese PLA General Hospital, Beijing, China. E-mails: 13301234516@163.com (SUN ZJ) & hekl301@aliyun.com (HE KL).
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of potential biomarkers that could contribute to the prognosis of HF are exponentially emerging over the recent years. Growth-differentiation factor-15 (GDF-15) is one of the most attractive biomarkers that provide strong prognosis information.

GDF-15 is a member of transforming growth factor β super-family, acting as an anti-hypertrophic,[5] anti-inflammatory[6] and anti-apoptotic[7] cytokine responding to cardiac injury. Clinical studies found GDF-15 was associated with the risk of all-cause death in CHF patients, mainly caucasion.[8–10] Comparatively little is known about the association between repeated measurement of GDF-15 and CHF within the Chinese, which is very different in lifestyle, nutrition, and metabolism compared with the Western.

Therefore, this prospective study aimed to investigate and evaluate the clinical value of repeated measurements of GDF-15 in postmyocardial infarction on Chinese Han patients with CHF.

2 Methods

2.1 Study population

A total of 232 consecutive patients with CHF admitted to the Department of Cardiology of Chinese PLA General Hospital were enrolled prospectively from January 2014 to June 2016, with the following inclusion criteria: (1) age ≥ 18; (2) NYHA cardiac functional classification II-IV;[3] (3) LVEF < 40%; and (4) a history of MI, and stabilized ≥ one months. Participants were excluded based on the following criteria: (1) having an ethnic origin other than Han (defined as one of the subject's parents not being Han as ascertained by the identification card of China or the subject having a cultural identity other than Han); (2) being in the acute onset phase of acute coronary syndrome (ACS) or HF or within less than three months of achieving a stable condition as judged by the researchers; (3) having been diagnosed with HF before myocardial infarction; (4) having a history of corticosteroids intake within six months; (5) having a history of plasma GDF-15-related disease [renal impairment (defined as estimated glomerular filtration rate < 30 mL/min), malignant tumor or chronic obstructive pulmonary disease]; (6) having a history of mental disorder; (7) being pregnant; (8) exhibiting intolerance to dual antiplatelet therapy or statin; and (9) being unable or unwilling to provide informed consent. All participants were followed up by telephone or at the outpatient clinic of the Department of Cardiovascular of Chinese PLA General Hospital. The study had two primary end points: all-cause death and a composite endpoint of major adverse cardiac events (MACE) including all-cause death, myocardial infarction and first HF rehospitalization.

This study protocol was approved by the Ethics Committee of Chinese PLA General Hospital and registered in Chinese Clinical Trial Registry (ChiCTR-RRC-17013396). All subjects provided informed consent and all experiments were performed in accordance with relevant guidelines and protocols.

2.2 Data collection

Demographic characteristics, history of chronic disease, long-term medication use, and lifestyle factors were recorded using a standardized questionnaire by two experienced cardiologists. Standard physical and biochemical examinations were completed for all participants. A diagnosis of HF and myocardial infarction was based on national guidelines.[11,12]

All blood samples were withdrawn after overnight fasting and were placed in a freezer at 4°C immediately after phlebotomy. Centrifugation for the separation of plasma was performed within 1 h of collection, and specimens were stored at −81°C until analyzed. A total of 172 patients had blood samples drawn again when they were rehospitalized for HF.

The plasma concentrations of GDF-15 and high-sensibility cardiac troponin T (hs-cTnT) were determined by electrochemiluminescence immunoassay (Roche Diagnostics, GmbH). Routine assays of other biochemical parameters such as hemoglobin (Hb), albumin, creatinine, uric acid (UA), and C-reaction protein (CRP), interleukin-6 (IL-6) and NT-proBNP were performed in the Clinical laboratory or Biochemistry Department of Chinese PLA General Hospital at the same time. Estimated glomerular filtration rate (eGFR) was calculated based on the Modification of Diet in Renal Disease (MDRD) equation: $eGFR = 186.8 \times \text{plasma creatinine}^{-1.154} \times \text{age}^{-0.203}$ (× 0.742 if female patients).

A resting 12-lead electrocardiogram (ECG) was obtained in the ECG room of the Department of Cardiovascular of Chinese PLA General Hospital, and QRS intervals were recorded. Echocardiography was performed in the echocardiography room of the Department of Cardiovascular of Chinese PLA General Hospital. Left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD) were recorded. All examinations were performed and recorded by two experienced specialists.

2.3 Data analysis

All data were analyzed with the statistical software R packages and SPSS version 20.0. All statistical evaluations were carried out assuming a two-sided test at the 5% level

of significance. Baseline characteristics were reported as follows: categorical variables as percentages (%), continuous variables as the mean ± SD if normally distributed or medians (25^{th} and 75^{th} percentiles) if not normally distributed. Continuous data with a normal distribution and homogeneity of variance were compared by one-way ANOVA, otherwise by Kruskal-Wallis test. Categorical data were compared by X^2 analysis. Spearman rank correlation was used to explore the relationship between baseline GDF-15 quartiles or an increase of GDF-15 over 12 months and related clinical parameters. Kaplan-Meier (KM) survival curves and the log-rank test were performed according to the time of the endpoints. Cox regression analysis using backward selection was used to determine whether baseline GDF-15 was independently associated with the time to endpoint events. A receiver operating characteristic (ROC) curve was generated to statistically assess the sensitivity and specificity of baseline GDF-15 measurements and their additional prognostic utility using the method of Delong, *et al*.[13] The Wilcoxon matched-pair signed rank test was used to compare repeated GDF-15 measurements in the same individual. Joint modeling of longitudinal data[14] was used to separately analyze the repeated measurements of GDF-15 in 173 patients who survived over one year. Differences were considered significant at $P < 0.05$ (two-sided).

3 Results

3.1 Baseline characteristics of study population

Our study cohort consisted of 232 patients (70.3% male) with a mean age of 65.6 ± 12.1 years. The baseline GDF-15 level was 2,025 (interquartile range, 1,213 to 3,372; range, 259 to 25,637; $n = 232$) ng/L. A total of 75.9% of the patients presented with GDF-15 levels over 1,200 ng/L, the upper limit of normal in healthy elderly individuals.[15] All of the patients were categorized by GDF-15 quartiles. The baseline characteristics of the patients in relation to baseline GDF-15 quartiles are shown in Table 1. Spearman rank correlation analysis showed GDF-15 quartiles were associated with a series of variables. (Table 2) Correlations between GDF-15 and variables other than baseline NT-proBNP (coefficient 0.561; $P < 0.001$)were weak (all coefficient < 0.4). No significant correlation was found between GDF-15 and other inflammatory factors, C-reaction protein (CRP, coefficient = –0.036; $P = 0.587$) and interleukin- 6 (IL-6, coefficient = –0.026; $P = 0.699$), respectively.

3.2 Association between baseline GDF-15 and endpoints

During a median follow-up of 20 months (interquartile range, 12 to 26 months), 53 patients (21%) died and 100 patients (43.1%) had a MACE. KM survival curves showed higher baseline GDF-15 quartiles were associated with higher rates of all-cause death and MACE (Figure 1).

Baseline GDF-15, NT-proBNP, hs-cTnT, CRP and IL-6 were natural log transformed to meet a normal distribution and comparative variance before being entered in theCox regression analysis. A one unit increase in Ln (biomarker) was equivalent to a 172% increase of absolute biomarker value. Predictors of endpoints identified from single-variable Cox regression analysis were performed to evaluate every variable. LnGDF-15, LnNT-proBNP and Lnhs-cTNT were significantly correlated with all-cause death and MACE, but not LnCRP and LnIL-6. LnGDF-15 had the highest HR (3.813, 95% CI: 2.471–5.886) compared with other biomarkers.

Variables with a significant ($P < 0.05$) correlation with endpoint events were included in the multiple-variable Cox regression analysis. Firstly, previously recognized clinical prognostic variables including age > 70, history of hypertension, NYHA class, LVEF < 30%, QRS interval > 120 ms, albumin, Hb < 13 g/L and eGFR were entered into the multiple-variable Cox regression analysis, generating Model 1. Secondly, LnNT-proBNP and Lnhs-cTNT were added to Model 1 to generate Model 2. GDF-15 remained a strong independent predictor of endpoints, even after adjusting for Model 1 and Model 2 (Table 3).

ROC curves for the prediction of all-cause death and MACE identified an incremental predictive utility of GDF-15 in Models 1 and 2. (Figure 2) In ROC curves for the prediction of all-cause death, Model 1 combined with GDF-15 raised AUCs from 0.752 to 0.820 ($P < 0.001$), and Model 2 combined with GDF-15 raised AUCs from 0.864 to 0.874 ($P = 0.212$). In ROC curves for the prediction of MACE, AUCs were raised from 0.646 to 0.788 ($P < 0.001$) and from 0.758 to 0.808 ($P = 0.006$) for Models 1 and 2, respectively. Additionally, no significant difference was observed between the AUCs of Model 1 combined with GDF-15 and Model 1 combined with GDF-15 in ROC curves for the prediction of MACE (0.788 *vs.* 0.808, $P = 0.187$). The largest AUC for GDF-15 was obtained at the optimal cutoff value of 1964 ng/L, with a sensitivity of 88.7%, a specificity of 59.2%, and a Youden index = 0.479, in ROC curves for prediction of all-cause death. In addition, for MACE, the largest AUC of GDF-15 was obtained at the optimal cutoff value of 2257 ng/L, with a sensitivity of 74%, a specificity of 78%, and a Youden index = 0.529.

3.3 Change of GDF-15 over 12 months

In all, 173 patients survived 12 months and had repeated

measurements of GDF-15 and other biomarkers. There was no significant difference between baseline GDF-15 levels [2501(1255, 3062) ng/L] and GDF-15 levels over 12 months [1886(1247, 3199) ng/L] (P = 0.432). Fifty-two

Table 1. Baseline Characteristics in relation to quartiles of GDF-15.

Characteristics	Total (n = 232)	GDF-15 quartile, ng/L				*P* -value
		Q1 ≤ 1213	Q2 1213–2025	Q3 2025–3372	Q4 > 3372	
Age, yrs	65.6 ± 12.1	63.5 ± 10.4	66.1 ± 10.3	65.7 ± 14.1	67.3 ± 13.2	0.391
Male	70.3%	69%	69%	74.1%	69%	0.906
BMI, kg/m^2	25 (23,27)	26 (24,27)	24 (23,27)	25 (22,27)	25 (22,27)	0.013
Smoking	44%	43.1%	48.3%	34.5%	50%	0.330
Hypertension	64.7%	67.2%	60.3%	62.1%	69%	0.733
Diabetes mellitus	31.9%	31%	25.9%	34.5%	36.2%	0.644
Atrial fibrillation	14.2%	13.8%	12.1%	13.8%	17.2%	0.880
NYHA class						< 0.001
II	58.2%	75.9%	60.3%	60.3%	36.2%	
III	33.6%	24.1%	26.2%	27.6%	46.6%	
IV	8.2%	0%	3.4%	12.1%	17.2%	
LVEF	33%	34%	33%	34%	31%	0.034
QRS, ms	94 (77,116)	96 (79,117)	98 (81,119)	93 (75,115)	86 (71,117)	0.369
SBP, mmHg	114 (104,132)	123 (106,138)	116 (105,133)	112 (105,130)	113 (102,128)	0.180
DBP, mmHg	71.8 ± 12.7	75.7 ± 13.5	69 ± 13	72 ± 10	70.3 ± 13	0.028
Heart rate, beats/min	74.6 ± 10.8	74.9 ± 10	72.3 ± 11	74.7 ± 10.9	76.6 ± 11	0.204
LVEDD, mm	55.1 ± 7.6	52.8 ± 7.8	56 ± 7.7	53 ± 7.6	53.9 ± 8.4	0.114
Diuretic	73.3%	70.7%	72.4%	84.5%	84.5%	0.175
ACEI/ARB	75%	72.4%	70.7%	84.5%	72.4%	0.287
Beta-blocker	69.8%	67.2%	77.6%	69%	60.3%	0.419
Spironolactone	74.6%	65.5%	70.7%	86.2%	75.9%	0.067
Revascularization						0.917
PCI	74.6%	79.3%	72.4%	74.1%	72.4%	
CABG	13.4%	12.1%	13.8%	15.5%	12.1%	
None	12.1%	8.6%	13.8%	10.3%	15.5%	
IL-6, ng/L	70 ± 10.9	61 ± 11.1	60.9 ± 10.3	60.6 ± 10.3	61.3 ± 12.1	0.985
CRP, ng/L	1890 ± 448	1989 ± 372	1749 ± 491	1930 ± 428	1890.9 ± 467.4	0.027
Biochemical markers						
Haemoglobin, g/dL	13 (12,15)	14 (12,15)	13.5 (12,15)	13 (12,15)	13 (11,14)	0.010
Albumin, g/L	41.7 ± 10	41.2 ± 10.4	43 ± 9.6	41.8 ± 9.6	40.8 ± 10.6	0.682
Uric acid, umol/L	374 ± 117	344 ± 110	383 ± 100	379 ± 133	391 ± 121	0.137
eGFR, mL/min	62.1 ± 16.8	67.9 ± 16.6	61.2 ± 13.7	63 ± 17.3	56.3 ± 17.8	0.02
NT-proBNP, ng/L	1237 (635, 3228)	585 (322,917)	1139 (622,2225)	1613 (910,3797)	3666 (1996,5219)	< 0.001
Hs-cTnT, ng/mL	18 (10,43)	12 (7,22)	14 (7,26)	25 (12, 55)	32 (16, 115)	< 0.001
IL-6, ng/L	70 ± 10.9	61 ± 11.1	60.9 ± 10.3	60.6 ± 10.3	61.3 ± 12.1	0.985
CRP, ng/L	1890 ± 448	1989 ± 372	1749 ± 491	1930 ± 428	1890.9 ± 467.4	0.027

Data are presented as means ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitor; BMI: body mass index; CABG: coronary artery bypass graft; DBP: diastolic blood pressure; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; QRS: QRS intervals; SBP: systolic blood pressure.

Table 2. Correlates of baseline GDF15 quartiles from Spearman rank correlation.

Correlates	Coefficient	*P*-value
BMI > 25 kg/m^2	–0.147	0.025
NYHA	0.298	< 0.001
LVEF < 30%	0.236	< 0.001
Hb < 13 g/L	0.142	0.031
Uric acid, μmol/L	0.148	0.025
eGFR, mL/min	–0.222	0.001
NT-proBNP, ng/L	0.561	< 0.001
Hs-cTnT, ng/mL	0.317	< 0.001
Diuretic	0.129	0.049

BMI: body mass index; Hb: Haemoglobin; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

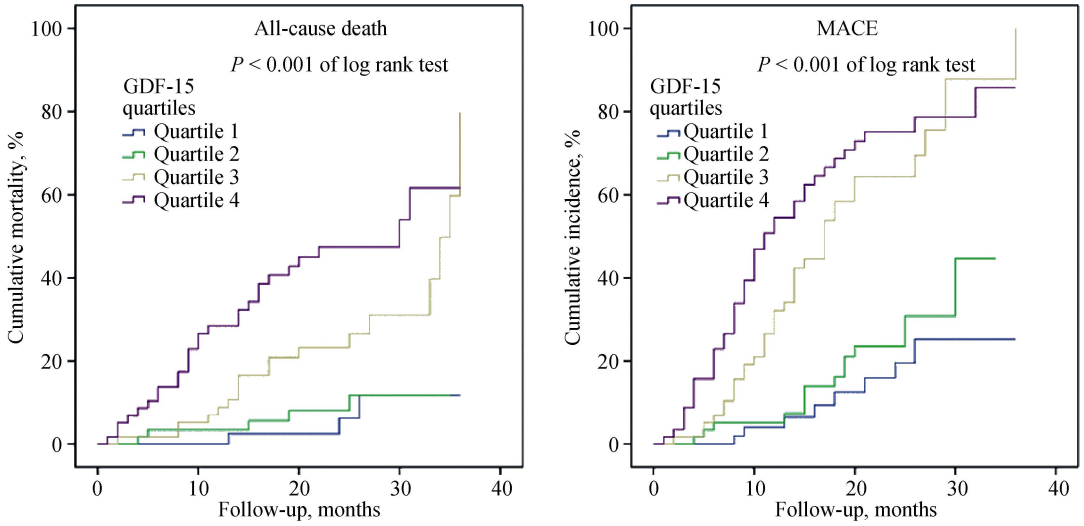

Figure 1. Kaplan–Meier curves for time to all-cause death and MACE according to quartiles of baseline GDF-15.

Table 3. Adjusted predictive utility of GDF-15 for endpoint events from multivariate Cox regression.

	All-cause death		MACE	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Adjusted for model 1	3.270 (2.077, 5.148)	< 0.001	3.108 (2.303, 4.195)	< 0.001
Adjusted for model 2	1.826 (1.056, 3.159)	0.031	2.243 (1.580, 3.183)	< 0.001

percent of the survivals had a decreased GDF-15 level (defined as GDF-15 level over 12 months lower than baseline), the rest had a increased GDF-15 level (defined as GDF-15 level over 12 months higher than baseline). When grouped by change in GDF-15 level, an increase in GDF-15 level was weakly correlated with baseline heart rate (coefficient = 0.218, $P = 0.004$), baseline LVEDD (coefficient = 0.305, $P < 0.001$), LVEDD over 12 months (coefficient = 0.347, $P < 0.001$) and change of NT-proBNP (coefficient = 0.347, $P = 0.001$). These results indicated an association between repeated measurements of GDF-15 and left ventricular remodeling (defined as LVEDD over 12 months larger than baseline). Therefore, we performed further correlation analyses between repeated measurements of GDF-15 and LVEDD, identifying the significant difference in baseline GDF-15 levels between a remodeling group and controls (median level 2832 *vs.* 1116 ng/L, $P < 0.001$ (Figure 3).

Single-variable Cox regression identified left ventricular remodeling and an increase in GDF-15 level, but not a change in NT-proBNP or hs-cTnT, to be risk factors for endpoints beyond previously found variables. In consideration of the measurement error in GDF-15, analysis using joint modeling of longitudinal and survival data for the 173 patients survived one year was performed with the methods of piecewise-PH-aGH. Risk factors previously recognized and LVEDD (found significant correlated with change of

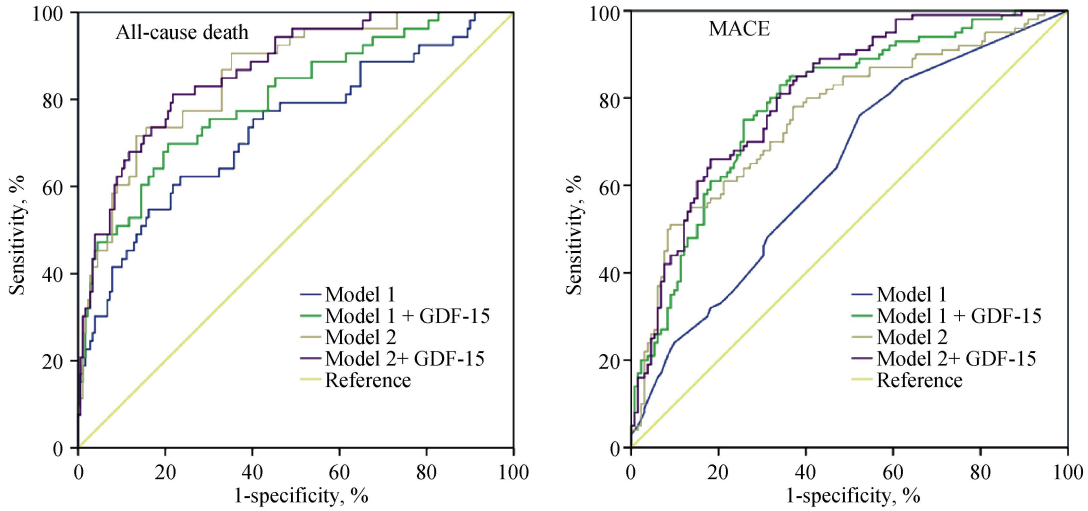

Figure 2. Receiver operating characteristics curves prediction of all-cause death and MACE. Full model contains all the clinical risk factors, NT-proBNP, hs-cTnT and GDF-15 had the highest AUCs in ROC curves both for all-cause death and MACE. Comparison of AUCs between the full model and the model without LnGDF15 was significant in ROC for MACE (P = 0.006).

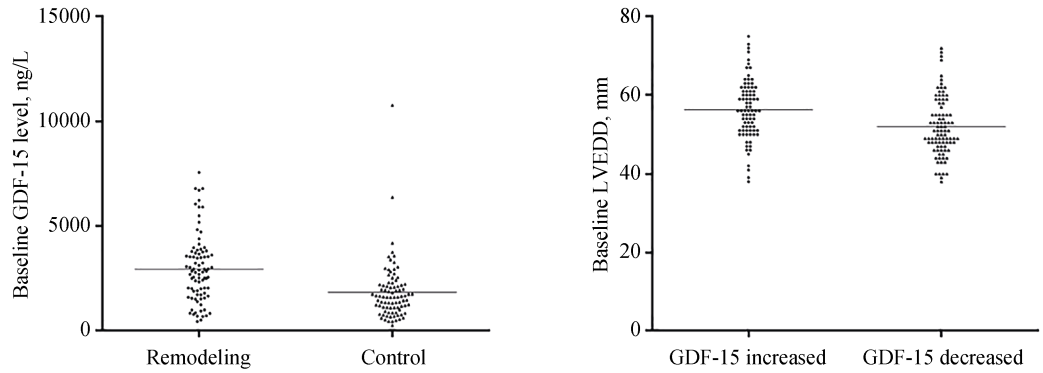

Figure 3. GDF-15 and left ventricular remodeling. Distribution of baseline GDF-15 levels in patients with remodeling and controls was shown in the left; distribution of LVEDD in patients with increased and decreased GDF-15 was shown in the right. LVEDD: left ventricular end diastolic diameter.

GDF-15 level) were added into the joint model. And to facilitate operation of the model, Albumin and eGFR were also natural log transformed. Results was shown in Table 4. We found that 1% increase in GDF-15 level was associated with a 2.7% (95% CI: 1.7%–3.8%) increased hazard for All-cause death and 2.4 (95% CI: 1.4%–3.4%) increased hazard for MACE.

Moreover, to evaluate prognostic value of the changing trend of GDF-15 level, Model 3 was generated after Left ventricular remodeling and LnGDF15 over 12 months added into Model 2. After adjustment for Model 3, multivariable COX regression analysis indicated increase of GDF-15 level was an independent predictor for subsequent all-cause death (adjusted HR = 3.164, 95% CI: 1.245–0.041; P = 0.015), but not for MACE (HR = 1.219, 95% CI: 0.679– 2.189; P = 0.507). Adding increase of GDF-15 level into Model 3 raised AUCs of ROC for subsequent all-cause death from 0.874 to 0.877, but the improvement was no significant (P = 0.738).

4 Discussion

This prospective observational study identifies baseline GDF-15 level and change of GDF-15 over 12 months as useful predictors for all-cause mortality in Chinese Han patients with post-myocardial infarction CHF.

In the present study, we restricted our subjects to HF patients with exclusive aetiology of myocardial infarction, the most common cause. The baseline GDF-15 level of our CHF cohort was consistent with similar cohorts from Western populations[8–10] and South Asian[16], but notably higher than another Chinese CHF cohort[17] that only determined

Table 4. Results of joint modeling analysis for 173 patients survived one year

Variables	All-cause death		MACE	
	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Longitudinal sub-model				
Intercept	6.653 (5.813, 7.492)	< 0.001	6.653 (5.813, 7.492)	< 0.001
Baseline age	0.003 (–0.001, 0.007)	0.513	0.003 (–0.001, 0.007)	0.513
Follow-up	–0.002 (–0.008, 0.004)	0.713	–0.002 (–0.008, 0.004)	0.713
Hypertension	0.093 (–0.023, 0.163)	0.185	0.093 (–0.023, 0.163)	0.185
NYHA	0.075 (0.012, 0.138)	0.049	0.075 (0.012, 0.138)	0.049
LVEF < 30%	0.097 (0.074, 0.120)	0.019	0.097 (0.074, 0.120)	0.019
QRS > 120ms	0.031 (–0.062, 0.124)	0.735	0.031 (–0.062, 0.124)	0.735
Hb < 13g/L	0.017 (–0.067, 0.081)	0.812	0.017 (–0.067, 0.081)	0.812
LnAlbumin	0.057 (–0.083, 0.197)	0.685	0.057 (–0.083, 0.197)	0.685
LneGFR	–0.294 (–0.440, –0.148)	0.014	–0.294 (–0.440, –0.148)	0.014
LnNT-proBNP	0.234 (0.198, 0.270)	< 0.001	0.234 (0.198, 0.270)	< 0.001
Lnhs-cTNT	0.077 (0.049, 0.105)	0.006	0.077 (0.049, 0.105)	0.006
LnLVEDD	0.074 (–0.012, 0.160)	0.078	0.074 (–0.012, 0.160)	0.078
Survival sub-model				
LnGDF-15	2.749 (1.667, 3.831)	< 0.001	2.434 (1.425, 3.443)	< 0.001
Baseline age	1.053 (1.028, 1.078)	< 0.001	1.003 (0.986, 1.021)	0.712
Hypertension	1.568 (0.876, 2.809)	0.130	1.006 (0.669, 1.513)	0.977
NYHA	3.243 (2.150, 5.206)	0.003	2.353 (1.276, 3.430)	0.002
LVEF < 30%	1.542 (0.795, 2.787)	0.054	2.017 (1.332, 2.702)	0.001
QRS > 120ms	1.438 (0.761, 2.700)	0.232	1.841 (1.229, 2.453)	0.002
Hb < 13g/L	1.795 (0.934, 2.656)	0.061	1.517 (1.009, 2.025)	0.047
LnAlbumin	0.566 (0.433, 0.679)	0.023	1.114 (0.984, 1.244)	0.708
LneGFR	0.538 (0.454, 0.622)	< 0.001	0.606 (0.500, 0.712)	< 0.001
LnNT-proBNP	2.684 (1.870, 3.498)	< 0.001	2.317 (1.882, 2.752)	< 0.001
Lnhs-cTNT	1.364 (1.136, 1.592)	< 0.001	1.385 (1.207, 1.563)	< 0.001
LnLVEDD	1.005 (0.972, 1.040)	0.072	1.015 (0.971, 1.059)	0.059

Hb: Haemoglobin; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

the baseline GDF-15 level (median level 2025 *vs.* 647 ng/L). Rather different subjects may have resulted in the bias. Our study had restricted inclusion criteria with LVEF < 40%, comparatively the previous Chinese CHF cohort included 53% patients with preserved ejection fraction (LVEF > 45%) and analyzed data of different HF terminology homogeneously. Moreover the previous Chinese CHF cohort did not exclude some co-morbidity (for example, chronic obstructive pulmonary disease[18]) that may influence plasma GDF-15 level. The discrepancy may also be caused by assay differences.

The associations with GDF-15 identified from our study were consistent with previous studies in clinical (BMI, NYHA Class), echocardiographic (LVEF), and traditional biochemical markers (Hb, UA, eGFR, *et al*). However, inflammatory markers (CRP, IL-6) were not related to GDF-15 in the present study, which differed from the results from Valsartan Heart Failure Trial (Val-HeFT).[9] Though inflammatory cytokines have been shown to enhance the expression of GDF-15 in heart, these were found in animal model of acute stage of heart injury. The pathophysiological effects of GDF-15 may vary with the stage of the disease.[6, 19–21] Our study population was in stable stage of heart failure, we postulated that our patients had lower inflammation. However discrepancy in lifestyle, nutrition, and metabolism between different ethnic groups may also cause these varieties in characters of disease. Furthermore, this study was an observational study, all participants were treated according to national guidelines and patients real status, in another word our study was more real world study compared with the randomized control design of Val-HeFT.

It is notable that higher baseline levels of GDF-15 were associated with left ventricular remodeling. In contrast, left ventricular dilatation predicted increasing levels of GDF-15

over 12 months. Dominguez-Rodriguez, *et al*.[22] and Wang, *et al*.[23] elicited the similar conclusion. These results suggest that GDF-15 may exacerbate the progression of HF by interacting with left ventricular remodeling and further support the utility of following GDF-15 levels for guiding management decisions aimed at inhibiting left ventricular remodeling.

Prognostic analysis in our study identified baseline GDF-15 level and increase of GDF-15 over 12 months provided independent prognostic information about all cause-death beyond established clinical and biomarkers in Chinese Han Patients with post-myocardial infarction CHF. An increase of 172% increase of baseline GDF-15 was associated with a 1.826-fold higher risk of all-cause death and a 2.243-fold higher risk of MACE. In order to obtain an unbiased estimate of the effect of a GDF-15 on all-cause death and MACE using standard survival analysis methods, it is necessary that GDF-15 can be measured at all times and without error. Therefore a joint modeling of longitudinal and survival data for the 173 patients survived one year was performed. The results of joint modeling also revealed that GDF-15 to be an independent risk factor for All-cause death and MACE, even with a higher hazard ratio than the separate analysis of all subjects, 2.749 *vs.* 1.826 and 2.434 *vs.* 2.243, respectively. The independent prognostic value of baseline GDF15 in our CHF population is consistent with previous studies that investigated mainly in Caucasian CHF population. Kempf, *et al*.[8] provided the first evidence of the incremental prognostic utility of GDF15 over NT-proBNP and NYHA functional class or other established clinical risk factors from a Caucasian cohort in 2007. In 2010, Inder S. Anand, *et al*.[9] confirmed that plasma GDF-15 are associated with prognosis independently of many established risk factors of CHF from part of Val-HeFT database (1734 of 5010 CHF patients). Lok, *et al*.[10] observed GDF-15 to be an even stronger predictor than NT-proBNP. Recently, a study[13] on Southeast Asian CHF cohort came to the same conclusion that elevated circulating GDF-15 identified patients at increased risk of death or HF re-hospitalization in CHF. The latest evidence elicited from HF-ACTION (Heart Failure: A Controlled Investigating Outcomes of Exercise Training) trial[24] supported GDF-15 to be an independent prognostic biomarker in CHF. However, GDF-15 had been previously reported as a predictor of all-cause mortality associated with non-cardiac conditions (such as malignancies and pulmonary diseases) from many researchers.[25–27] Therefore, it should be cautioned to use GDF-15 as a interpreting endpoints of all-cause mortality. Despite the different change over time, increase of GDF-15 predicted subsequent adverse outcomes both in our study and other two studies[9,15] with repeated measurement. In addition, therapy at discharge and during follow-up should need to be related to prognosis, even though there was no significant correlation between therapy and outcomes in our study. The real world observational study design could account for the unreasonable results, as all subjects were treated according to relevant guidelines[3,4] by two experienced clinicians and the therapy was not studied as the intervention factor. For example, the only reason why less than 30% of subjects didn't received ACEI or ARB therapy was the subjects' intolerance to side effects or hypotension.

Moreover, we found potential of GDF-15 to improve risk stratification as adding GDF-15 to basic model including previously identified risk predictors raised AUCs of ROC for all-cause mortality and MACE. What more prevalent nowadays is multi-biomarkers strategy with GDF-15 to optimize the risk stratification.[28,29]

4.1 Limitations

Our study has several limitations, which should be taken into account while interpreting the results. Firstly, this is a single center investigation with a relative small sample size and short follow-up. Secondly, there is a debate on whether GDF-15 is triggered post left ventricular remodeling, or whether GDF-15 itself is a mediator of remodeling, this study did not answer the question. Third, the analysis of these 173 patients is only exploratory and biased, including only patients who survived 12 months and had repeated measurement of GDF-15. Lastly, all treatment did not show influence on GDF-15 level, prospective and preferably randomized studies are needed to further evaluate the utility of GDF-15 for guiding management decisions and treatment selection, in comparison to and in combination with other biomarkers and clinical predictors.

4.2 Conclusions

An elevated baseline plasma level of GDF-15 and further increase over 12 months are independent risk factors of all-cause death in Chinese Han patients with post-myocardial infarction CHF. GDF-15 may influence the prognosis of post-myocardial infarction CHF through the pathophysiological pathway of myocardial remodeling.

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References

1 Moran AE, Forouzanfar MH, Roth GA, *et al.* The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation* 2014; 129: 1493–1501.

2 Zhong N, Wang C, Yao W, *et al.* Prevalence of chronic obstructive pulmonary disease in China:a large, population-based survey. *Am JRespir Crit Care Med* 2007; 176: 753–760.

3 Yancy CW, Jessup M, Bozkurt B, *et al.* 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; 23: 628–651.

4 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; 18: 891–975.

5 Xu J, Kimball TR, Lorenz JN, *et al.* GDF15/MIC-1 functions as a protective and anti-hypertrophic factor released from the myocardium in association with SMAD protein activation. *Circ Res* 2006; 98: 342–350.

6 Kempf T, Zarbock A, Widera C, *et al.* Gdf-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. *Nat Med* 2011; 17: 581–588.

7 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.

8 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.

9 Anand IS, Kempf T, Rector TS, *et al.* Serial measurement of growth differentiation factor-15 in heart failure: relation to disease severity and prognosis in the valsartan heart failure trial. *Circulation* 2010; 122: 1387–1395.

10 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.

11 O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013; 82: E1–E27.

12 Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 62: E147–E239.

13 DeLong ER, DeLong DM, Clarke-Pearson DL, *et al.* Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44: 837–845.

14 Ozgur Asar, James Ritchie, Philip A Kalra, *et al.* Joint modelling of repeated measurement and time-to-event data: an introductory tutorial. *Int J Epidemiol* 2015; 44: 334–344.

15 Kempf T, Horn-Wichmann R, Brabant G, *et al.* Circulating concentrations of growth differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immune-radiometric sandwich assay. *Clin Chem* 2007; 53: 284–291.

16 Michelle M.Y. Chan, Rajalakshmi Santhanakrishnan, Jenny P.C. Chong, *et al.* Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. *European Journal of Heart Failure* 2016;18: 81–88.

17 Hua Wang, Qingyong Chen, Yingying L, *et al.* Prognostic value of growth differentiation factor-15 in Chinese patients with heart failure: A prospective observational study. *Cardiol J* 2018; 25: 245–253.

18 Mutlu LC, Altintas N, Aydin M, *et al.* Growth Differentiation Factor-15 Is a Novel Biomarker Predicting Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Inflammation* 2015; 38: 1805–1813.

19 de Jager SC, Bermudez B, Bot I, Koenen RR, Bot M, Kavelaars A, *et al.* Growth differentiation factor 15 deficiency protects against atherosclerosis by attenuating CCR2-mediated macrophage chemotaxis. *J Exp Med* 2011; 208: 217–225.

20 Bonaterra GA, Zugel S, Thogersen J, *et al.* Growth differentiation factor-15 deficiency inhibits atherosclerosis progression by regulating interleukin-6-dependent inflammatory response to vascular injury. *J Am Heart Assoc* 2012; 1: 1–14.

21 Sai VW, Lin S, Brown DA, Salis A, Breit SN, *et al*. Anorexia-cachexia and obesity treatment may be two sides of the same coin: role of the TGF-β superfamily cytokine MIC- 1/GDF15. *Int J Obes* 2016; 40: 193–197.

22 Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P, *et al.* Relation of growth-differentiation factor 15 to left ventricular remodeling in ST-segment elevation myocardial infarction. *Am J Cardiol* 2011; 108: 955–958.

23 Wang F, Guo Y, Yu H, *et al.* Growth differentiation factor 15 in different stages of heart failure: potential screening implications. *Biomark Biochem Indic Expo Response Susceptibility Chem* 2010; 15: 671–676.

24 Sharma A, Stevens SR, Lucas J, *et al*.Utility of Growth Differentiation Factor-15, A Marker of Oxidative Stress and Inflammation, in Chronic Heart Failure: Insights From the HF-ACTION Study. *JACC Heart Fail* 2017; 5: 724–734.

25 George M, Jena A, Srivatsan V, Muthukumar R, *et al.* GDF 15--A Novel Biomarker in the Offing for Heart Failure. *Curr Cardiol Rev* 2016; 12: 37–46.

26 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: 82–88.

27 Wollert KC, Kempf T, Wallentin L, *et al*. Growth Differentiation Factor 15 as a Biomarker in Cardiovascular Disease. *Clin Chem* 2017; 63: 140–151.

28 Jungbauer CG, Riedlinger J, Block D, *et al*. Panel of emerging cardiac biomarkers contributes for prognosis rather than diagnosis in chronic heart failure. *Biomark Med* 2014; 8: 777–789.

29 Widera C, Pencina MJ, Bobadilla M, *et al.* Incremental prognostic value of biomarkers beyond the GRACE (Global Registry of Acute Coronary Events) score and high-sensitivity cardiac troponin T in non-ST-elevation acute coronary syndrome. *Clin Chem* 2013; 59: 1497–1505.