

# Serum GDF-15 Predicts In-Hospital Mortality and Arrhythmic Risks in Patients With Acute Myocardial Infarction

Clinical and Applied  
Thrombosis/Hemostasis  
Volume 28: 1-5  
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DOI: 10.1177/10760296211063875  
journals.sagepub.com/home/cat



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## Abstract

This study aims to evaluate the association of serum growth differentiation factor 15 (GDF-15) with in-hospital mortality and arrhythmic risks in patients with acute myocardial infarction (AMI). A total of 296 consecutive patients with AMI were enrolled in our hospital from Jan. 2018 to Dec. 2020. Serum GDF-15 levels were measured at baseline. The primary endpoint was in-hospital all-cause mortality, and the secondary endpoint was major adverse cardiac events (MACEs) during hospitalization, defined as a composite of cardiovascular death, heart failure, sustained ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation), and bleeding. During hospitalization, patients with a higher GDF-15 level had significantly higher incidences of in-hospital mortality (7.4% vs 1.4%;  $P = .02$ ) and MACEs (9.5% vs 20.9%,  $P < .01$ ) than those with a lower GDF-15 level. Multivariate logistic regression analysis showed that a higher GDF-15 level was significantly associated with increased risks of in-hospital mortality (OR = 1.92, 95% CI: 1.44-2.50;  $P < .01$ ) and MACEs (OR = 2.19, 95% CI: 1.56-2.77;  $P < .01$ ). In conclusion, GDF-15 was associated with the risks of in-hospital mortality and MACEs, indicating that it should be a prognostic biomarker for patients with AMI.

## Keywords

GDF-15, acute myocardial infarction, major adverse cardiovascular events, mortality

## Introduction

Acute myocardial infarction (AMI) is an acute and fatal form of ischemic heart disease, which is the second leading cause of death in China.<sup>1</sup> In contrast to the declining trend in AMI in the United States and European countries,<sup>2,3</sup> the number of AMI cases in China is increasing rapidly and is expected to reach 23 million in 2030. Moreover, a recent study has shown that AMI tends to occur in younger individuals,<sup>4</sup> which will undoubtedly put a huge strain on the health care system. Therefore, identification of biomarkers with strong prognostic powers is a potential approach for early risk stratification as well as a future guide for the appropriate use of resources and therapies following an AMI.<sup>5</sup>

The growth differentiation factor-15 (GDF-15) is a cytokine belonging to the transforming growth factor beta (TGF- $\beta$ ) family.<sup>6</sup> In normal conditions, GDF-15 is expressed at lower levels in different organ and cell line,<sup>7</sup> but increased expression levels are associated with disease states, such as inflammation,<sup>8</sup> oxidant stress,<sup>9</sup> and ischemia/reperfusion.<sup>10</sup> Several clinical studies have demonstrated that GDF-15

could serve as a prognostic marker of coronary artery bypass grafting (CABG),<sup>11</sup> acute coronary syndromes (ACS),<sup>12</sup> and heart failure (HF).<sup>13</sup> A study conducted by Liu et al reported that serum GDF-15 levels were independently associated with the risk of MI ( $P = .01534$ ) after adjusting for age, sex, smoking status, and left ventricular ejection fraction (LVEF).<sup>14</sup> However, the prognostic value of GDF-15 in AMI is still unclear.

The present study aims to evaluate the association of serum GDF-15 with in-hospital mortality and arrhythmic events in patients with AMI.

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## Materials and Methods

### Patients

A total of 296 consecutive adult patients (aged  $\geq 18$  years) with AMI were enrolled in our hospital from Jan. 2018 to Dec. 2020.

**Table 1.** Comparison of Baseline Characteristics Between Patients With High and Low GDF-15 levels.

	Low GDF-15 level (n = 148)	High GDF-15 level (n = 148)	P value
<b>Demographic</b>			
Age, years	53.7 $\pm$ 12.1	54.1 $\pm$ 11.8	.77
Male, n (%)	115 (77.7%)	121 (81.8%)	.47
BMI, kg/m <sup>2</sup>	22.6 $\pm$ 3.5	23.2 $\pm$ 3.1	.12
Current smoker, n (%)	34 (23.0%)	38 (25.7%)	.68
<b>Medical history</b>			
Hypertension, n (%)	99 (66.9%)	103 (69.6%)	.71
Dyslipidemia, n (%)	78 (52.7%)	82 (55.4%)	.64
Diabetes mellitus, n (%)	54 (36.5%)	59 (39.9%)	.63
Chronic kidney disease, n (%)	14 (9.5%)	17 (11.5%)	.70
Previous CAD, n (%)	57 (38.5%)	50 (33.8%)	.47
Previous atrial fibrillation, n (%)	13 (8.8%)	10 (6.8%)	.66
Previous heart failure, n (%)	2 (1.4%)	5 (3.4%)	.44
LVEF, %	50.1 $\pm$ 10.5	52.3 $\pm$ 11.3	.08
STEMI, %	125 (84.5%)	122 (82.4%)	.75
NSTEMI, %	23 (15.5%)	26 (17.6%)	.75
<b>Laboratory data</b>			
Hemoglobin, g/dl	13.6 $\pm$ 2.0	13.9 $\pm$ 1.8	.18
Estimated GFR, mL/min/1.73 m <sup>2</sup>	70.6 $\pm$ 25.1	70.8 $\pm$ 24.9	.95
Triglycerides, mg/dL	126.6 $\pm$ 117.3	121.7 $\pm$ 114.3	.72
HDL-cholesterol, mg/dL	45.3 $\pm$ 10.8	47.1 $\pm$ 11.2	.16
LDL-cholesterol, mg/dL	118.3 $\pm$ 36.4	121.5 $\pm$ 39.0	.47
HbA1c, %	6.2 $\pm$ 1.4	6.3 $\pm$ 1.3	.52
GDF-15, pg/mL	1278.7 $\pm$ 203.2	1767.3 $\pm$ 268.4	<.01
<b>Procedure</b>			
Type of revascularization			
CABG	12 (8.1%)	13 (8.8%)	1.00
PCI	136 (91.9%)	135 (91.2%)	
Drug-eluting stent in PCI	133 (89.9%)	131 (88.5%)	.72
Type of access in PCI intervention			
Transradial	120 (88.2%)	121 (89.6%)	.85
Transfemoral	16 (11.8%)	14 (10.4%)	
Day of revascularization from NSTEMI admission			
PCI	1 (0-2)	1 (0-2)	.74
CABG	3 (1-4)	3 (1-5)	.68

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Diagnosis of AMI was based on the ESC/ACC Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction.<sup>15</sup> AMI was diagnosed by the rise and/or fall of cardiac biomarkers with at least 1 value above the 99th percentile of the upper reference limit observed together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, electrocardiography (ECG) changes indicative of new ischemia, development of pathological Q waves in the ECG, or imaging evidence of a new loss of viable myocardium or new regional wall motion abnormalities.

All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Review Board of our hospital and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

### Data Collection

Data about patient demographics, comorbidities, clinical and physical examination findings were recorded at the time of admission. ST-elevation MI (STEMI) was defined by the presence of persistent (>20 min) ST-segment elevation;<sup>16</sup> In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation MI (NSTEMI).<sup>17</sup> Patients with STEMI were treated with primary percutaneous coronary intervention (PCI). The transradial and transfemoral interventions were used to perform PCI. Patients with NSTEMI underwent invasive coronary angiography according to risk stratification and treatment strategy.<sup>17</sup> The revascularization strategy (PCI or CABG) was based on the clinical status, comorbidities, disease severity and distribution, and lesion characteristics. These procedure parameters were also recorded.

Venous blood samples were obtained from each patient at admission. The serum was separated from the cells by centrifuging at 1500 g for 10 min and stored at  $-80^{\circ}\text{C}$  until assayed. Serum GDF-15 level was measured by a Human Quantikine ELISA Kit (DGD150 for GDF-15, R&D Systems). Samples, reagents, and buffers were prepared according to the manufacturers' manuals. The detection threshold of GDF-15 was 2.0 pg/mL. The intra and interassay coefficients of variation for GDF-15 were <5% and <10%, respectively.

### Outcomes

The primary endpoint was in-hospital all-cause mortality, and the secondary endpoint was major adverse cardiac events (MACE), defined as a composite of cardiovascular death, HF, sustained ventricular arrhythmias including ventricular tachycardia (VT) and ventricular fibrillation (VF), and bleeding during hospitalization.

## Statistical Analysis

Continuous variables are presented as mean  $\pm$  SD and compared with the use of unpaired Student's *t*-test. All categorical variables were summarized as counts and percentages and compared by chi-square test or by Fisher's exact test as appropriate. Multivariate logistic regression analysis was employed to explore the association of GDF-15 with the risks of in-hospital mortality and MACEs. All tests were 2-sided and a *P* value of less than .05 was considered significant.

All statistical analyses were performed with the SPSS statistical software program package (SPSS version 20.0 for Windows, Armonk, NY: IBM Corp.).

## Results

A total of 296 patients were divided into high ( $n = 148$ ) or low ( $n = 148$ ) GDF-15 groups according to median level of GDF-15 (1523.4 pg/ml). The GDF-15 levels in the high GDF-15 group were significantly higher than those in the low GDF-15 group ( $1767.3 \pm 568.4$  vs  $1278.7 \pm 503.2$  pg/ml;  $P < .01$ ). As indicated in Table 1, the demographic variables, medical history, laboratory data, and procedure parameters were comparable between 2 groups (all  $P > .05$ ).

During a median hospital stay of 5.0 (3.0-8.0) days, the number of deaths was significantly more in the high GDF-15 group than in the low GDF-15 group (7.4% vs 1.4%,  $P = .02$ ; Figure 1A). Multivariate logistic regression analysis (Table 2) showed that after adjusting for baseline characteristic variables, GDF-15 (OR = 1.92, 95% CI: 1.44-2.50;  $P < .01$ ), age (OR =

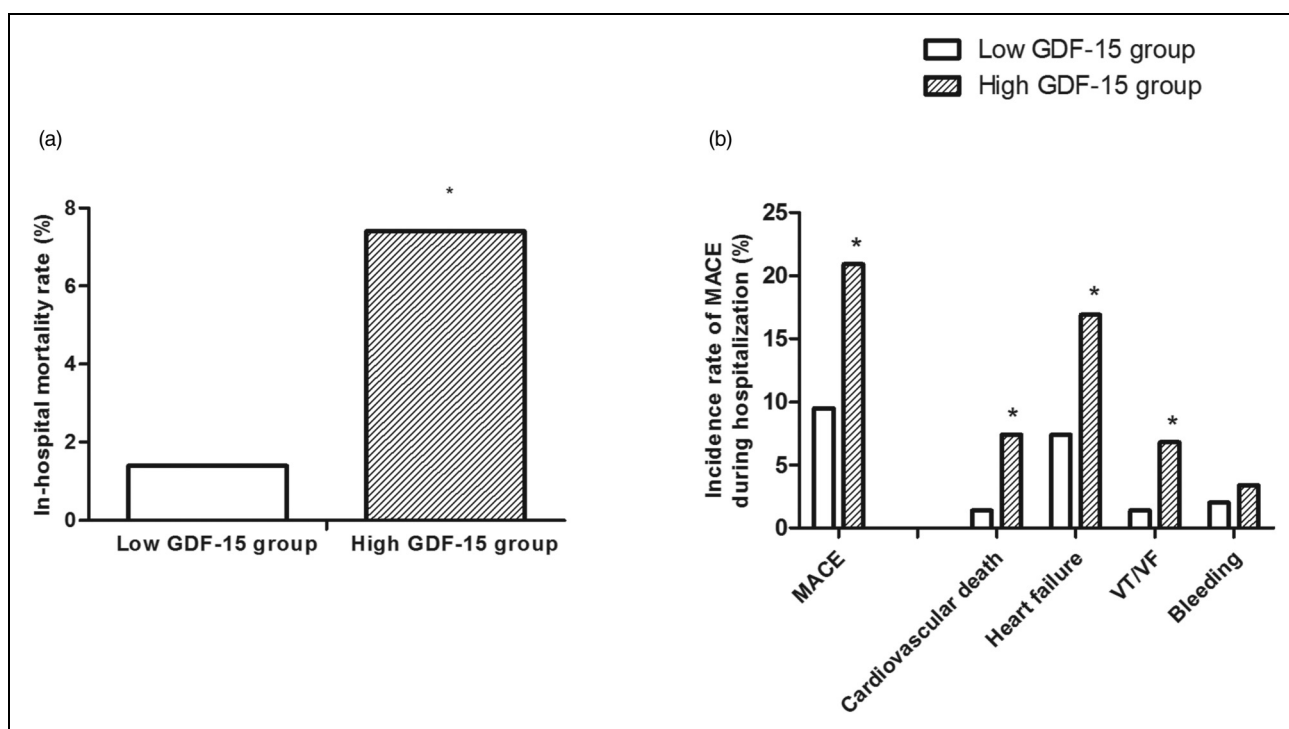
1.06, 95% CI: 1.02-1.14;  $P < .01$ ), LVEF (OR = 0.91, 95% CI: 0.79-0.98;  $P = .03$ ), and transradial intervention (OR = 0.53, 95% CI: 0.42-0.68;  $P < .01$ ) were significantly associated with in-hospital mortality risk.

During hospitalization, the difference in the percentage of patients suffering MACEs was statistically significant between 2 groups (9.5% vs 20.9%,  $P < .01$ ; Figure 1B). Specifically, most composites of MACEs including cardiovascular death (7.4% vs 1.4%;  $P = .02$ ), HF (7.4% vs 16.9%;  $P = .02$ ), and VT/VF (1.4% vs 6.8%;  $P = .04$ ) occurred more in the high GDF-15 group compared with the low GDF-15 group. Multivariable logistic regression analysis (Table 2) showed that GDF-15 (OR = 2.19, 95% CI: 1.56-2.77;  $P < .01$ ), age (OR = 1.07, 95% CI: 1.04-1.11;  $P < .01$ ), LVEF (OR = 0.88, 95% CI: 0.81-0.96;  $P = .02$ ), transradial intervention (OR = 0.56, 95% CI: 0.44-0.71;  $P < .01$ ), and previous CAD (OR = 1.74, 95% CI: 1.44-2.07;  $P < .01$ ) were all significantly associated with the risk of MACEs after controlling for potential confounding factors.

## Discussion

Our study findings showed that elevated GDF-15 concentrations were significantly associated with increased risks of in-hospital mortality and MACEs in patients with AMI.

In line with our study, the independent association of GDF-15 level with in-hospital all-cause mortality has been conclusively reported among subjects from the general population as well as in various patient cohorts.<sup>6,18,19</sup> Moreover, several studies have demonstrated that GDF-15 predicted all-cause



**Figure 1.** Incidence rates of in-hospital mortality (A) and MACEs (B). \* $P < .05$ .

**Table 2.** Multivariate Logistic Regression for Prediction of In-hospital Mortality and Major Adverse Cardiac Events (MACEs).

	In-hospital mortality			In-hospital MACEs		
	OR	95% CI	P value	OR	95% CI	P value
GDF-15	1.92	1.44-2.50	<.01	2.19	1.56-2.77	<.01
Age	1.06	1.02-1.14	<.01	1.07	1.04-1.11	<.01
LVEF	0.91	0.79-0.98	.03	0.88	0.81-0.96	.02
Transradial	0.53	0.42-0.68	<.01	0.56	0.44-0.71	<.01
Previous CAD				1.74	1.44-2.07	<.01

LVEF, left ventricular ejection fraction; CAD, coronary artery disease.

mortality independently of and more accurately than other biomarkers like NT-proBNP, hs-CRP, or hs-cTn.<sup>20,21</sup>

A number of studies have reported the association of elevated GDF-15 concentration at admission with MACEs in cardiovascular diseases such as HF, cardiac hypertrophy, and coronary heart disease. In a cohort of 14 577 patients with stable angina and history of revascularization, multivessel disease or infarction,<sup>22</sup> GDF-15 levels above 1827 pg/ml were associated with increased risk of cardiovascular death, cardiac sudden death and hospitalization for heart, regardless of other markers such as troponin, reactive C protein, and BNP. Among 16 876 patients with ACS in the PLATO (PLATElet inhibition and patient Outcomes) trial,<sup>23</sup> GDF-15 levels above 1550 pg/ml were significantly associated with a higher risk of composite of cardiovascular death, spontaneous myocardial infarction, and stroke. Interestingly the predefined cut-off values used in these studies were pretty closed to the one in our population (1523.4 pg/ml).

The underlying mechanisms explaining the independent associations between GDF-15 and cardiovascular disease and events are unknown. While weakly expressed under physiological conditions, GDF-15 is highly secreted as a stress response to inflammation, oxidative stress, hypoxia, telomere erosion, and oncogene activation, indicating that GDF-15 should be a downstream marker of established cell stress.<sup>24</sup> In addition, GDF-15 is associated with several cardiovascular risk factors and other biomarkers, such as LV mass and IL-6 and matrix metalloproteinase (MMP)-9 levels.<sup>25</sup> There is also a potential for a specific mechanism as GDF-15 has been shown to have an inhibitory effect on platelet aggregation and was associated with thrombus severity.<sup>18</sup> Therefore, measurement of the GDF-15 level might provide unique information on underlying disease processes leading to a raised risk of severe events.

Previous randomized clinical trial and observational studies demonstrated fewer periprocedural complications, shorter length of stay, and better patient satisfaction associated with transradial intervention relative to transfemoral intervention.<sup>26–28</sup> A review provided an overview of the clinical evidences comparing the transradial versus transfemoral approach to reduce hemorrhagic event.<sup>29</sup> It is shown that radial access significantly reduced the incidence of hemorrhagic events and mortality

compared to transfemoral access, which are consistent with the outcomes in the present study.

There are several limitations of this study. First, the single-center, nonrandomized nature of the study with a relatively small sample size may have led to subject selection bias, larger-scale studies should be conducted to better evaluate the relationship between the serum GDF-15 and cardiac events. Second, the post-AMI serial changes in the GDF-15 concentration in the serum were not evaluated, resulting in an inability to identify the best time for peak value measurement of GDF-15 following AMI.

In conclusion, GDF-15 was associated with the risks of in-hospital mortality and MACEs, indicating that it should be a prognostic biomarker for patients with AMI.


### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Research Foundation of Liuzhou People's Hospital (lryjc201912) and Project of science and technology research plan of Health Commission of Guangxi Zhuang Autonomous Region (Z20180303).

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